EXPLORING GENDER AND SEX DIFFERENCES IN BEHAVIORAL DYSCONTROL: FROM DRUG ADDICTION TO IMPULSE CONTROL DISORDERS

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EXPLORING GENDER AND SEX DIFFERENCES IN BEHAVIORAL DYSCONTROL: FROM DRUG ADDICTION TO IMPULSE CONTROL DISORDERS

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Males and females exhibit discrete attitudes and skills, experience dissimilar emotional and psychological needs, and react differently to peer pressure, lack of self-realization, or other personal and social expectations. In addition, they are differently influenced by family history, and diverge in the perception of self-image and health risks. To complicate the matter on gender dichotomy, male testosterone levels markedly vary over the course of the day, while female levels of sex hormones significantly fluctuate depending upon the menstrual cycle, the pre- or post-menopausal age, and the use of oral contraceptives. All of these factors interact with genetic background and sex hormonal fluctuations, and determine the differences observed in their predisposition to develop an addiction. This term is traditionally associated to the abuse of legal and illegal substances. However, a compulsion toward the engagement in a non-drug-related rewarding behavior, usually involving a natural reward, also activates the brain reward system and engenders persistent behavior, thus resulting in a diminished control over it. These latter behaviors are defined as "behavioral addictions".

This definition encompasses any behavior characterized by the followings: i) feeling of tension or arousal before the action; ii) gratification and/or relief at the time of performing the act; iii) inability to resist an urge or drive even against great obstacles or dangers; iv) absence of consideration for the negative consequences that may affect family, friends, and/or work. As such, behavioral addictions include compulsive food intake and sexual activity, pathological gambling and Internet addiction, excessive exercising, compulsive buying and pyromania. These behaviors, which are often classified as "impulse control disorders", result in actions that are harmful to oneself and/or others, share common features (e.g. compulsiveness, impulsivity, impaired decision-making, craving, tolerance, withdrawal, high rates of relapse), and involve dysfunction of several brain circuits. Derangement from functional neurobiological

mechanisms underpinning both sensitivity to reward and inhibitory control can also lead to compulsive behaviors. For instance, pathological gambling and other impulse control disorders (e.g., hypersexuality, compulsive painting, eating and buying) are often reported in Parkinson's disease patients.

Gender-dependent differences in the rate of initiation and frequency of misuse of addicting drugs have been widely described. Yet, men and women also differ in their propensity to become addicted to other rewarding stimuli (e.g. sex, food) or activities (e.g. gambling, exercising). The goal of the present Research Topic is to explore and summarize current evidence for gender (and sex) differences not only in drug addiction, but also in other forms of addictive behaviors. Thus, it will include studies showing gender-dependent differences in drug addiction, food addiction, compulsive sexual activity, pathological gambling, Internet addiction and physical exercise addiction. Psychiatric comorbidity, potential risk factors and the underlying neural mechanisms will be also examined, with particular emphasis to the role of sex hormones in modulating addictive and compulsive behaviors.

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Table of Contents

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EDITORIAL
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Editorial: Exploring Gender and Sex Differences in Behavioral Dyscontrol: From Drug Addiction to Impulse Control Disorders

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Keywords: gender differences, sex differences, behavioral addictions, drug addiction, impulse control disorders, sex hormones, sexual brain dimorphism

The Editorial on the Research Topic

Exploring Gender and Sex Differences in Behavioral Dyscontrol: From Drug Addiction to Impulse Control Disorders

This Research Topic gathers animal and human research articles, reviews, and opinion articles on current research in the field of sex and gender differences in behavioral addictions, which are complex disorders with interacting factors, including environmental factors, comorbidity, and personality traits (1, 2). Research in this field adds to the long-held argument that male and female brains do differ. However, while evidence exists on how male and female brains functionally differ (3–5), conflicting findings suggest that human brains cannot be narrowly classified into sexes/genders (6).

Over the past decade, there have been major advances in our understanding of sex and gender differences in behavioral addictions and underlying motivations (7, 8), brain reward processes (9), and impulsive behaviors (10). Potential factors, which could provide a neurobiological basis for sex- and gender-based differences in behavioral addictions, have been identified. Among them, there are organizational and activational effects of gonadal hormones, socio-cultural factors, different impulse-control ability, and responsiveness to stress (11, 12). It is important to note that, although often used as synonymous, the terms "sex" and "gender" are not interchangeable. In fact, the term "sex" is referred to biological attributes and characteristics associated with the adjectives "male" and "female" (i.e., anatomy and physiology inherent male-female differences), while "gender" concerns sociocultural distinctions between males and females (i.e., culture-related dogmas and roles, behaviors embraced by men and women that shape their daily life and activities).

In this Research Topic, basic researchers and clinicians that are leading experts in the field provide original findings and overviews on the role of sex and gender in modulating addictive behaviors and developing behavioral addictions. First, sex and gender differences in addiction to cannabis, methamphetamine, cocaine, and alcohol are discussed. Rubino and Parolaro systematically reviewed human and animal studies showing how males and females respond differently to cannabinoid compounds. In particular, dichotomy in the pharmacokinetics of THC observed in males and females may contribute to their dissimilar responses to cannabinoids. The role of sexual dimorphism in the brain endocannabinoid system and its interaction with gonadal hormones may also play a part (13–18). Accordingly, Ruda-Kucerova et al. presented evidence that sex-dependent differences exist in the reinstatement of methamphetamine-seeking behavior in abstinent rats. Notably, females displayed higher vulnerability to relapse to methamphetamine seeking independently of the current estrous

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cycle phase, thus suggesting that central mechanisms responsible for the enhanced response displayed by females are not affected by circulating ovarian hormones.

In humans, sex and gender differences are reported in psychiatric comorbidity and plasma biomarkers in abstinent cocaine addicts and in behavioral impulsivity in heavy alcohol drinkers. Specifically, Pedraz et al. demonstrated that cocaine addicted men and women differ with regard to the levels of plasma biomarkers for cocaine addiction. Notably, while men exhibit a higher incidence of substances use comorbidity (e.g., alcohol), cocaine addicted women display a higher prevalence of comorbid psychiatric disorders (e.g., anxiety). In addition, Weafer et al. demonstrated that heavy alcohol female drinkers show poorer inhibitory control than male drinkers do, although it remains to be determined whether the reported higher behavioral impulsivity in women is the cause or the consequence of heavy drinking. That behavioral control is impacted by sex and gender is further supported by evidence compellingly reviewed by Carroll and Smethells revealing sex- and gender-dependent differences in impulsivity, food, and drug addiction. Importantly, authors discussed pharmacological and behavioral treatments for improving control of impulses in a sex-tailored manner, an approach also suggested for drug and behavioral addictions (19, 20). Among behavioral addictions, sexual addiction (often referred to as compulsive sexual behavior) is discussed by Weinstein et al. who found that men are more likely to use cybersex and experience craving for pornography than women. Importantly, both craving for pornography and frequency of cybersex were associated with difficulty in forming intimate relationship. In another clinical setting, Davis et al. used a moderator-mediation model to perform an elegant analysis of personality risk-factors and sex in moderating the relationship between ADHD symptomatology and addictive behaviors. According to their observations, no sex differences in personality risk for addiction or in the use of addictive behaviors were found in ADHD patients. A positive affective neuroendocrinology (PANE) approach to study the mechanisms of reward motivation and dysregulation is herein proposed by Welker et al., which investigated sources of potential sex differences in the hormonal mechanisms of behavioral dyscontrol. Finally, Mitchell and Potenza highlighted the importance of investigating the relationship between sexual hormones and impulsivity traits to disentangle sex and gender differences in impulse control and behavioral addictions. Equally, Mendrek et al. emphasize the need of considering sex and gender in neuroscience by focusing on psychiatric disorders, such as schizophrenia and drug addiction, where research on such differences is still in its infancy.

We wish to thank all the Authors of this Research Topic for presenting and discussing their work and sharing their personal expertise and opinions on this emerging field. Moreover, we express gratitude to all reviewers that found time in their busy schedules to provide us with useful and constructive comments. We feel that research on factors and mechanisms allowing for the pursuit of drug and non-drug rewards is essential to deliver innovative gender-tailored treatments and to develop preventive strategies that may efficiently reduce in men and women the risk of becoming addicted to a substance or an activity. Improving our knowledge on sex and gender differences in drug addiction and reward processing will remarkably have therapeutic implications and help the development of sex-tailored, gender-sensitive treatment interventions. Some evidence has been already provided. In fact, pharmacological treatments differently affect male and female addicts. That is, the long-acting injectable form of naltrexone was found to be efficacious for males but not for females (21). This finding was further supported by the observation that oral naltrexone lacked efficacy relative to placebo in alcoholic women (22). Conversely, a 16-week course of fluoxetine initiated 8 weeks pre-quit cigarette smoking ("sequential" fluoxetine) reduced pre-quit depressive symptoms, withdrawal-relevant negative affect, and craving to smoke during a pre-quit period only in women (23). These and similar studies confirmed the importance of considering gender when examining treatment efficacy, and highlight the timeliness of this Research Topic.

AUTHOR CONTRIBUTIONS

LF and MM equally contributed to this Editorial for the Research Topic entitled: "Exploring gender and sex differences in behavioral dyscontrol: from drug addiction to impulse control disorders."

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MINI REVIEW
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Sex-dependent vulnerability to *Cannabis* abuse in adolescence

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The goal of this review is to summarize current evidence for sex differences in the response to cannabinoid compounds, focusing mainly on a specific age of exposure, i.e., adolescence. Preclinical as well as clinical studies are examined. Among the different possible underlying mechanisms, the consistent dimorphism in the endocannabinoid system and delta9-tetrahydrocannabinol metabolism may play a part. All the collected data point to the need of including females in basic research as well as of analyzing results for sex differences in epidemiological studies.

Keywords: *Cannabis* abuse, adolescence, sex, human studies, animal models

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Introduction

Cannabis continues to be the most widely used illicit substance among adolescents in the world, and more users are seeking treatment each year (1). Accumulating evidence suggests that exposure to *Cannabis* or its psychoactive ingredient delta9-tetrahydrocannabinol (THC) during the adolescent developmental window may act as a risk factor for the occurrence of psychiatric disorders later in life (2–4).

Despite the well-accepted notion that several neuropsychiatric disorders, such as depression, conduct problems, and autism, are sex-related [see, for review, Ref. (5–7)], very few papers have dealt with sex vulnerability to adolescent *Cannabis* abuse, both at the preclinical and clinical level. The main obstacle to this lies in the fact that research is still mainly focused on the male sex: male animals in preclinical research and male subjects in clinical studies. The potential sex influence is still routinely ignored or dismissed even when both sexes are included, as in some human studies where no sex-related analysis is performed, but all the subjects are regarded as "unisex." Fortunately, the view that biological sex is unimportant in neuroscience is increasingly seen as a false assumption [see for a commentary Ref. (8)]. Notably, the National Institute of Health has recently asked the scientific community for sex and gender inclusion plans in preclinical research (9).

We hope from now on to witness an increasing amount of research considering both sexes. However, so far, few papers have dealt with the influence of this variable on the response to cannabinoids during adolescence. Most work has been done at the preclinical level, but some literature on humans is now also appearing. For the sake of accuracy, in this review we will take into account only papers where both male and females are considered, or papers applying exactly the same paradigm of exposure in male and female animals.

Human Studies

Few studies exist on sex-dependent effects of adolescent *Cannabis* abuse in humans, so it is difficult to draw a precise picture of this phenomenon. Nonetheless, here we want to discuss some interesting observations. Generally, *Cannabis* use is more prevalent among males, who display an earlier age of onset of use and are more likely to be on a heavier use trajectory (10).

As a consequence, males appear to be more likely than females to become dependent on *Cannabis* (11, 12). However, females tend to have shorter intervals between the onset of use and regular use or development of dependence (13, 14). Accordingly, females enter treatment for *Cannabis* use disorders after fewer years and less cumulative use compared to males (15). In general, *Cannabis* abuse is associated with a broad range of adverse health measures in both adolescent girls and boys (14). The existence of an overall sex-dependent effect has already been reported for other drugs of abuse (16), and specifically, female adolescent users seem to experience negative consequences of drug use earlier than male peers, and appear to be more likely to suffer from an internalizing disorder, such as depressive and anxiety disorders (16). Conversely, male substance abusers have more externalizing behaviors, such as aggressiveness and impulsivity (16). This seems to be true also for *Cannabis*. One of the first papers describing this correlation reported that daily *Cannabis* use was associated with a fivefold increase in anxiety and depression in young females, but not males (17). Accordingly, higher rates of comorbid mood and anxiety disorders in women have been recently observed in a large epidemiological study performed in the United States (18). Adolescent female abusers, who developed greater internalizing symptoms, exhibited larger right amygdala volumes relative to males and female controls (19). Interestingly, larger amygdala volumes were associated with increased depression and anxiety symptomatology (19). Similarly, Lai and Sitharthan (20) reported a significant association between *Cannabis* use disorder and mental health disorders, and again, higher comorbidity rates were observed for females. The most common mental disorders were major depression, personality disorder, schizophrenia, and severe stress disorder (20). Potential sex-differences have also been reported for *Cannabis* use and neurocognitive functioning (21). Specifically, *Cannabis* use was more consistently associated with poorer episodic memory performance in females and with poorer decision-making performance in males. Female *Cannabis* users presented a larger prefrontal cortex (PFC) volume compared to controls, whereas male users presented a smaller one (22). It is worth noting that among users, larger PFC total volume was associated with worse executive functioning, thus implying that females performed the worst. Finally, studying the association between *Cannabis* use and earlier age of onset of psychosis (AOP), researchers found that male users are the group with the earliest AOP. However, this seems to be independent of sex, and instead linked to the fact that males start first and consume more than females (23).

In conclusion, *Cannabis* abuse in humans appears to be associated with different responses in male and females, resembling what has already been seen with other drugs of abuse. The molecular bases of these sex differences need further investigation. Future studies should take into account the interaction between the endocannabinoid system and sex hormones, but also the fact that adolescent males and females undergo neuromaturation at separate rates, thus presenting differential trajectories of neuronal maturation at the same age (24, 25), that could hence be differently affected by *Cannabis*.

Animal Studies

Animal models, although far from addressing the complexity of human disorders, allow experimental controls that are not possible in human studies. Moreover, they provide a valuable approach for the investigation of neurobiological substrates. Through this helpful tool, it has been confirmed that chronic administration of natural or synthetic cannabinoids during the adolescent period – using paradigms resembling heavy *Cannabis* abuse in humans – causes persistent behavioral alterations in adult animals [see, for review, Ref. (2, 4, 26)]. Cognition is one of the most explored brain functions after adolescent exposure to natural or synthetic cannabinoids. When sex was taken into account, it appeared that cannabinoid exposure during adolescence impaired learning and memory in both sexes. O'Shea et al. (27, 28) demonstrated that adolescent exposure to increasing doses of the synthetic cannabinoid agonist CP-55,940 for 21 days induced impaired recognition memory in the novel object recognition test long after discontinuation of the drug, in both female and male rats. However, when spatial memory was assessed in the Morris water maze test, adolescent cannabinoid exposure in both sexes disrupted learning immediately after the treatment (29), but not after a long drug-free period (29, 30). In the active place avoidance (APA) paradigm, where animal's ability to learn and retrieve spatial information as well as flexibility of learning is assessed, early adolescent THC exposure did not affect the task acquisition, nor the performance after the 24-h retention interval in adult animals of both sexes (31). However, when flexibility was considered, impaired performance on the reversal trial of the APA task was observed (31). In the radial maze test, used to assess spatial working memory, both male and female rats showed deficits when tested long after adolescent exposure to THC (32, 33). These data suggest that adolescent exposure to cannabinoids induces long-term cognitive impairments specifically in recognition and spatial working memory, as well as in flexibility, whereas pure spatial memory does not seem to be affected. However, these effects do not display sex differences, since they are present in both male and female animals. Less consistent results have been obtained about the impact of adolescent cannabinoid treatment on anxiety behaviors. In fact, results coming from adult animals of both sexes exposed to cannabinoids during their adolescence showed all type of responses: anxiolytic-like response (34), anxiogenic-like effect (27, 28), or no changes in their behavior (35). Neither conclusions regarding the impact of adolescent exposure on anxiety behaviors nor about possible sex differences can be drawn from these findings. A different picture is present when the forced swim test was used: adolescent exposure to THC induced a significant increase in immobility that was apparent only in female rats (35, 36). Also, the effect of adolescent cannabinoid exposure on adult drug self-administration seems to present sex-dependency. Higher adult cocaine self-administration rates have been reported in female rats only (37), whereas increase in morphine self-administration under the fixed ratio 1 schedule has been described in males but not in females (38). As a whole, animal models seem to confirm the existence of some sex-dependent responses to adolescent cannabinoid exposure, with females appearing more sensitive than males in the emotional sphere.

These differences in behavior are substantiated by differences at the cellular/molecular level. Pharmacokinetics seems to play a part. It has been recently reported that adolescent female rats exhibit pronounced metabolism of THC to the still active compound 11-OH-THC compared to their male conspecifics, particularly after repeated THC administration (39). Thus, THC exposure could conceivably be potentiated by its active metabolite in female adolescents. This fact together with the observation that adolescent female rats possess more efficient CB1 receptors (40), suggests that they may be more vulnerable to THC effects. Accordingly, chronic THC exposure in adolescence induced more intense CB1 receptor desensitization in females, with more brain areas involved, despite similar down-regulation (35, 41). If confirmed also in humans, this would explain, at least in part, why females tend to have shorter intervals between the onset of use and the development of dependence, the so-called "telescoping effect" (13–15, 18). Another observation that comes from animal studies and deserves further investigation is that sex-dependent sensitivity appears to exist also with regard to the brain regions that are affected by the treatment. Specifically, in female animals, among all the cerebral areas investigated, the PFC seems to be the most affected, whereas it is the hippocampus in males. For example, Higuera-Matas et al. (30) reported that while periadolescent exposure to a fixed dose of a synthetic cannabinoid agonist did not produce robust behavioral effects, it did induce an increase of the plasticity marker PSA-NCAM in the hippocampus of males only. Similarly, Lee et al. (42) showed that a sustained adolescent CB1 receptor activation reduced adult hippocampal neurogenesis in both sexes; however, for some parameters, males appeared to be more greatly affected than females. Our group, in the search for a possible molecular correlate for the impaired spatial working memory induced by adolescent THC administration, investigated some markers of neuroplasticity in the PFC and hippocampus of both male and female rats (32, 33). Interestingly, a significant decrease in pre- and post-synaptic markers was present in the hippocampus of male rats, whereas the same proteins changed in the PFC of female animals (32, 33). Of note, in human *Cannabis* abusers, the occurrence of significant changes in the hippocampus of males (43) and in the PFC and amygdala of females (19, 22) have been observed. These brain regions are differently involved in the modulation of cognition (hippocampus and PFC) and emotion (amygdala and PFC), and this may explain the greater effect on emotionality in females.

Conclusion

In conclusion, some sex-dependent effects exist in the response to cannabinoid compounds between adolescent males and females. These effects may rely on the different pharmacokinetics described for THC between males and females as well as on sex differences present in the endocannabinoid system. To complicate the picture, a fact that is specific for the adolescent population and should also be taken into account is represented by the observation that some brain developmental characteristics are different in the two sexes. For example, neurodevelopmental trajectories are significantly different between males and females [(25); see, for review, Ref. (44)]. Total brain size and regional gray matter volumes follow an inverted U shaped maturational curve and peak earlier in females, thus suggesting that the pruning process occurring in the adolescent brain might be present with different intensity in boys and girls of the same age. Since it has been recently suggested that the endocannabinoid system in the adolescent brain may play a part in synaptic pruning (45), exposure to cannabinoids during adolescence might differently interact with the pruning event in boys and girls, thus leading to different impairments in brain and behavior. Not least, interactions of the endocannabinoid system with gonadal hormones may also play a part. Interestingly, it has been recently suggested that sex hormones and the endocannabinoid system might work in symphony to promote maturational processes within the adolescent brain, specifically in those circuits important for the emotional and motivational response to sexually relevant stimuli (46). However, the existence of a close interaction between the endocannabinoid system and sex hormones has long been known. For example, CB1 receptor expression and density appear to be under the control of sex steroids in both males and females in some cerebral areas (47, 48). More recently, it has been reported that endocannabinoids and gonadal hormones may reciprocally regulate each other, and interestingly, estrogen can recruit endocannabinoids to modulate emotionality (49, 50). This is particularly important when considering that ovarian hormones may actively contribute to the remodeling event in the female brain during puberty and adolescence, as recently suggested by Juraska et al. (51). This was demonstrated for few brain areas; among them, there are the PFC and amygdala, the very same areas mainly affected by cannabinoids in adolescent females. A deeper knowledge of all these interactions would be helpful in designing proper sex-specific treatments or interventions to prevent or recover the long-term adverse effects induced by adolescent heavy *Cannabis* abuse.

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Sex differences in the reinstatement of methamphetamine seeking after forced abstinence in Sprague-Dawley rats

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Preventing relapse to drug abuse is one of the struggles faced by clinicians in order to treat patients with substance use disorders (DSM-5). There is a large body of clinical evidence suggesting differential characteristics of the disorder in men and women, which is in line with preclinical findings as well. The aim of this study was to assess differences in relapse-like behavior in methamphetamine (METH) seeking after a period of forced abstinence, which simulates the real clinical situation very well. Findings from such study might add new insights in gender differences in relapse mechanisms to previous studies, which employ a classical drug or cue-induced reinstatement procedure following the extinction training. Adult male and female Sprague-Dawley rats were used in IV self-administration procedure conducted in operant boxes using nose-poke operandi (Coulborn Instruments, USA). Active nose-poke resulted in activation of the infusion pump to deliver one intravenous infusion of METH (0.08 mg/kg). After baseline drug intake was established (maintenance phase), a period of forced abstinence was initiated and rats were kept singly in their home cages for 14 days. Finally, one reinstatement session in operant boxes was conducted. Females were found to self-administer significantly lower dose of METH. The relapse rate was assessed as a number of active nose-pokes during the reinstatement session, expressed as a percentage of active nose-poking during the maintenance phase. Females displayed approximately 300% of active nose-pokes compared to 50% in males. This indicates higher vulnerability to relapse of METH seeking behavior in female rats. This effect was detected in all females, independently of current phase of their estrous cycle. Therefore, this paradigm using operant drug self-administration and reinstatement of drug-seeking after forced abstinence model can be used for preclinical screening for potential new anti-relapse medications specific for women.

Keywords: methamphetamine, reinstatement of drug-seeking behavior, forced abstinence, sex/gender differences, Sprague-Dawley rats

Introduction

Methamphetamine (METH) addiction is a serious psychosocial problem, which leads to organic harm of the body as well as distortion of the normal functioning of affected people within the society and family. There is a large body of clinical evidence suggesting differential characteristics of the disorder in men and women. Despite the absolute number of female METH abusers being lower than the male ones, women usually appear more dependent, show higher escalation rates (1, 2) and most importantly tend to experience more frequent relapses (3, 4). These gender specific differences require specific treatment strategies for men and women (5–7). This particularly applies to relapse-prevention, which represents a key treatment challenge especially for women (8).

The preclinical approach to model drug addiction with the highest validity is usually considered as the operant drug self administration. To mimic relapse in this paradigm, a period of extinction procedure can be employed when the animal still has a regular access to the operant box but the drug delivered by infusion pump is replaced by vehicle. After certain number of sessions, the subject stops to respond to the active operandum (e.g., lever or nose-poke). After reaching a specific extinction criteria (number of active/inactive responses lower than a set number), one last session is conducted and the reinstatement of the drug-seeking behavior is primed by an environmental factor (stress, cues) or a drug dose. Such studies have repeatedly shown female rats to be more vulnerable to drug-primed relapse of METH seeking behavior at conditions of time limited sessions (2 h), which mimic rather consummatory behavior, as well as prolonged self-administration sessions. This is considered to provide a better model for loss of control over drug taking, leading to escalation of drug consumption (9) known from a clinical situation (3). Similarly, a higher relapse-like behavior was found in female rats after priming by conditioned cue and to even higher extent by METH dose (10). Earlier, analogous results were reported in studies with cocaine (11, 12) and fentanyl (13).

However, this paradigm does not mimic the human treatment very well, because the patient usually discontinues the drug abuse in the drug rehabilitation center and for some time does not have access to the drug-related environments. Therefore, a forced abstinence model was developed where the animal does not have access to the operant box and is kept in the home cage for some time (14–16); thus, the motivation of drug response behavior is not influenced by any training procedures.

Furthermore, many preclinical studies, which assess sex-dependent differences, isolate the hormonal effect either by ovariectomy and subsequent hormonal supplementation (17, 18) or by constant tracking of the estrous cycle phase (10, 19). These approaches already explained extensively the role of gonadal hormones in the reward processes showing enhancement of drug intake by estradiol (17, 18, 20–22) and attenuation of drug seeking by progesterone (4, 23). However, the possibilities of clinical applications of these findings are limited, so far only progesterone was tested as a treatment for nicotine relapse in women (24) and such treatment would have many undesirable side effects. Consequently, an ideal animal model with high face, construct, and predictive validity for testing new relapse-prevention treatments should not be based on hormonal levels only.

The intact animals (males and freely cycling females) showed no sex differences to effects of amphetamines in the animal model of conditioned place preference (CPP) (25, 26). Interestingly, CPP for METH did not occur in ovariectomized rats but developed in females treated with estradiol (27). Therefore, gender differences in the CPP paradigm might be biased by fluctuating hormonal levels in intact females. However, results supporting higher vulnerability to METH in intact female rats were reported too. Female rats displayed higher increase of locomotor activity, which lasted for longer time and had higher scores of stereotypies than male rats (28). These results indicate the sex differences may depend, besides hormonal influences, also on different pharmacokinetic processes in females (29).

Therefore, the aim of this study was to assess gender differences in all stages of operant IV self-administration of METH in male and female rats while the gonads of all animals were kept intact assuring physiological estrous cycle in females. We expected a higher variability in the female group, especially in the reinstatement of METH seeking behavior due to different hormonal stages. However, we hypothesized that this variability may be overpowered by all other significant gender differences. Furthermore, we assessed possible gender differences in acquisition and maintenance of food self-administration in order to compare the operant behavior toward natural reward (food) and the drug of abuse.

Materials and Methods

Animals

Eight-week-old male and female albino Sprague-Dawley rats weighing 175–200 g (females) and 200–225 g (males) at the beginning of the experiment were purchased from Charles River (Germany). The rats were housed individually in standard rat plastic cages, the experiments on males and females were performed separately, to assure the self-administration room is dedicated to one gender at a time only. Environmental conditions during the whole study were constant: relative humidity 50–60%, temperature 23 ± 1°C, inverted 12-h light–dark cycle (6 a.m. to 6 p.m. darkness). Food and water were available *ad libitum*. All experiments were conducted in accordance with all relevant laws and regulations of animal care and welfare. The experimental protocol was approved by the Animal Care Committee of the Masaryk University, Faculty of Medicine, Czech Republic, and carried out under the European Community guidelines for the use of experimental animals.

Drugs and Treatments

Methamphetamine from Sigma Chemical, Co., St Louis, MO, USA available in the operant cage for IV self-administration was 0.08 mg/kg per infusion with the maximum number of infusions obtainable in one session set to 50. The solutions were prepared for specific animals depending on their body weights rounded to the closest category of 250, 300, 350 g, etc. This paradigm is adapted from Emmett-Oglesby MW (Fort Worth, TX, USA) (30) and routinely used in our laboratory (17, 31–33).

Locomotor Activity Test

After adaptation period at the beginning of the study basal behavioral profile was assessed in both males and females. In brightly lit room, rats were individually tested for locomotor activity using the Actitrack system (Panlab, Spain) as previously described (34, 35). Each Plexiglas arena (45 cm × 45 cm × 30 cm) was equipped with 2 frames equipped with photocells located one above another 2 and 12 cm above the cage floor. Each animal was placed in the center of arena and the spontaneous behavior was tracked for 10 min. During the test, the horizontal locomotor activity (the trajectory as calculated by the system from beam interruptions that occurred in the horizontal sensors) and vertical activity (number of rearing episodes breaking the photocell beams of the upper frame) were recorded. At the end of the session, animals were returned to their home cage and arenas were wiped with 1% acetic acid to avoid olfactory cues.

Intravenous Drug Self-Administration Surgery

Animals were deeply anesthetized with i.p. injections of 50 mg/kg ketamine plus 8 mg/kg xylazine. Under aseptic conditions, a permanent intracardiac silastic catheter was implanted through the external jugular vein to the right atrium. The outer part of the catheter exited the skin in the midscapular area. After surgery, each animal was allowed for recovery, individually in its home cage with food and water freely available. Since the implantation, the catheters were flushed daily by heparinized cephazoline (Vulmizolin 1.0 g) solution followed by 0.1 ml of a heparinized (1%) sterile saline solution to prevent infection and occlusion of the catheter. During recovery, changes in general behavior and body weight were monitored. When a catheter was found to be blocked or damaged, the animal was excluded from the analysis. At the end of the study, there were $n = 6$ male and $n = 6$ female rats included to the analysis.

Intravenous Self-Administration Protocol

Methamphetamine self-administration was conducted as previously described (17, 32) in 10 standard experimental boxes (30 cm × 25 cm × 30 cm, Coulbourn Instruments, USA) using nose-poking as operandum under a FR-1 schedule of reinforcement, i.e., animal had to make 1 nose-poke on the active hole to obtain a single drug infusion. Each cage was provided with two nose-poke holes allocated on one side and programed by software Graphic State Notation 3.03 (Coulbourn Instruments, USA). Nose-pokes in the active hole led to the activation of the infusion pump and administration of a single infusion followed by a 10 s timeout, while nose-poke stimulation was recorded but not rewarded. The cage was illuminated by a house light during the session. The light was flashing when administering infusion and off during the time-out period. Self-administration sessions lasted 90 min and took place 7 days/week for 2 weeks in total between 8 a.m. and 3 p.m. during the dark period of the inverted light–dark cycle.

After 14 days of stable METH intake, the maintenance phase was terminated and rats were returned to their home cages for the 14 days of the forced abstinence period. On day 15, rats were placed into self-administration chambers for the last 90 min reinstatement session. The numbers of responses on the active drug-paired nose-poke and the inactive nose-poke were recorded but the drug was not delivered. Responses on the active nose-poke are considered to reflect the reinstatement of drug-seeking behavior, while responses on inactive nose-poke reflect non-specific locomotor and exploratory activity.

Food Self-Administration Protocol

Food self-administration was conducted in the same experimental boxes as METH study (Coulbourn Instruments, USA) in a separate batch of animals. Under the FR-1 schedule of reinforcement 1 nose-poke lead to activation of a feeder and delivery of a single palatable pellet (BioServ, sweet dustless rodent pellets, F0021-Purified Casein Based Formula – 45 mg). The cage was illuminated by a house light during the whole session. Self-administration sessions lasted 30 min during the dark period of the inverted light–dark cycle.

Statistical Data Analysis

Primary data were summarized using arithmetic mean and SE of the mean estimate. Behavioral data were analyzed by *t*-test. IV METH self-administration data during the 14 days of maintenance were analyzed at individual days by *t*-test and at 5-day intervals by mixed ANOVA model with Greenhouse–Geisser correction. Acquisition of food self-administration was evaluated by comparison of mean day of reaching 70% preference of active nose poke by Mann–Whitney *U* test. Maintenance of food self-administration was analyzed at individual days by *t*-test. Statistical analyses were computed using SPSS 19.0.1 (IBM Corporation, 2010). A p-value <0.05 was recognized as boundary of statistical significance in all applied tests.

Results

Basal Locomotor Characteristics

Before starting the IV self-administration protocol, basal locomotor and exploratory activity was assessed in both males and females to exclude the possibility that these characteristics would lead to different drug taking behavior. Horizontal and vertical locomotor activity was measured and a proportion of each in the inner zone of the arena was calculated in order to evaluate differences in the status of anxiety in male and female rats. **Figure 1** illustrates the results on total distance traveled, vertical activity (number of rearing episodes), and inner part of arena preference. There were no basal behavioral differences between the sexes, which could contribute to dissimilar behavior in the operant cage. As expected, both sexes avoided the central part of the arena, which represents normal rodent behavior and neither one shows highly anxiogenic behavior or locomotor hyper- or hypo-activity.

Acquisition and Maintenance of Methamphetamine Self-Administration in Male and Female Rats

The acquisition and maintenance of METH taking behavior were assessed, first, in terms of mean number of infusions self-administered per session and, second, by the mean METH dose per session in milligram per kilogram. **Figure 2A** shows number of infusions obtained per daily session and mean number of infusions during the entire acquisition phase in male and female

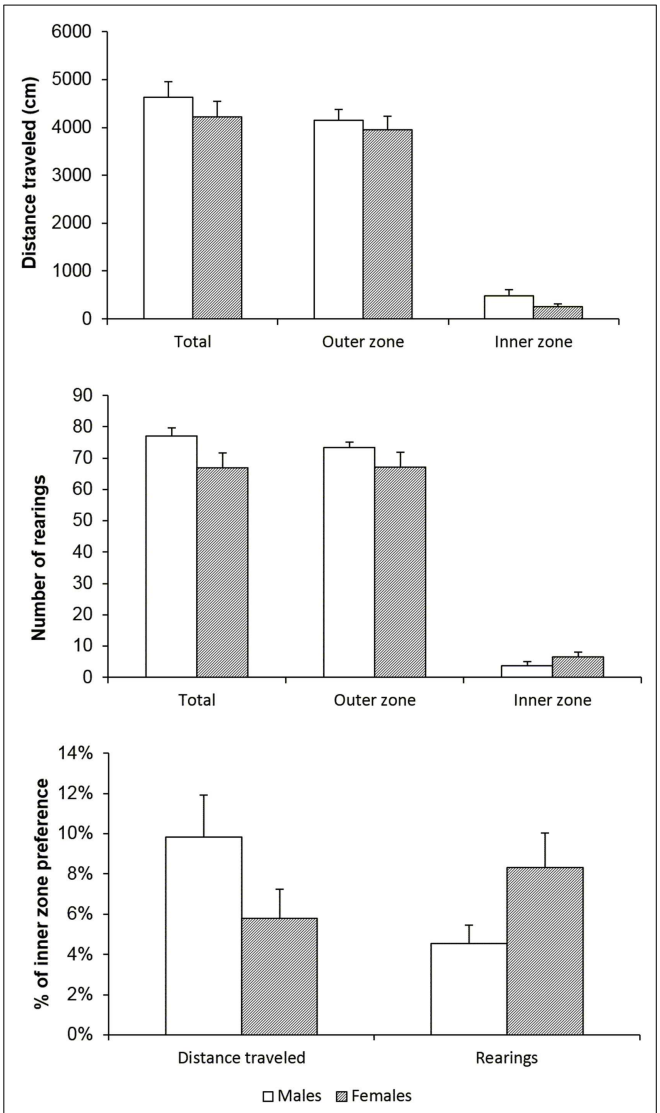

FIGURE 1 | Male and female rats have the same basal behavioral profile. Total distance traveled (in centimeters), number of rearing episodes (vertical activity), and % of preference of the central part of the arena did not reveal any gender difference. Data are shown as means (±SEM), *t*-test, n.s.

rats during the acquisition phase of METH self-administration training. ANOVA revealed no significant effects over the whole period. However, when the number of infusions was converted to a METH dose per kilogram of body weight, males were found to self-administer higher dose at the end of the acquisition phase as compared to females. More specifically, as depicted in the **Figure 2B**, mean METH intake during the last 5 days of training was significantly higher in males than in females, i.e., 2.5 and 1.5 mg/kg, respectively (mixed ANOVA model: $p = 0.038$).

Reinstatement of Methamphetamine Self-Administration in Male and Female Rats

After the 2-week-long period of forced abstinence one last reinstatement session was performed with no drug availability. The only measure of the drug-seeking behavior is the number of active operandum responses. This number was converted to a percent of mean basal nose-poking (14 days of acquisition and maintenance). There was a massive difference between the sexes recorded: male rats showed mean percent of responding 48.3% whereas females showed 295.7% (mixed ANOVA model, $p = 0.001$). Results are reported on the **Figure 3**.

Acquisition of Food Self-Administration in Male and Female Rats

The acquisition of food taking behavior (sweet pellets) was assessed in terms of day when the animals started to prefer the active nose-poke more than 70%. **Figure 4A** shows the development of active nose poke preference (%) over all sessions in male and female rats. **Figure 4B** reports the mean day for reaching 70% preference of the active operandum, which was 4.7 in males and 2.2 in females (Mann–Whitney *U* test, $p = 0.014$). The maintenance phase of the food self-administration was evaluated as a mean number of self-administered pellets during the last 5 days when the intake was stable. **Figure 5** depicts the significantly higher pellet intake in female rats as compared to males (138–175 and 51–73, respectively, $p \leq 0.05$).

Discussion

Findings of the present study demonstrated that male and female rats had equal basal locomotor and exploratory activity. Thus, differences in operant IV self-administration cannot be accounted for differences in locomotor activity. Furthermore, the food self-administration has shown a very different dynamics than the METH study, suggesting higher motivation to obtain natural reward (sweet pellet) in females, which learned the operant procedure faster (acquisition) and self-administered approximately three times more pellets than males. This behavior toward natural reward is very different from METH-related operant behavior, which rules out the possibility of general gender specific difference in the reward processes.

During the maintenance phase of the METH self-administration, female rats were found to self-administer the same number of infusion, but their METH intake in terms of dose per kilogram of body weight was found lower. This measure is not widely used among the self-administration studies, usually only the numbers of nose pokes (or lever presses) and infusions are reported. However, we propose this measure to be considered as highly valid for several reasons. Despite the solution of the drug being available in the operant box matches the body weight of the particular animal, the solutions are prepared for certain body weight category, e.g., solution for animal weighting 300 g can be used for rats reaching approximately 280–320 g (this fact is usually not described exactly in the Section "Materials and Methods" of the papers). This discrepancy, aggravated by the fact that the body weight of the animal changes over the course of the experiment, could be a source of significant differences in the dose taken even at conditions of the same number of infusions. This is a confounding factor, which complicates the comparison of findings from different laboratories. Furthermore, this approach should be used when the number of behavioral

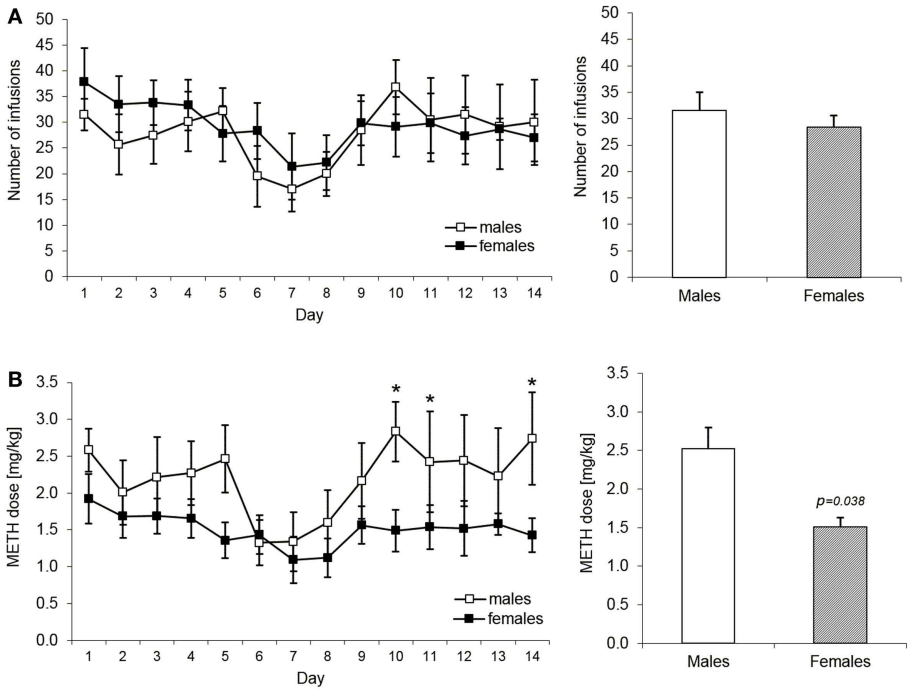

FIGURE 2 | Acquisition and maintenance of methamphetamine intake in male and female rats. The **(A)** part shows number of infusions expressed as daily means over the 14 days of acquisition and maintenance of the METH IV self-administration. The bar graph depicts the mean number of infusions over the whole 14 days period. There were no statistically significant differences in this measure (mixed ANOVA model). The **(B)** part shows in an analogical way the mean dose in milligram per kilogram of METH self-administered by male ($n = 6$) and female ($n = 6$) rats. The groups start to differ significantly from the day 10 with *t*-test results: day 10 ($p = 0.021$), day 11 ($p = 0.049$), and day 14 ($p = 0.048$). The bar graph shows the mean number of infusions over the last 5 days of the maintenance period (day 10–14) when the drug intake started to be significantly higher in male rats ($p = 0.038$, mixed ANOVA model).

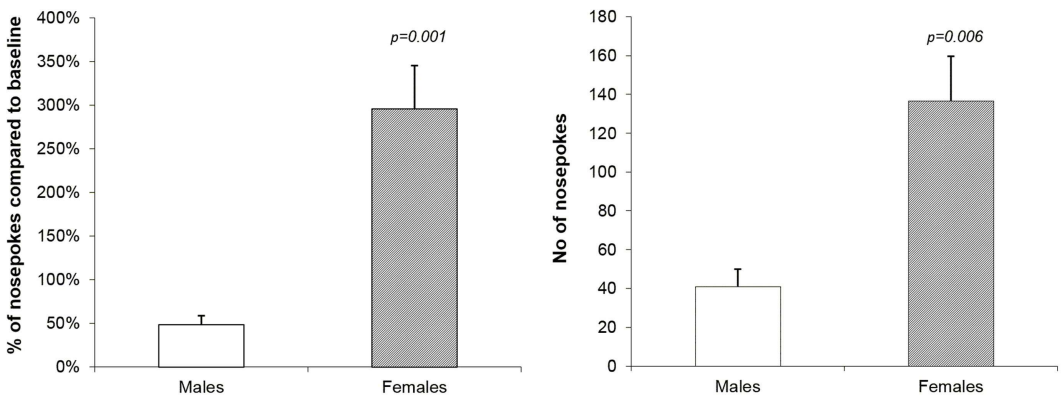

FIGURE 3 | Reinstatement of methamphetamine seeking behavior in male and female rats. The graphs show a percent of mean basal nose-poking (14 days of acquisition and maintenance) and number of nose-pokes in the reinstatement session in male and female rats. There was a statistically significant difference between the sexes in both measures: male rats showed mean % of responding 48.3% and females 295.7% (mixed ANOVA model, $p = 0.001$). The apparent difference between the sexes is further confirmed by behavioral activity reflected in a mean number of nose-pokes: 41.0 in males and 136.5 in females (mixed ANOVA model, $p = 0.006$).

responses (nose pokes or lever presses) does not match the number of infusions delivered. This is always the case when the system uses nose poke operandi (and in some cases levers which do not retract after infusion delivery).

Previous studies have shown that female rats to be more vulnerable to behavioral effects of psychomotor stimulants including cocaine (36–38) and, in particular, amphetamines (including METH), which elicited a higher increase of locomotion in females than males or reach the same behavior profile at lower dose (25, 28, 39, 40). Other studies have repeatedly shown that females with intact gonads tend to develop readily behavioral sensitization to psychostimulant drugs after repeated treatment (41–43).

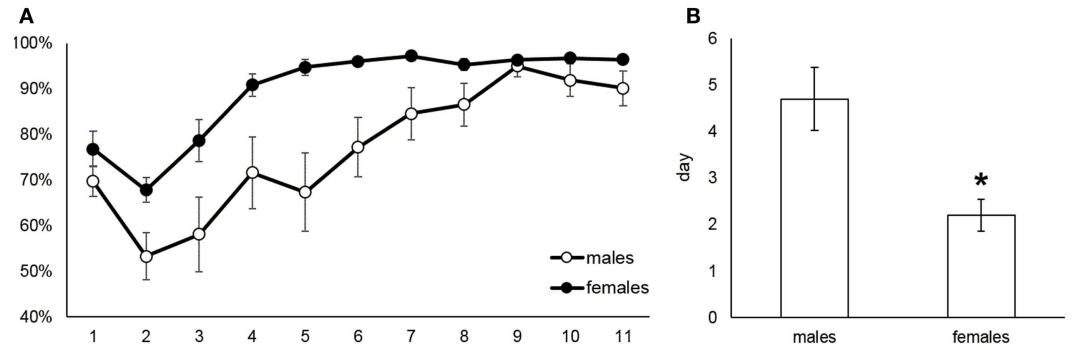

FIGURE 4 | Acquisition of food self-administration behavior in male and female rats. The **(A)** part shows the course of the active nose poke preference development during acquisition and maintenance of the food self-administration. The bar graph **(B)** depicts the mean day the animals reached and kept 70% preference of the active operandum: 4.7 in males and 2.2 in females (Mann–Whitney *U* test, $p = 0.014$).

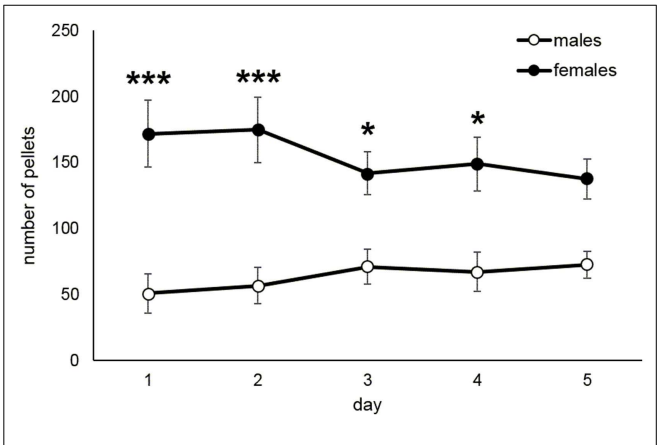

FIGURE 5 | Maintenance of food self-administration in male and female rats. The graph shows pellet intake in female rats as compared to males (*t*-test, $*p \leq 0.05$, $***p \leq 0.001$).

Furthermore, there is new evidence of specific pharmacokinetic differences in METH self-administration studies, where males were shown to have lower area under curve (AUC) of METH probably due to rapid drug elimination (29). The apparent higher efficacy of the amphetamines found in this and previously mentioned studies in female rats could be explained by the pharmacokinetic differences.

Similarly, in clinical studies, there has been shown that men are more sensitive to the reinforcing effects of a high dose of D-amphetamine than women, who respond rather to low doses at a random phase of the menstrual cycle (44). This is consistent with our data, which showed that males developed higher stable intake of METH than females (2.5 and 1.5 mg/kg daily, respectively). Furthermore, women were shown to experience greater increases in diastolic pressure and nausea than men at the same doses while the ability to discriminate D-amphetamine was equal in both sexes (45). These lines of evidence further support translational validity of our finding of lower METH intake in female rats.

However, in fixed ratio self-administration paradigms, the reports on gender differences in the maintenance phase are numerous and quite contradictory in both clinical (45, 46) and preclinical studies, showing both higher and lower drug intake in female subjects (21, 47).

Progressive ratio IV self-administration paradigm or prolonged access to the drug might be better tools to unravel gender differences as these may be linked to appetitive behavior (21). Female rats have been repeatedly shown to achieve higher breaking points in METH self-administration study suggesting higher motivation to obtain the drug (10, 48). This is consistent with the robust gender difference in the reinstatement found in this study, where the motivation of animals for the drug-seeking was not abolished by extinction training. At this point, active responses to the operandum are the only measure to report because the session is performed without delivering the drug. We found a highly significant difference in the percent of mean basal nose-poking, as well as in the absolute number of active operant responses. The enhancing effect of estradiol and attenuating effects of progesterone on psychostimulant (D-amphetamine, METH, cocaine) intake in female gender is repeatedly and consistently reported in both clinical (49–52) and preclinical studies (17, 20–22). Therefore, the higher variability in the reinstatement operant responding in the female group detected in this study probably originated from different hormonal stage. This conclusion can be supported by an earlier study, which employed the extinction and both drug- and cue-primed reinstatement, where females were found more vulnerable in both reinstatement procedures and also exhibited higher variability than males. Interestingly, the numbers of lever presses in the conditioned cue-primed reinstatement session were approximately 40 in males and 120 in females (10). These absolute numbers are similar to those reported in the present study: 41 and 136, respectively. Therefore, this effect seems to be well reproducible and strain independent (Long-Evans vs. Sprague-Dawley rats).

The forced abstinence model was proposed as a potentially better tool to model a spontaneous relapse in rodents (15, 53). To our knowledge, this is the first report of gender differences in the paradigm of reinstatement after forced abstinence. Extinction-based approach to study relapse-like behavior phase in the preclinical setting show contradictory results – females appear to meet the extinction criteria later than males (11), but negative results have been reported as well (54). Both studies were conducted with cocaine.

Taken together, this study reports lower consummatory METH intake during maintenance phase of the self-administration together with higher vulnerability to the reinstatement of METH seeking behavior in female rats after forced abstinence. These effects seem to be robust enough, thus relatively independent on the current hormonal level. Therefore, we propose this paradigm for preclinical screening for potential new medications specific for women. However, the main limitation for the translation of these results to human medicine is the absence of psychosocial aspects, which are impossible to reflect in animal studies.

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frontiers in PSYCHIATRY

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Sex differences in psychiatric comorbidity and plasma biomarkers for cocaine addiction in abstinent cocaine-addicted subjects in outpatient settings

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There are sex differences in the progression of drug addiction, relapse, and response to therapies. Because biological factors participate in these differences, they should be considered when using biomarkers for addiction. In the current study, we evaluated the sex differences in psychiatric comorbidity and the concentrations of plasma mediators that have been reported to be affected by cocaine. Fifty-five abstinent cocaine-addicted subjects diagnosed with lifetime cocaine use disorders (40 men and 15 women) and 73 healthy controls (48 men and 25 women) were clinically assessed with the diagnostic interview "Psychiatric Research Interview for Substance and Mental Disorders." Plasma concentrations of chemokines, cytokines, *N*-acyl-ethanolamines, and 2-acyl-glycerols were analyzed according to history of cocaine addiction and sex, controlling for covariates age and body mass index (BMI). Relationships between these concentrations and variables related to cocaine addiction were also analyzed in addicted subjects. The results showed that the concentrations of chemokine (C-C motif) ligand 2/monocyte chemotactic protein-1 (CCL2/MCP-1) and chemokine (C-X-C motif) ligand 12/stromal cell-derived factor-1 (CXCL12/SDF-1) were only affected by history of cocaine addiction. The plasma concentrations of interleukin 1-beta (IL-1β), IL-6, IL-10, and tumor necrosis factor-alpha (TNFα) were affected by history of cocaine addiction and sex. In fact, whereas cytokine concentrations were higher in control women relative to men, these concentrations were reduced in cocaine-addicted women without changes in addicted men. Regarding fatty acid derivatives, history of cocaine addiction had a main effect on the concentration of each acyl derivative, whereas *N*-acyl-ethanolamines were increased overall in the cocaine group, 2-acyl-glycerols were decreased. Interestingly, *N*-palmitoleoyl-ethanolamine (POEA) was only increased in cocaine-addicted women. The covariate BMI had a significant effect on POEA and *N*-arachidonoyl-ethanolamine concentrations. Regarding psychiatric comorbidity in the cocaine group, women had lower incidence rates of comorbid substance use disorders than did men. For example, alcohol use disorders were found in 80% of men and 40% of women. In contrast, the addicted women had increased prevalences of comorbid psychiatric disorders (i.e., mood, anxiety, and psychosis disorders). Additionally, cocaine-addicted subjects showed a relationship between the concentrations of *N*-stearoyl-ethanolamine and 2-linoleoyl-glycerol and diagnosis of psychiatric comorbidity. These results demonstrate the existence of a sex influence on plasma biomarkers for cocaine addiction and on the presence of comorbid psychopathologies for clinical purposes.

Keywords: cocaine use disorders, psychiatric comorbidity, cytokine, endocannabinoid, sex, outpatient, biomarker, abstinence

INTRODUCTION

Over the last 10 years, cocaine has established itself as the most commonly used illicit stimulant drug in Europe, although most users are found in a small number of high-prevalence countries. Cocaine use is particularly high in Spain, with a lifetime prevalence of 10.2% in the general population, and it represents a significant public health concern (1).

There are several factors that influence the acquisition, maintenance, and progression to addiction, such as social context, age, genetic characteristics, and sex (2). In this respect, sex differences have been found in cocaine use and addiction, including cocaine use initiation, progression to abuse and dependence, relapse following abstinence, and responsiveness to treatment (3–5).

Epidemiological data suggest that women have a rapid escalation in drug use and progress more quickly to cocaine addiction compared with men (6). Women are more sensitive to social stressors, and abstinent cocaine-addicted women report higher levels of craving in response to cocaine-related cues (7, 8). Sex also influences treatments and relapses because women report shorter abstinence periods and higher relapse rates after stressful or depressive events (9). All of these observations parallel preclinical animal models using rodents showing that females are more vulnerable to the abuse-related effects of cocaine than males (10).

Despite evidence that women are more vulnerable than men to cocaine addiction, the rates of cocaine use are currently higher in men than in women, and the proportion of cocaine users seeking treatment in outpatient cocaine programs is approximately five men to every woman in Europe (1). Considering that cocaine addiction is commonly associated with altered executive functions, impaired emotional processing capacity, and elevated incidence of comorbid mental disorders (11, 12), sex is a primary factor underlying these behavioral complications. In fact, sex differences in psychopathologies and substance use disorders have been linked to the activity of hormones (i.e., gonadal steroid hormones), menstrual cycle, HPA axis reactivity, and neurobiological factors (13–15).

Recently, the search for biomarkers for psychiatric disorders and addiction has generated a number of putative biomarkers that includes circulating mediators with neuromodulatory functions (16–18). Among these molecules, inflammatory proteins and fatty acid derivatives have been reported to be altered in abstinent cocaine-addicted subjects (19, 20). Moreover, changes in plasma cytokine and chemokine concentrations have been shown to be related to the pathological cocaine use and cocaine symptom severity (20), whereas changes in endocannabinoids and congeners are related to cocaine use disorders and psychiatric comorbidity (19). However, the influence of sex was not directly studied in these reports.

Abbreviations: 2-AG, 2-arachidonoyl-glycerol; 2-LG, 2-linoleoyl-glycerol; AEA, *N*-arachidonoyl-ethanolamine; CCL2/MCP-1, chemokine (C-C motif) ligand 2/monocyte chemotactic protein-1; CXCL12/SDF-1, chemokine (C-X-C motif) ligand 12/stromal cell-derived factor-1; CX3CL1/fractalkine, chemokine (C-X_3-C motif) ligand 1/fractalkine; IL-1β, interleukin-1 beta; IL-6, interleukin-6; IL-10, interleukin-10; LEA, *N*-linoleoyl-ethanolamine; OEA, *N*-oleoyl-ethanolamine; PEA, *N*-palmitoyl-ethanolamine; POEA, *N*-palmitoleoyl-ethanolamine; SEA, *N*-stearoyl-ethanolamine; TNFα, tumor necrosis factor-alpha.

Because previous studies have reported sex differences in all phases related to the progression to cocaine addiction and because gonadal hormones can affect other signaling systems sensitive to cocaine addiction, those molecules identified as putative biomarkers for cocaine addiction and common psychiatric comorbidity may be influenced by sex.

The primary purpose of the present observational study was to examine the plasma concentrations of chemokines, cytokines, and fatty acid derivatives in a cohort of abstinent cocaine-addicted subjects on an outpatient basis according to their sex. Additionally, the prevalences of comorbidity of other substance and mental disorders were evaluated.

MATERIALS AND METHODS

SUBJECTS AND RECRUITMENT

All participants were white Caucasians grouped into abstinent cocaine users and healthy controls. Fifty-nine cocaine users (17 women and 42 men) were initially enrolled from outpatient treatment programs for cocaine addiction in the province of Málaga (Spain) for a 24-month period (2011–2013). Seventy-six healthy individuals (25 women and 51 men) were recruited from a multidisciplinary staff working at the Hospital Regional Universitario de Málaga.

Cocaine users had to meet eligibility criteria based on inclusion and exclusion criteria. Inclusion criteria were as follows: ≥18–65 years of age, intranasal cocaine use, diagnosis of lifetime cocaine use disorders, and abstinence from cocaine for at least 2 weeks before testing (urine and plasma analyses). Exclusion criteria were as follows: personal history of chronic diseases (e.g., cardiovascular, respiratory, renal, hepatic, neurological, or endocrine diseases), personal history of cancer, infectious diseases, incapacitating cognitive alterations, and pregnancy.

Controls were matched with the cocaine group for sex ratio, age, and body mass index (BMI). In addition to the mentioned exclusion criteria for abstinent cocaine users, controls were excluded if they had a personal history of drug abuse or lifetime psychiatric disorders. All women were recruited without considering their menstrual cycle.

Finally, 55 abstinent cocaine-addicted subjects (15 women and 40 men) and 63 controls (25 women and 48 men) met the eligibility criteria and completed the study.

All cocaine-addicted subjects were under current treatment interventions, including pharmacological and behavioral approaches. Regarding the pharmacological interventions, 20 participants (12 men and 8 women) were treated with anxiolytics ($n = 9$), antipsychotics ($n = 2$), antidepressants ($n = 8$), and disulfiram ($n = 1$).

CLINICAL ASSESSMENTS

Cocaine users were evaluated according to "Diagnostic and Statistical Manual of Mental Disorders-4th Edition-Text Revision" (DSM-IV-TR) criteria, using the Spanish version of the "Psychiatric Research Interview for Substance and Mental Disorders" (PRISM) (21, 22). Controls were evaluated by PRISM (for substance screening and abuse and dependence) and the Spanish version of the "Composite International Diagnostic Interview" (CIDI) to detect psychiatric disorders (23). All interviews were

performed by experienced psychologists who had received both PRISM and CIDI training. Two cocaine users did not meet the criteria for cocaine use disorders and three controls were diagnosed with lifetime mental disorders (major depression and anxiety). They were consequently excluded from the study.

Psychiatric research interview for substance and mental disorders (PRISM)

The PRISM is a semistructured interview to diagnose psychiatric disorders among substance users (22, 24, 25). Diagnoses were made using two time-frames: "current" (criteria were met within the past year) and "past" (criteria were met before the previous 12 months). Lifetime prevalence was used to present the frequency of substance use disorders, non-substance use disorders, and psychiatric comorbidity. The cocaine symptom severity was assessed combining the DSM-IV-TR criteria for cocaine use disorders: 7 dependence criteria (for a diagnosis of dependence, 3 or more co-occurring symptoms in a 12-month period are required) and 4 abuse criteria (1 symptom is necessary for a diagnosis of abuse) (19, 20).

LABORATORY METHODS FOR HUMAN SAMPLES

Collection and analysis of plasma samples

Blood samples were obtained in the morning (09:00–11:00 a.m.) after fasting for 8–12 h (previous to the psychiatric interviews). Venous blood was collected into 10 mL K_2-EDTA tubes (BD, Franklin Lakes, NJ, USA) and processed to obtain plasma. Blood samples were centrifuged at $2{,}200 \times g$ for 15 min (4°C), and plasma was analyzed for HIV and hepatitis types B and C.

Analysis for HIV and hepatitis types B and C. Plasmas samples were individually assayed by three rapid tests for detecting HIV (Retroscreen HIV, QualPro Diagnostics-Tulip Group Ltd., Goa, India), hepatitis B (HBsAg Test, Toyo Diagnostics-Turklab Inc., Izmir, Turkey), and hepatitis C (Flaviscreen HCV, QualPro Diagnostics-Tulip Group Ltd., Goa, India). No samples that tested positive were detected. Plasma samples were stored at −80°C until further analyses.

Analysis for the cocaine metabolite benzoylecgonine. Plasma analyses for cocaine metabolites (Benzoylecgonine Specific Direct ELISA Kit Immunalysis, Pomona, CA, USA) were performed to confirm cocaine abstinence. Two cocaine users who tested negative for drugs of abuse in urine analyses at the outpatient treatment centers for cocaine addiction were positive for benzoylecgonine in plasma, and they were excluded from this study.

Multiplex immunoassay analysis

A Bio-Plex Suspension Array System 200 (Bio-Rad Laboratories, Hercules, CA, USA) was used to quantify the plasma concentrations of inflammatory cytokines and chemokines following the manufacturer's instructions as previously reported (20). Human protein panels were used to simultaneously detect the following analytes: tumor necrosis factor-alpha (TNFα); interleukin-1 beta (IL-1β); interleukin-6 (IL-6); interleukin-10 (IL-10); chemokine (C-X_3-C motif) ligand 1 [CX3CL1], commonly referred to as fractalkine; chemokine (C-C motif) ligand 2 [CCL2], also referred to as monocyte chemotactic protein-1 (MCP-1); and chemokine (C-X-C motif) ligand 12 [CXCL12], also referred to stromal cell-derived factor-1 (SDF-1). Raw data (mean fluorescence intensity) were analyzed using the Bio-Plex Manager Software 4.1 (Bio-Rad Laboratories, Hercules, CA, USA). Data of plasma concentrations were in pg of protein per mL of plasma.

Quantification of fatty acid derivatives

The following fatty acid derivatives and their respective deuterated forms were used for quantification: *N*-stearoyl-ethanolamine (SEA), *N*-palmitoyl-ethanolamine (PEA) and PEA-d_4, *N*-oleoyl-ethanolamine (OEA) and OEA-d_4, *N*-palmitoleoyl-ethanolamine (POEA), *N*-arachidonoyl-ethanolamine (AEA) and AEA-d_4, *N*-linoleoyl-ethanolamine (LEA) and LEA-d_4, 2-arachidonoyl-glycerol (2-AG) and 2-AG-d_5, and 2-linoleoyl-glycerol (2-LG). PEA-d_4 and OEA-d_4 were used for the quantification of POEA and SEA, respectively, because their deuterated forms were not commercially available. All reagents were obtained from Cayman Chemical (Ann Arbor, MI, USA).

Sample extraction and chromatographic separation were performed in a liquid chromatography-tandem mass spectrometry system (Agilent Technologies, Wilmington, DE, USA) as previously reported (19, 26). Data of plasma concentrations were in ng of acyl derivative per mL of plasma.

ETHICS STATEMENT

Written informed consent was obtained from each subject after they had received a complete description of the present study and had been given the chance to discuss any questions or issues. The study and protocols for recruitment were approved by the Ethics Committee of the Hospital Regional Universitario de Málaga (07/19/2009 PND049/2009 and PI0228-2013; CEI Provincial de Málaga) and were therefore conducted in accordance with the Declaration of Helsinki (seventh revision in 2013, Fortaleza, Brazil).

STATISTICAL ANALYSES

All data for graphs and tables are expressed as number and percentage of subjects [*n* (%)] or the mean and standard deviation [mean (SD)]. Samples were grouped by sex and the significance of differences was assessed by Fisher's exact test or Student's *t*-test. The statistical analyses of plasma concentrations were performed using two-way analysis of covariance (ANCOVA) [factors: history of cocaine addiction (cocaine/control) and sex (men/women); covariates: age and BMI]. Multiple comparisons were performed with unadjusted (observed) or adjusted (estimated marginal) according to the effects of covariates. Plasma concentrations in subjects with a history of cocaine addiction were analyzed by univariate general linear models to evaluate relationships with sex, age, BMI, and group-specific variables (cocaine symptom severity, diagnosis of comorbid psychiatric disorders, and length of cocaine abstinence). A *p*-value less than 0.05 was considered statistically significant. Statistical analyses were performed using the GraphPad Prism version 5.04 software (GraphPad Software, San Diego, CA, USA) and IBM SPSS Statistical version 22 software (IBM, Armonk, NY, USA).

RESULTS

SOCIAL AND DEMOGRAPHIC CHARACTERISTICS

A total of 128 subjects met the eligibility criteria for this study and were grouped into the cocaine ($n = 55$) and control ($n = 73$) groups. Both groups were divided into men and women. A description of the sample is presented in **Table 1**.

Men seeking treatment for cocaine addiction were more common than women, at a ratio of one woman to eight men in the centers for cocaine addiction where the recruitment was conducted (data not shown). During a 24-month period (January 2011–December 2012), 20 women were contacted to participate in this study; 17 accepted and were diagnosed with lifetime cocaine use disorders. Finally, 15 cocaine-addicted women completed the study. Whereas the abstinent cocaine-addicted men had a mean age of 37 years, the cocaine-addicted women were older (mean: 43 years; $p < 0.01$). We observed no differences between the sexes in other socio-demographic variables in the cocaine group. Considering both sexes, the addicted subjects were married/cohabiting (47%), lived in couple (49%), had a low educational level (42% with secondary level or more), and were unemployed (58%). In contrast, the control subjects had a higher educational level (96% with secondary level or more) and employment rate (89%).

Interestingly, the cocaine-addicted subjects displayed a higher incidence in the use of psychological counseling, excluding treatments of severe/serious mental disorders, with 30% in men and 60% in women. These percentages were reduced in the control group to 8% in men and 48% in women.

COMORBID MENTAL AND SUBSTANCE USE DISORDERS IN ABSTINENT COCAINE-ADDICTED SUBJECTS GROUPED BY SEX

Comorbid substance use disorders and cocaine use-related variables

As shown in **Table 2**, the cocaine group had an elevated prevalence of comorbid substance use disorders in addition to cocaine use disorders, primarily alcohol (69%) and cannabis (20%) use disorders. We observed sex differences in the prevalences of these other substance use disorders because they were more common in men than in women: alcohol use disorders were diagnosed in 80% of men and 40% of women ($p < 0.01$), and cannabis use disorders were diagnosed in 25% of men and 7% of women.

Focusing on the variables related to cocaine use, we did not observe sex differences in the prevalences of abuse and dependence, length of cocaine abstinence, duration of cocaine use, or cocaine symptom severity. Therefore, the average cocaine-addicted subject, including men and women, displayed cocaine abstinence for 178.6 (281.7) days [mode: 120 days (range: 730)], a cumulative cocaine use of 8.2 (6.6) years [mode: 4 years (range: 31)] and 8.1 (2.5) DSM-IV criteria for cocaine use disorders.

Comorbid mental disorders

Regarding the common psychiatric disorders assessed with the PRISM, we found high prevalences of comorbid psychopathologies (60%): mood (38%), anxiety (22%), psychosis (20%), and personality (35%) disorders.

Table 1 | Baseline socio-demographic variables in abstinent cocaine-addicted and control subjects grouped by sex.

Variable		Cocaine group		Control group	
		Men	Women	Men	Women
Sex [*n* (%)]		40 (72.7)	15 (27.3)	48 (65.8)	25 (34.2)
Age (≥18) [Mean (SD)]		37.1 (6.7)	42.8 (6.2)*	38.6 (9.8)	42.6 (8.4)
Body mass [Mean (SD)]	Body mass index	26.2 (4.3)	25.4 (5.9)	25.4 (5.9)	23.9 (4.7)
Current marital status [*n* (%)]	Never married	12 (30.0)	4 (26.7)	23 (47.9)	10 (40.0)
	Married/cohabiting	19 (47.5)	7 (46.7)	22 (45.8)	10 (40.0)
	Divorced/separated	9 (22.5)	3 (20.0.)	3 (6.3)	4 (16.0)
	Widowed	0 (0.0)	1 (6.7)	0 (0.0)	1 (4.0)
Living together last year [*n* (%)]	Friends, squatters	1 (2.5)	1 (6.7)	3 (6.3)	0 (0.0)
	Parents	14 (35.0)	5 (33.3)	9 (18.8)	7 (28.0)
	Couple	20 (50.0)	7 (46.7)	25 (52.1)	12 (48.0)
	Alone	4 (10.0)	1 (6.7)	10 (20.8)	6 (24.0)
	Others	1 (2.5)	1 (6.7)	1 (2.1)	0 (0.0)
Educational level [*n* (%)]	≤ Primary level	24 (60.0)	8 (53.3)	3 (6.3)	0 (0.0)
	≥ Secondary level	16 (40.0)	7 (46.7)	45 (93.8)	25 (100.0)
Work status [*n* (%)]	Employed	16 (40.0)	4 (26.7)	42 (87.5)	23 (92.0)
	Unemployed	22 (55.0)	10 (66)	5 (10.4)	2 (8.0)
	Retired/disabled	2 (5.0)	1 (6.7)	0 (0.0)	0 (0.0)
	Student	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)
Use of psychological resources [*n* (%)]	No	28 (70.0)	6 (40.0)	44 (91.7)	13 (52.0)
	Yes	12 (30.0)	9 (60.0)	4 (8.3)	12 (48.0)

$p < 0.05$ denotes significant differences between cocaine-addicted men and women.

Table 2 | Cocaine use-related variables in abstinent cocaine-addicted subjects grouped by sex.

Variable		Cocaine group		*p*-Value
		Men ($n=40$)	Women ($n=15$)	
Lifetime substance use disorders [*n* (%)]	Cocaine use disorders	40 (100.0)	15 (100.0)	ns
	Alcohol use disorders	32 (80.0)	6 (40.0)	**0.008**
	Cannabis use disorders	10 (25.0)	1 (6.7)	ns
	Other substance use disorders	9 (22.5)	2 (13.3)	ns
Lifetime cocaine use disorders [*n* (%)]	Cocaine abuse	35 (87.5)	14 (93.3)	ns
	Cocaine dependence	36 (90.0)	13 (86.7)	ns
	Cocaine abuse and dependence	31 (77.5)	12 (80.0)	ns
Cocaine abstinence [Mean (SD)]	Days	184.2 (323.2)	163.7 (145.2)	ns
Cocaine use [Mean (SD)]	Years	8.0 (6.8)	9.6 (6.5)	ns
DSM-IV criteria for cocaine use disorders [Mean (SD)]	Counts	8.1 (2.5)	7.9 (1.9)	ns

ns, non-significant.

Bold indicates statistically significant p-values.

Table 3 | Psychiatric comorbidity in abstinent cocaine-addicted subjects grouped by sex.

Variable		Cocaine group		*p*-value
		Men ($n=40$)	Women ($n=15$)	
Lifetime psychiatric disorders[a] [*n* (%)]	No	18 (45.0)	4 (26.7)	ns
	Mood disorders	13 (32.5)	8 (53.3)	ns
	Anxiety disorders	5 (12.5)	7 (46.7)	**0.011**
	Psychosis disorders	6 (15.0)	5 (33.3)	ns
	Eating disorders	0 (0.0)	0 (0.0)	–
	Personality disorders	14 (35.0)	5 (33.3)	ns
Mood disorders [*n* (%)]	Primary	6 (15.0)	2 (13.3)	ns
	Cocaine-induced	7 (17.5)	5 (33.3)	
	Primary and cocaine-induced	0 (0.0)	1 (6.7)	
Anxiety disorders [*n* (%)]	Primary	2 (5.0)	3 (20.0)	ns
	Cocaine-induced	3 (7.5)	2 (13.3)	
	Primary and cocaine-induced	0 (0.0)	2 (6.7)	
Psychosis disorders [*n* (%)]	Primary	0 (0.0)	0 (0.0)	ns
	Cocaine-induced	6 (15.0)	5 (33.3)	
	Primary and cocaine-induced	0 (0.0)	0 (0.0)	
Personality disorders [*n* (%)]	Borderline	6 (15.0)	3 (20.0)	ns
	Antisocial	6 (15.0)	1 (6.7)	
	Borderline and antisocial	2 (5.0)	1 (6.7)	

[a] *Psychiatric disorders diagnosed with PRISM.*

ns, non-significant.

Bold indicates statistically significant p-values.

According to sex, cocaine-addicted women showed higher prevalences of mood, anxiety ($p < 0.05$), and psychosis disorders compared with cocaine-addicted men (**Table 3**). Though some women were diagnosed with both primary and cocaine-induced disorders for mood and anxiety disorders, no men were diagnosed with primary and cocaine-induced disorders (the two together). However, these psychiatric prevalences were not significantly different between men and women, although there was a limitation in the sample size considered.

Regarding personality disorders, we observed no differences between the sexes.

PLASMA CONCENTRATIONS OF CHEMOKINES ACCORDING TO HISTORY OF COCAINE ADDICTION AND SEX

The mean plasma concentrations of CX3CL1/fractalkine, CCL2/MCP-1, and CXCL12/SDF-1 in the cocaine and control groups are shown in **Figure 1**. Two-way ANCOVAs were performed to analyze the chemokine concentrations. Covariates age and BMI were

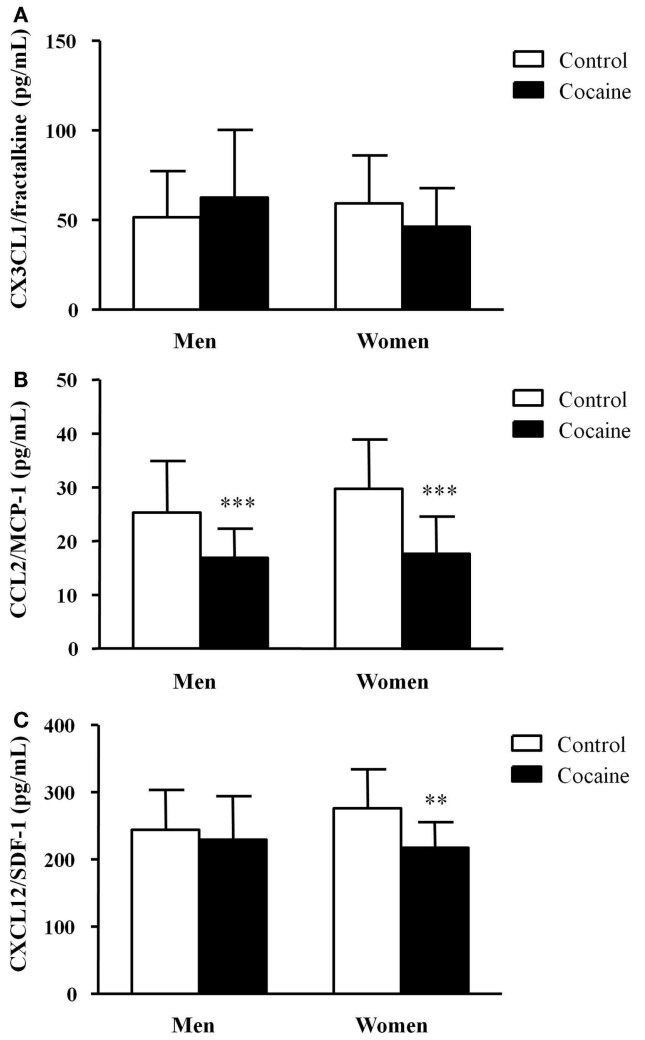

FIGURE 1 | Plasma concentrations of chemokines in abstinent cocaine-addicted and control subjects grouped by sex. **(A)** CX3CL1/fractalkine (pg/mL); **(B)** CCL2/MCP-1 (pg/mL); and **(C)** CXCL12/SDF-1 (pg/mL). The bars represent means ± SD. The data were analyzed by two-way ANCOVA and multiple comparison tests. (**) $p < 0.01$ and (***) $p < 0.001$ denote significant differences compared with the respective control men or control women.

included in the analyses but there was not a significant effect of the covariates on either chemokine concentrations.

We did not observe main effects of history of cocaine addiction and sex on plasma CX3CL1 concentrations, but there was a significant interaction effect ($F_{1,122} = 4.60$, $p = 0.034$) (**Figure 1A**). However, the plasma concentrations of CCL2 were significantly affected by history of cocaine addiction ($F_{1,122} = 42.03$, $p < 0.001$) (**Figure 1B**). The multiple comparisons showed that cocaine-addicted men and women had significantly decreased CCL2 concentrations ($^{***}p < 0.001$) compared with their respective controls. Similarly, history of cocaine addiction ($F_{1,122} = 7.72$, $p = 0.006$) had a significant main effect on CXCL12 concentrations (**Figure 1C**). In this case, we detected a significant decrease in cocaine-addicted women ($^{**}p < 0.01$) compared with control women, but this difference was not found in men.

Therefore, sex had no significant primary effect on chemokine concentrations.

PLASMA CONCENTRATIONS OF CYTOKINES ACCORDING TO HISTORY OF COCAINE ADDICTION AND SEX

The plasma concentrations of IL-1β, IL-6, IL-10, and TNFα in the cocaine and control groups are illustrated in **Figure 2**. Again, there was not a significant relationship between the covariates and cytokine concentrations.

As shown in **Figure 2A**, the IL-1β concentrations were significantly affected by history of cocaine addiction ($F_{1,122} = 5.73$, $p = 0.018$) and by sex ($F_{1,122} = 20.41$, $p < 0.001$). An interaction between history of cocaine addiction and sex was also detected ($F_{1,122} = 8.36$, $p = 0.005$). The paired comparisons revealed that control women had significantly increased IL-1β concentrations ($+ + + p < 0.001$) compared with control men (3.81 ± 2.06 and 1.40 ± 1.55 pg/mL, respectively). However, cocaine-addicted women had a significant decrease in the IL-1β concentrations ($^{**}p < 0.01$) relative to control women but exhibited no differences compared with cocaine-addicted men.

The IL-6 concentrations (**Figure 2B**) were also significantly affected by history of cocaine addiction ($F_{1,122} = 13.46$, $p < 0.001$) and sex ($F_{1,122} = 11.05$, $p = 0.001$). Additionally, there was a significant interaction between the factors ($F_{1,122} = 13.35$, $p < 0.001$). Thus, although control women had higher IL-6 concentrations ($+ + + p < 0.001$) than did control men (5.98 ± 2.41 and 3.37 ± 2.08 pg/mL, respectively), the IL-6 concentrations in cocaine-addicted women were significantly lower ($^{***}p < 0.001$) than in control women.

In relation to IL-10 (**Figure 2C**), history of cocaine addiction ($F_{1,122} = 8.69$, $p = 0.004$) and sex ($F_{1,122} = 11.14$, $p = 0.001$) had a significant primary effect on the IL-10 concentrations. There was an interaction between the factors ($F_{1,122} = 25.63$, $p < 0.001$). Considering the *post hoc* comparisons, control women had increased IL-10 concentrations ($+ + p < 0.01$) relative to control men (2.20 ± 1.12 and 1.32 ± 1.06 pg/mL, respectively). In addition, cocaine-addicted women exhibited a significant decrease in IL-1β concentrations ($^{*}p < 0.05$) compared with control women, but cocaine-addicted women had higher concentrations ($+ p < 0.05$) than did cocaine-addicted men.

Finally, the statistical analysis of TNFα concentrations (**Figure 2D**) revealed a significant main effect of history of cocaine addiction ($F_{1,122} = 34.98$, $p < 0.001$) and sex ($F_{1,122} = 20.90$, $p < 0.001$) after adjusting for covariates. There was an interaction between history of cocaine addiction and sex ($F_{1,122} = 22.46$, $p < 0.001$). Once again, control women had higher TNFα concentrations ($+ + + p < 0.001$) than did control men (32.55 ± 16.21 and 13.47 ± 11.28 pg/mL, respectively). Cocaine-addicted women showed a significant decrease in TNFα concentrations ($^{***}p < 0.001$) compared with control women, but no differences compared with cocaine-addicted men.

Therefore, we observed higher cytokine concentrations in women than in men. Moreover, a specific and dramatic decrease in cytokine concentrations was observed in cocaine-addicted women but not in cocaine-addicted men.

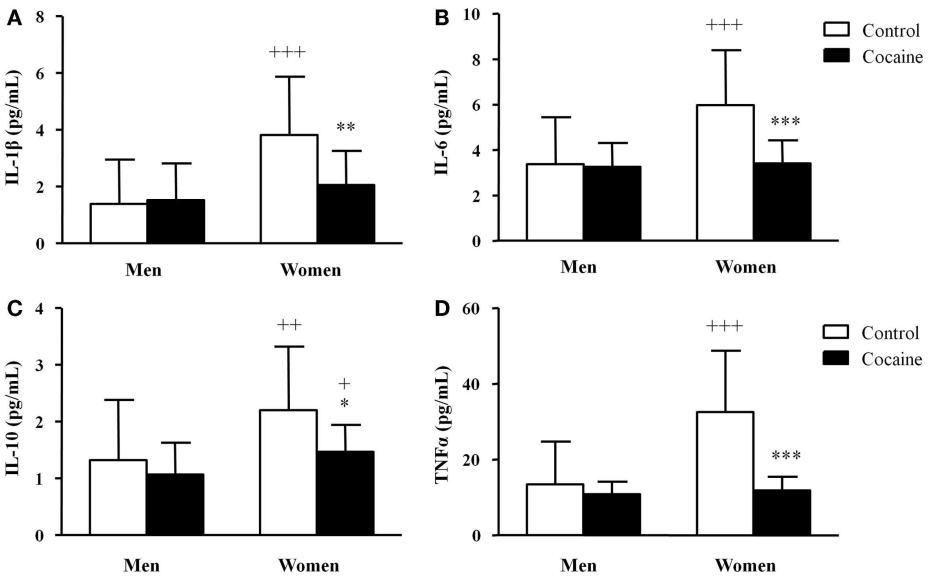

FIGURE 2 | Plasma concentrations of cytokines in abstinent cocaine-addicted and control subjects grouped by sex. **(A)** IL-1β (pg/mL); **(B)** IL-6 (pg/mL); **(C)** IL-10 (pg/mL); and **(D)** TNFα (pg/mL). The bars represent means ± SD. The data were analyzed by two-way ANCOVA and multiple comparison tests. (*) $p < 0.05$, (**) $p < 0.01$, and (***) $p < 0.001$ denote significant differences compared with control women. (+) $p < 0.05$, (++) $p < 0.01$, and (+ + +) $p < 0.001$ denote significant differences compared with the respective control men or cocaine-addicted men.

PLASMA CONCENTRATIONS OF FATTY ACID DERIVATIVES ACCORDING TO HISTORY OF COCAINE ADDICTION AND SEX

The plasma concentrations of fatty acid derivatives were grouped into the following categories: (i) saturated (SEA and PEA), monounsaturated (POEA and OEA), and polyunsaturated (AEA and LEA) *N*-acyl-ethanolamines (**Figure 3**) and (ii) 2-acyl-glycerols (2-AG and 2-LG) (**Figure 4**). Significant relationships between the covariates (age and BMI) and these fatty acid derivative concentrations were detected by the statistical analysis.

N-acyl-ethanolamines

History of cocaine addiction ($F_{1,122} = 11.09$, $p = 0.001$) had a significant main effect on plasma SEA concentrations, but sex had no effect (**Figure 3A**). There was not a significant effect of the covariates on SEA concentrations, and the *post hoc* tests using unadjusted means only indicated a significant decrease in the cocaine-addicted men ($^{***}p < 0.001$) compared with the control men. Regarding the other saturated lipid derivative (**Figure 3B**), plasma PEA concentrations were also significantly affected by history of cocaine addiction ($F_{1,122} = 11.04$, $p = 0.001$) without effect of the covariates. However, cocaine-addicted subjects showed significantly higher plasma PEA concentrations than did controls in both men ($^{*}p < 0.01$) and women ($^{**}p < 0.01$).

A two-way ANCOVA revealed a significant primary effect of history of cocaine addiction ($F_{1,122} = 13.79$, $p < 0.001$) and sex ($F_{1,122} = 16.07$, $p < 0.001$) on plasma POEA concentrations (**Figure 3C**). Additionally, there was a significant interaction between history of cocaine addiction and sex ($F_{1,122} = 8.45$, $p = 0.004$). In this case, there was a significant relationship between BMI and POEA concentrations ($F_{1,122} = 5.11$, $p = 0.026$), and BMI explained 4.7% of the variance. Consequently, all pairwise comparisons were performed using estimated marginal means with fixed values of covariates (age = 39.41 and BMI = 25.34). The confidence interval (CI) adjustments for the Bonferroni test indicated the following estimated marginal means of POEA concentrations and standard errors: 0.084 ± 0.008 ng/mL (0.068–0.100, 95% CI) in control men, 0.097 ± 0.010 ng/mL (0.077–0.11, 95% CI) in control women, 0.093 ± 0.009 ng/mL (0.076–0.110, 95% CI) in cocaine-addicted men and 0.170 ± 0.015 ng/mL (0.139–0.200, 95% CI) in cocaine-addicted women. Multiple comparisons with adjusted means indicated that the main effect of history of cocaine addiction was exclusively observed in cocaine-addicted women. A marked increase in plasma POEA concentrations was observed in cocaine-addicted women ($^{***}p < 0.001$) relative to control women but also in comparison with cocaine-addicted men (+ + + $p < 0.001$). There were no changes in POEA concentrations in men.

Regarding the other monounsaturated lipid derivative (**Figure 3D**), plasma OEA concentrations were only affected by cocaine use ($F_{1,122} = 30.73$, $p < 0.001$). There was a significant relationship between age and OEA concentrations ($F_{1,122} = 6.84$, $p = 0.010$), and the covariate explained 6.2% of the variance. The adjusted means (age = 39.41 and BMI = 25.34) of OEA concentrations and standard errors of the means were as follows: 2.263 ± 0.137 ng/mL (1.991–2.536, 95% CI) in control men, 2.120 ± 0.175 ng/mL (1.774–2.466, 95% CI) in control women, 3.258 ± 0.147 ng/mL (2.966–3.550, 95% CI) in cocaine-addicted men and 3.180 ± 0.259 ng/mL (2.666–3.693, 95% CI) in cocaine-addicted women. Multiple comparisons of these adjusted means indicated that the cocaine group had significantly higher plasma OEA concentrations than did the controls in both men ($^{**}p < 0.01$) and women ($^{***}p < 0.001$).

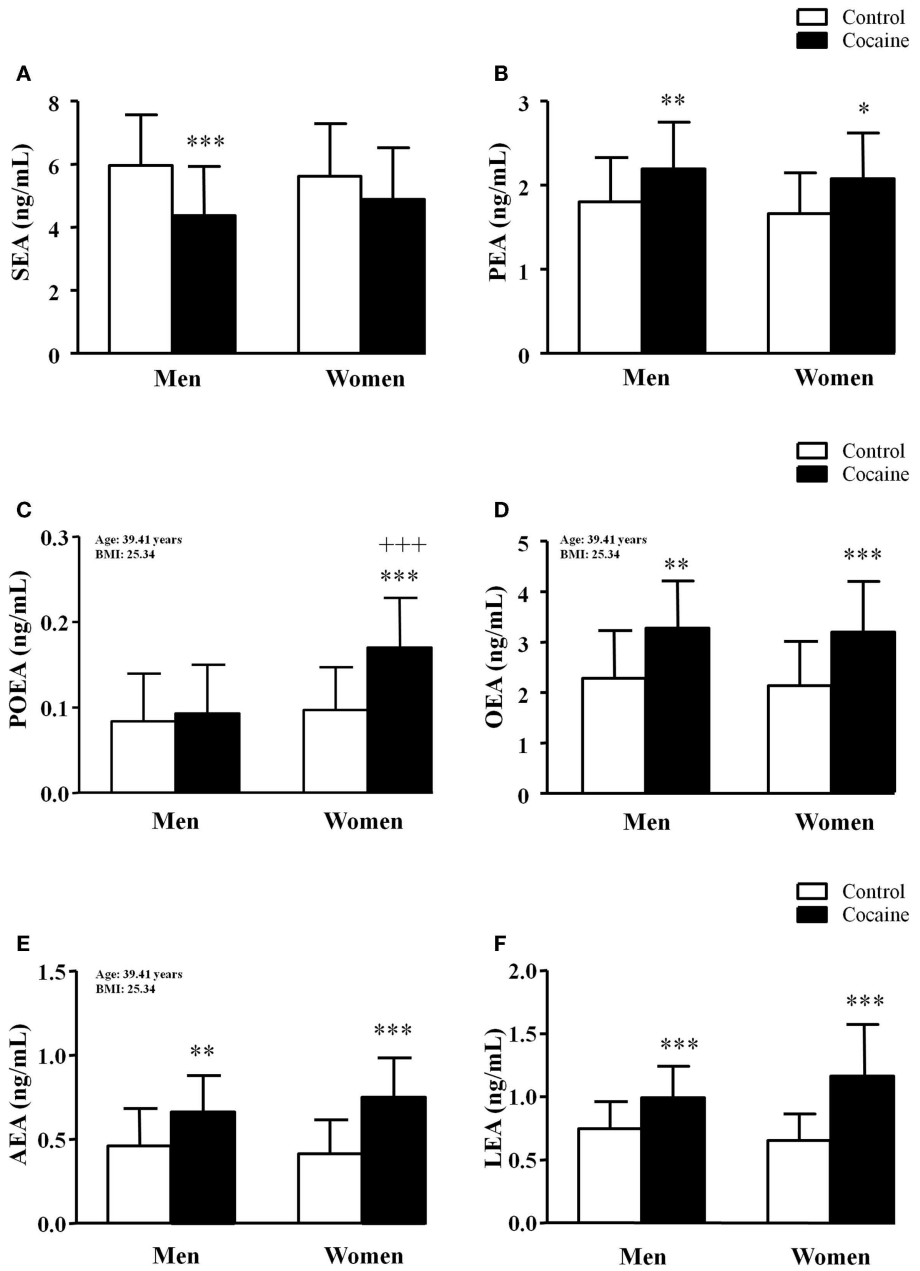

FIGURE 3 | Plasma concentrations of *N*-acyl-ethanolamines in abstinent cocaine-addicted and control subjects grouped by sex. **(A)** SEA (ng/mL); **(B)** PEA (ng/mL); **(C)** POEA (ng/mL); **(D)** OEA (ng/mL); **(E)** AEA (ng/mL); and **(F)** LEA (ng/mL). The bars represent means ± SD. The data were analyzed by two-way ANCOVA and multiple comparison tests. (*) $p < 0.05$, (**) $p < 0.01$, and (***) $p < 0.001$ denote significant differences compared with the respective control men or control women. (+++) $p < 0.001$ denotes significant differences compared with cocaine-addicted men. POEA, OEA, and AEA concentrations are adjusted means with the following values of covariates: age = 39.41 years and BMI = 25.34.

Two polyunsaturated *N*-acyl-ethanolamines, AEA and LEA, were also measured and statistically analyzed. Similar to OEA and the saturated lipid mediators, history of cocaine addiction produced a main effect on plasma AEA concentrations ($F_{1,122} = 38.59$, $p < 0.001$) (**Figure 3E**). However, there was a significant effect of BMI ($F_{1,122} = 6.29$, $p = 0.014$) that explained 5.8% of the variance. The estimated marginal means (age = 39.41 and BMI = 25.34) of AEA concentrations were as follows: 0.467 ± 0.032 ng/mL (0.404–0.530, 95% CI) in control men, 0.421 ± 0.040 ng/mL (0.341–0.501, 95% CI) in control women, 0.668 ± 0.034 ng/mL (0.601–0.736, 95% CI) in cocaine-addicted men and 0.753 ± 0.060 ng/mL (0.634–0.872, 95% CI) in cocaine-addicted women. The paired comparisons showed that both cocaine-addicted men and women had a significant increase in

AEA concentrations (**$p < 0.01$ and ***$p < 0.001$, respectively) compared with their respective controls.

When LEA concentrations were analyzed (**Figure 3F**), we observed a significant primary effect of history of cocaine addiction ($F_{1,122} = 45.80$, $p < 0.001$). Here, an interaction between both factors was also detected ($F_{1,122} = 5.58$, $p = 0.020$). BMI and age had no effect on LEA concentrations. Multiple comparisons showed significant increases in the plasma LEA concentrations of cocaine-addicted men (***$p < 0.001$) and women (***$p < 0.001$) in comparison with their respective controls, but we observed no differences between both sexes.

Overall, free *N*-acyl-ethanolamine concentrations were found to be increased in the plasma of cocaine-addicted subjects with no effect of sex. However, there were two exceptions: (i) SEA concentrations were decreased in the cocaine group and (ii) POEA concentrations were increased exclusively in cocaine-addicted women. The covariates age and BMI were found to be significantly related to the plasma concentrations of certain acyl derivatives (i.e., POEA, OEA, and AEA).

2-acyl-glycerols

As shown in **Figure 4**, the plasma concentrations of 2-AG and 2-LG were determined to be glycerol-derived molecules.

Statistical analysis revealed a significant main effect of history of cocaine addiction ($F_{1,122} = 7.60$, $p = 0.007$) on 2-AG concentrations (**Figure 4A**). There was a significant relationship between age and 2-AG concentrations ($F_{1,122} = 9.85$, $p = 0.002$), and the covariate explained 8.7% of the variance. The adjusted means (age = 39.41 and BMI = 25.34) of 2-AG concentrations and standard errors were as follows: 6.869 ± 0.508 ng/mL (5.861–7.877, 95% CI) in control men, 5.779 ± 0.646 ng/mL (4.497–7.060, 95% CI) in control women, 5.116 ± 0.545 ng/mL (4.035–6.197, 95% CI) in cocaine-addicted men, and 3.749 ± 0.958 ng/mL (1.849–5.650, 95% CI) in cocaine-addicted women. Paired comparisons did not indicate significant differences among groups.

Finally, we also found a significant primary effect of history of cocaine addiction ($F_{1,122} = 16.57$, $p < 0.001$) on plasma 2-LG concentrations. We observed no effects of age or BMI on the 2-LG concentrations. The *post hoc* tests indicated significant decreases in the 2-LG concentrations of cocaine-addicted subjects compared with the control group for both men (***$p < 0.001$) and women (*$p < 0.05$).

Unlike *N*-acyl-ethanolamines, the plasma concentrations of glycerol derivatives were decreased in the cocaine group, but sex differences were not found. Interestingly, there was a robust relationship between BMI and 2-AG concentrations.

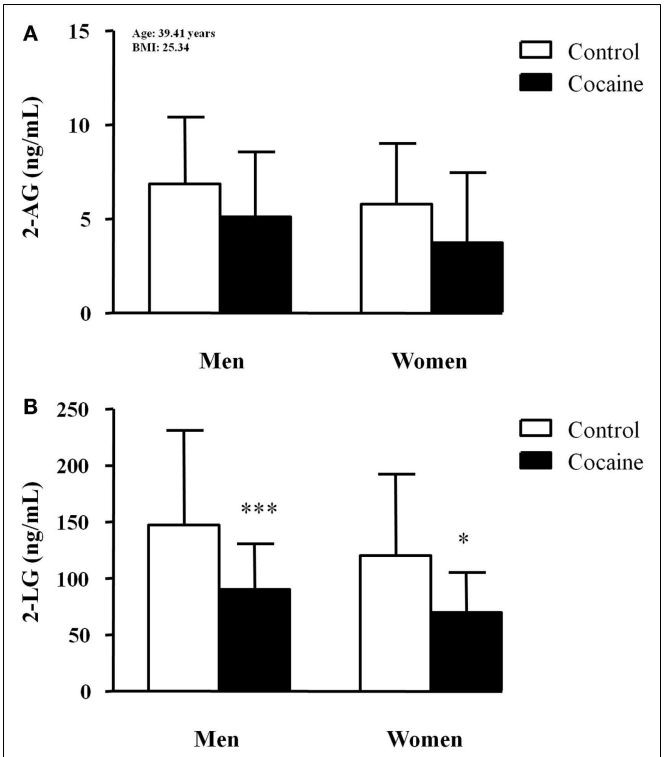

FIGURE 4 | Plasma concentrations of 2-acyl-glycerols in abstinent cocaine-addicted and control subjects grouped by sex. **(A)** 2-AG (ng/mL); and **(B)** 2-LG (ng/mL). The bars represent means ± SD. The data were analyzed by two-way ANCOVA and multiple comparison tests. (*) $p < 0.05$ and (***) $p < 0.001$ denote significant differences compared with the respective control men or control women. 2-AG concentrations are adjusted means with the following values of covariates: age = 39.41 years and BMI = 25.34.

PLASMA CONCENTRATIONS OF CHEMOKINES, CYTOKINES, AND FATTY ACID DERIVATIVES IN SUBJECTS WITH A HISTORY OF COCAINE ADDICTION

The plasma concentrations of chemokines, cytokines, and fatty acid derivatives in the cocaine group were analyzed by univariate general linear models to evaluate their relationships with cocaine symptom severity, diagnosis of comorbid psychiatric disorders, and length of cocaine abstinence (**Table 4**). Additionally, the relationships with BMI, age, and sex were also evaluated.

We observed no relationships between plasma concentrations of chemokines and cytokines and such variables. In fact, the main effect of sex on cytokine concentrations in the control and cocaine groups was not observed when only the cocaine group was analyzed. However, the plasma concentrations of several fatty acid derivatives were found to be associated with certain variables.

Thus, SEA concentrations were related to the diagnosis of comorbid psychopathologies ($p < 0.01$), and an increase in SEA concentrations was observed in cocaine-addicted subjects diagnosed with psychiatric comorbidity. As previously observed, POEA and AEA concentrations in the cocaine group were found to be affected by BMI ($p < 0.05$). Additionally, there was a main effect of sex ($p = 0.001$) on POEA concentrations. Regarding 2-acyl glycerol derivatives, whereas 2-AG concentrations were significantly affected by age and sex ($p < 0.05$), 2-LG concentrations were affected by diagnosis of psychiatric comorbidity and sex ($p < 0.05$). Similar to SEA, an increase in 2-LG concentrations was observed in cocaine subjects diagnosed with psychiatric comorbidity.

Thus, among the independent variables related to cocaine addiction in the cocaine group that were evaluated, we only found significant associations between comorbid psychiatric disorders and fatty acid derivative concentrations (i.e., SEA and 2-LG).

Table 4 | Multiple relationships between plasma concentrations of chemokines, cytokines, and fatty acid derivatives (dependent variables) and independent variables in abstinent cocaine-addicted subjects.

Dependent variable	Main effect (independent variable)[a]											
	Sex		Body mass index		Age		Length of cocaine abstinence		Cocaine symptom severity		Comorbid psychiatric disorders	
	F	*p*-value	*F*	*p*-value	*F*	*p*-value	*F*	*p*-value	*F*	*p*-value	*F*	*p*-value
UNIVARIATE GENERAL LINEAR MODELS												
CX3CL1 (fractalkine)	2.194	ns	0.930	ns	0.222	ns	0.010	ns	2.469	ns	0.354	ns
CCL2 (MCP-1)	0.005	ns	0.949	ns	0.657	ns	0.524	ns	0.687	ns	3.204	ns
CXCL12 (SDF-1)	0.452	ns	0.018	ns	0.026	ns	0.001	ns	2.651	ns	0.011	ns
IL-1β	1.162	ns	0.433	ns	0.545	ns	0.121	ns	2.550	ns	2.434	ns
IL-6	0.012	ns	0.272	ns	0.854	ns	0.411	ns	1.872	ns	3.690	ns
IL-10	2.103	ns	1.091	ns	2.407	ns	1.791	ns	1.033	ns	2.765	ns
TNFα	0.165	ns	0.004	ns	0.036	ns	0.076	ns	0.218	ns	3.032	ns
SEA	0.004	ns	0.774	ns	0.266	ns	1.408	ns	1.842	ns	**11.49**	**0.002**
PEA	1.246	ns	0.911	ns	1.116	ns	0.490	ns	1.746	ns	1.858	ns
OEA	0.300	ns	0.095	ns	1.181	ns	0.098	ns	0.501	ns	2.177	ns
POEA	**12.88**	**0.001**	**6.798**	**0.013**	0.011	ns	0.427	ns	0.185	ns	0.037	ns
AEA	0.453	ns	**4.578**	**0.039**	0.166	ns	0.265	ns	2.842	ns	2.691	ns
LEA	2.601	ns	3.458	ns	0.144	ns	0.138	ns	1.584	ns	0.946	ns
2-AG	**4.593**	**0.039**	0.149	ns	**6.619**	**0.014**	0.503	ns	0.004	ns	2.288	ns
2-LG	**6.703**	**0.014**	0.063	ns	2.981	ns	0.003	ns	0.692	ns	**6.897**	**0.012**

[a]*Tests of between-subjects effects.*

ns, non-significant.

Bold indicates statistically significant p-values.

DISCUSSION

The present findings show that sex is a relevant modulatory factor in the presence of comorbid mental and substance use disorders in individuals with lifetime cocaine use disorders. As expected, cocaine-addicted men seeking treatment were more common than women. Whereas the abstinent cocaine-addicted men were characterized by increased rates of other substance use disorders such as alcohol and marijuana, the cocaine-addicted women showed a higher prevalence of comorbid mental disorders, such as mood, anxiety, and psychotic disorders. Additionally, the plasma concentrations of putative biomarkers for cocaine addiction and comorbidity were influenced by sex. In the present study, we examined sex differences in inflammatory mediators and fatty acid derivatives because these molecules were reported to be affected by the pathological use of cocaine (19, 20). The most relevant findings were that all of the evaluated inflammatory cytokines and the monounsaturated fatty acid derivative POEA were found to be differentially altered in cocaine-addicted women, extending the influence of sex to plasma biomarkers for cocaine addiction. In addition, SEA and 2-LG concentrations were associated with psychiatric comorbidity in abstinent cocaine-addicted subjects.

In the present study, subjects diagnosed with lifetime cocaine use disorders showed high rates of mental and other substance use disorders, as reported previously in cocaine users and abstinent cocaine-addicted subjects (11, 12, 27), and there were differences in the psychiatric prevalence according to sex. Several epidemiological studies have observed significant sex differences among subjects diagnosed with mood and anxiety disorders. The incidence of mental disorders is enhanced in women compared with men, particularly in periods of life such as pregnancy, maternity, menopause, or after traumatic events (15). These elevated rates of lifetime psychiatric disorders in women have also been reported with substance use disorders (14, 28). Consistent with these previous studies, we diagnosed a higher prevalence of comorbid mental disorders (i.e., mood, anxiety, and psychosis) in women, whereas higher rates of other substance use disorders (especially with alcohol) were observed in cocaine-addicted men. As expected, the lifetime cocaine symptom severity was severe in both sexes with no differences with respect to length of abstinence and duration of cumulative cocaine use.

Collectively, these findings suggest that any potential biomarker for cocaine addiction and psychiatric comorbidity must account for the influence of sex. Recent evidence indicates that cocaine and other psychostimulants alter the peripheral concentration of circulating mediators that may influence the cognitive and behavioral changes associated with the process of addiction. Among these mediators, we assessed the plasma concentrations of inflammatory mediators and fatty acid derivatives. Chemokines and proinflammatory mediators are affected by cocaine symptom severity, whereas anti-inflammatory fatty acid derivatives such as endocannabinoids and their congeners are affected by

the history of pathological use of cocaine and the presence of comorbid disorders. However, the impact of sex has not been sufficiently studied because the female population seeking outpatient treatment in centers for cocaine addiction is very low, as previously indicated (1).

CHEMOKINE AND CYTOKINE CONCENTRATIONS

Growing evidence has demonstrated naturally occurring sex differences in the immune response and inflammatory mediators. During their reproductive years, women have a more potentiated cellular and humoral immune response than do men (29). Indeed, it is thought that fluctuations in estrogen may alter immune cell function by affecting cytokine and chemokine production (30). Furthermore, several recent reports have related inflammatory mediators in blood and cerebrospinal fluid to addiction to drugs of abuse, such as alcohol, psychostimulants, and opiates (31).

Chemokines are chemoattractants that are involved in leukocyte trafficking to the site of inflammation (32), but they also play an important role in neuronal development, maturation, survival, and regeneration in the central nervous system (CNS) (33). Therefore, cerebral changes underlying addiction and psychiatric comorbidities might be reflected in peripheral alterations. Recently, chemokines have been proposed as pathologically relevant biomarkers or therapeutic targets for psychiatric disorders (34). In fact, we found that the CCL2 and CXCL12 concentrations were decreased in both male and female cocaine users. These changes in circulating chemokines are in accordance with the results from another study in abstinent cocaine-addicted population, which suggested that these chemokines were biomarkers for the pathological use of cocaine, although we observed no changes in plasma CX3CL12 concentrations (20). Moreover, we detected no differences by sex in the plasma concentrations of these chemokines.

In addition to chemokines, we evaluated plasma cytokine concentrations, including pro- and anti-inflammatory mediators. In this case, we found a clear sexual dimorphism in the circulating concentrations of all of the cytokines assessed in the present study. The plasma concentrations of IL-1β, IL-6, IL-10, and TNFα were higher in healthy women compared with men. Interestingly, these differences were absent in subjects diagnosed with lifetime cocaine use disorders.

Previous studies have reported that chronic exposure to drugs of abuse, such as alcohol and cocaine, suppresses immune responses. Contradictory data have been published in relation to alcoholism. For instance, whereas a significant increase in the production of IL-1β, IL-6, IL-12, and TNFα was observed in chronic alcoholics without liver disease, chronic alcoholics with liver disease who were drinking alcohol showed low production of IL-1β and TNFα (35). Regarding cocaine, it has been reported that cocaine-dependent subjects show a decreased capacity to express proinflammatory cytokines such as TNFα and IL-6 in monocytes (36). Further, we have recently shown that abstinent cocaine-addicted subjects have low TNFα concentrations and IL-1β concentrations, and that they are affected by the cocaine symptom severity (20). Our data may be related to long-term cocaine-induced changes in cytokine concentrations, but these changes were only produced in women with no effect in male addicts. The plasma concentrations of inflammatory cytokines were clearly reduced in women, and such cytokine reduction might be associated with decreased immune activity and an increased risk of developing mental disorders (15, 37). However, plasma concentrations of chemokines and cytokines were not associated with sex and comorbid psychopathologies in cocaine-addicted subjects.

FATTY ACID DERIVATIVE CONCENTRATIONS

Several lines of evidence suggest that bioactive lipids, such as endocannabinoids and related congeners, are involved in the acquisition and maintenance of drug-taking behavior and other processes associated with addiction (38, 39). However, all of these studies are based on preclinical observations because there are few studies concerning plasma lipid derivatives in individuals with substance use disorders (40, 41), principally with alcohol use (42, 43). Endocannabinoids act on cannabinoid receptors to exert their effects and are composed of two structural types of lipid derivatives: *N*-acyl-ethanolamines (e.g., AEA) and 2-acyl-glycerols (e.g., 2-AG).

Clinical studies in alcohol users reported that alcohol use affects circulating endocannabinoid concentrations after moderate and chronic consumption (42, 43). Regarding cocaine use, we recently showed that *N*-acyl-ethanolamine concentrations are increased in abstinent cocaine addicts, whereas both 2-AG and 2-LG are reduced (19). Interestingly, distinct profiles of both endocannabinoid types (AEA and 2-AG) have also been described in distinct brain areas after administering drugs of abuse in rodents (44, 45). In agreement with these studies, the present study shows that plasma concentrations of all lipid-derived molecules were distinctly affected by history of cocaine addiction. All *N*-acyl-ethanolamines, except SEA, were found to be increased in cocaine-addicted subjects, but 2-acyl-glycerols were decreased in relation to healthy subjects. Overall, we observed no sex differences in the changes of plasma concentrations of fatty acid derivatives. However, the POEA concentrations were found to be altered exclusively in women diagnosed with lifetime cocaine use disorders. Our current data show that plasma POEA was markedly increased in abstinent cocaine-addicted women, and similar changes have been previously observed in another study with cocaine addicts who were diagnosed with comorbid mood or anxiety disorders (19). Little is known about POEA, but it has been suggested that it regulates appetite and energy metabolism through a non-cannabinoid receptor (46, 47). Interestingly, palmitoleate is the fatty acid from which POEA is derived, and the former has been suggested to be a lipokine associated with metabolic abnormalities (48). In fact, we observed a significant effect of BMI on POEA concentrations of our sample, and this influence stayed with the cocaine group. However, there are no data related to the role of POEA in psychopathologies and addiction. In the present study, we did not observe relationships between POEA concentrations and variables related cocaine addiction such as length of abstinence, cocaine symptom severity, or diagnosis of comorbid psychopathologies, but sex was strongly associated with POEA in cocaine-addicted subjects. Although the small number of cocaine-addicted women does not allow for a conclusion of the impact of comorbid mental

disorders on POEA concentrations, we must note that female addicts have a higher prevalence of psychiatric comorbidity than do men.

The associations between circulating endocannabinoids and mental disorders have been extensively studied in clinical studies, and a common observation found in these disorders is the elevated concentrations of *N*-acyl-ethanolamines (49–51). Further, increased *N*-acyl-ethanolamine concentrations have been observed in psychiatric patients with substance use disorders, such as in schizophrenia patients (40). Accordingly, we observed a significant relationship between SEA and diagnosis of comorbid psychiatric disorders in cocaine-addicted subjects, with higher concentrations in comorbid addicts. However, classical endocannabinoids such as AEA and 2-AG were not influenced by comorbidity.

LIMITATIONS AND FUTURE PERSPECTIVES

Our findings support the importance of monitoring these putative predictors in the context of a history of cocaine addiction by accounting for both sex differences and psychiatric comorbidity.

We are aware of the limitations of the current study. First, the number of cocaine-addicted women is small, and replicating these data with a larger sample will be necessary to confirm the sexual dimorphism observed in the present study, primarily in plasma cytokines and POEA. Second, we must determine whether these alterations in cocaine-addicted women are exclusively attributable to sex or to comorbid psychiatric disorders. Therefore, new studies in female psychiatric patients with no history of drug abuse will be necessary to elucidate the influence of mental disorders in these circulating predictors of cocaine addiction. Related to these mentioned limitations, women were randomly recruited without considering the menstrual cycle, and this condition should be considered in future studies including cocaine-addicted women. Third, with regard to the cocaine use effect, we are unaware of the effects on the plasma concentrations of these molecules in active cocaine users because the presence of cocaine can induce prolonged activation, and the present data were obtained from subjects with a history of addiction. Animal models can be a useful tool to perform future investigations for responding to these questions. Finally, the recruitment of abstinent cocaine-addicted subjects under treatments in centers for addiction was performed on an outpatient basis; consequently, medications as well as social and environmental factors must be considered.

In summary, whereas the plasma concentrations of inflammatory and fatty acid-derived mediators may allow for a better stratification of cocaine addicts, the sexual dimorphism must also be considered for the adequate selection of biomarkers for cocaine addiction and therapeutic purposes.

AUTHOR CONTRIBUTIONS

FRF and FJP were responsible for the study concept and design. MP, PA, NGM, and JJR coordinated and recruited participants from outpatient treatment centers for addiction. MP, PA, NGM, and PR-S contributed to the acquisition of psychiatric data by means of interviews. AS, JS, and ECO processed the blood samples. AP and RdT supervised and performed the benzoylecgonine detection and the quantification of fatty acid derivatives in plasma. VB, JAC, and JA supervised and performed the quantification of cytokines and chemokines in plasma. FJP, AS, and PA assisted with data analysis and interpretation of findings. FRF and FJP drafted the manuscript. MT, RdT, and JA provided critical revision of the manuscript for important intellectual content. All the authors critically reviewed the content and approved the version for publication.

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Sex differences in behavioral impulsivity in at-risk and non-risk drinkers

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Introduction: Mounting evidence from both animal and human studies suggests that females are more vulnerable to drug and alcohol abuse than males. Some of this increased risk may be related to behavioral traits, such as impulsivity. Here, we examined sex differences in two forms of behavioral impulsivity (inhibitory control and impulsive choice) in young men and women, in relation to their level of alcohol consumption and alcohol-related problems (at-risk or non-risk).

Methods: Participants performed a go/no-go task to assess inhibitory control and a measure of delay discounting to assess impulsive choice.

Results: On the measure of inhibitory control, at-risk women committed significantly more inhibitory errors than at-risk men, indicating poorer behavioral control among the women. By contrast, no sex differences were observed between at-risk men and women in delay discounting, or between the male and female non-risk drinkers on any measure.

Conclusion: Heavy drinking women displayed poorer inhibitory control than heavy drinking men. It remains to be determined whether the sex differences in inhibitory control are the result of drinking, or whether they pre-dated the problematic drinking in these individuals.

Keywords: behavioral impulsivity, inhibitory control, impulsive choice, go/no-go, delay discounting, alcohol, AUDIT

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Introduction

Alcohol abuse has been traditionally considered a male-oriented problem and as a consequence research on risk factors specific to women has been minimal. However, the sex gap in alcohol consumption and alcohol-related problems is closing rapidly, especially among young adult drinkers (1–4). Specifically, sex differences in frequency and quantity of alcohol consumption, frequency of binge drinking, and prevalence of alcohol abuse and dependence are shrinking, due primarily to increased consumption and prevalence rates in women. In fact, binge drinking rates in women are beginning to surpass those in men in some areas (5). Further, findings from both animal and human studies suggest that females may actually be more vulnerable to drug and alcohol use than males (6–8). Given the increase in alcohol use among women and their increased vulnerability to alcohol-related problems, it is important to identify risk factors for alcohol abuse in women.

One potential risk factor is impulsive behavior. Growing evidence indicates that there are at least two separate components of impulsive behavior: poor inhibitory control (behavioral disinhibition) and impulsive choice (delay discounting), and both forms are strongly implicated in alcohol and drug abuse (9–11). Alcohol-dependent individuals display poor inhibitory control compared to

healthy, social drinking controls (12, 13), and poor inhibitory control prospectively predicts the development of alcohol-related problems (14–16). Heavy drinkers also display greater impulsive choice (i.e., steeper discounting of the value of rewards that are delivered after a delay) than social drinking controls (17, 18), and delay discounting prospectively predicts greater alcohol consumption among adolescents over a 2-year period (16).

There is some evidence that healthy men and women differ on measures of impulsive behaviors, although results are mixed and depend on specific tasks administered (19). Regarding inhibitory control, women and girls exhibit poorer inhibition than males on stop signal tasks, which measure the time required to inhibit a response (20, 21). By contrast, men exhibit poorer inhibition on go/no-go tasks, which measure the number of inhibitory failures (22–24). Regarding delay discounting, some studies have found that women discount more than men using hypothetical or chance (based on the role of the die) discounting procedures (25–27), whereas other studies have found greater discounting in men using both hypothetical and chance (based on a lottery) discounting procedures (28, 29). Taken together, sex differences do appear to exist, but the direction of the differences varies across specific domains of impulsive behavior.

To date, only a handful of studies have examined sex differences in impulsive behaviors among problematic drinkers. The interpretation of studies with experienced users is complex, as it is difficult to determine whether any observed behavioral differences pre-dated and contributed to the drinking, or whether the behaviors changed as a result of the drinking. Nevertheless, the findings are informative and useful in designing interventions. Initial evidence shows that heavy, binge drinking women display greater inhibitory deficits compared to both heavy drinking men and light drinkers, on both stop signal and go/no-go tasks (30, 31). By contrast, Bobova et al. (32) found that heavy drinking men discounted a hypothetical monetary reward more than heavy drinking women, although this sex difference was not specific to heavy drinkers. Finally, Yankelevitz et al. (33) examined sex differences in discounting of hypothetical money and hypothetical alcohol in regular drinkers. Although men and women did not differ for either commodity alone, women discounted alcohol more than money, whereas men discounted the two commodities equally. In sum, evidence suggests that poor inhibitory control could be a specific risk factor for heavy, problematic drinking in women, but the current findings regarding sex differences in impulsive choice among drinkers are equivocal.

The current study examined sex differences in both inhibitory control and impulsive choice as a function of drinking status in a community sample of young adult drinkers ($n = 743$). Participants were classified as "at-risk" or "non-risk" drinkers based on their scores on the Alcohol Use Disorders Identification Test [AUDIT; (34)]. The AUDIT is a screening instrument that classifies individuals based on both patterns of alcohol consumption (i.e., frequency and quantity) as well as occurrence of negative alcohol-related consequences. Participants who met the cutoff score of 8 or higher for hazardous drinking were classified as at-risk and those who scored below 8 were considered to be non-risk. Participants performed the go/no-go task to assess inhibitory control and the delay discounting task (DDT) to assess impulsive choice. We hypothesized that overall, at-risk drinkers would be more impulsive on both tasks (i.e., display greater inhibitory failures and steeper delay discounting) compared to non-risk drinkers. Additionally, we hypothesized that among at-risk drinkers, women would display poorer inhibitory control than men. Analyses of sex differences in delay discounting were considered exploratory, given the lack of consistent findings from previous studies.

Materials and Methods

Participants

Volunteers were recruited from the community through online and printed advertisements. Inclusion criteria included ages 18–30, at least a high school education, fluency in English, no current or past year diagnosis (including alcohol or substance dependence) on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (35), no lifetime alcohol or substance dependence (other than caffeine or nicotine), and at least some alcohol consumption within the past year. The study was approved by the Institutional Review Board of the University of Chicago, and was carried out in accordance with the Declaration of Helsinki. Participants provided informed consent and were compensated for their time.

Procedure

These data were obtained in the course of a larger genetic study. Participants attended a 4-h experimental session (morning or afternoon) during which they completed several behavioral tasks and self-report measures in counterbalanced order. Participants were instructed to abstain from alcohol and drugs (other than their usual amounts of caffeine and nicotine) for 24 h before the visit, and breath and urine samples were obtained to verify compliance. After compliance testing, participants completed the tasks and questionnaires reported here.

Measures

Go/No-Go Task

Inhibitory control was assessed using a go/no-go task (**Figure 1**) that measures the ability to inhibit inappropriate responses. This task has been used extensively in alcohol and drug abuse research, and findings have consistently found that heavy substance use is associated with greater inhibitory errors (9, 36). Go (X) and no-go (K) targets were presented on the computer screen. Participants were told to respond as quickly as possible to go targets but to inhibit their response to the no-go targets. Most (85%) of the trials were go targets, establishing the "go" response as prepotent, and making it more difficult to inhibit when the no-go targets occasionally appeared. The number of inhibitory failures (i.e., failures to inhibit a response to a no-go target) provided the dependent measure of interest. Data were considered invalid if go target accuracy was less than 55% or if there were no successful inhibitions (suggesting a lack of understanding of task instructions).

Delay Discounting Task

Impulsive choice was assessed using a delay discounting task (DDT; **Figure 2**) that assesses the relative value of immediate

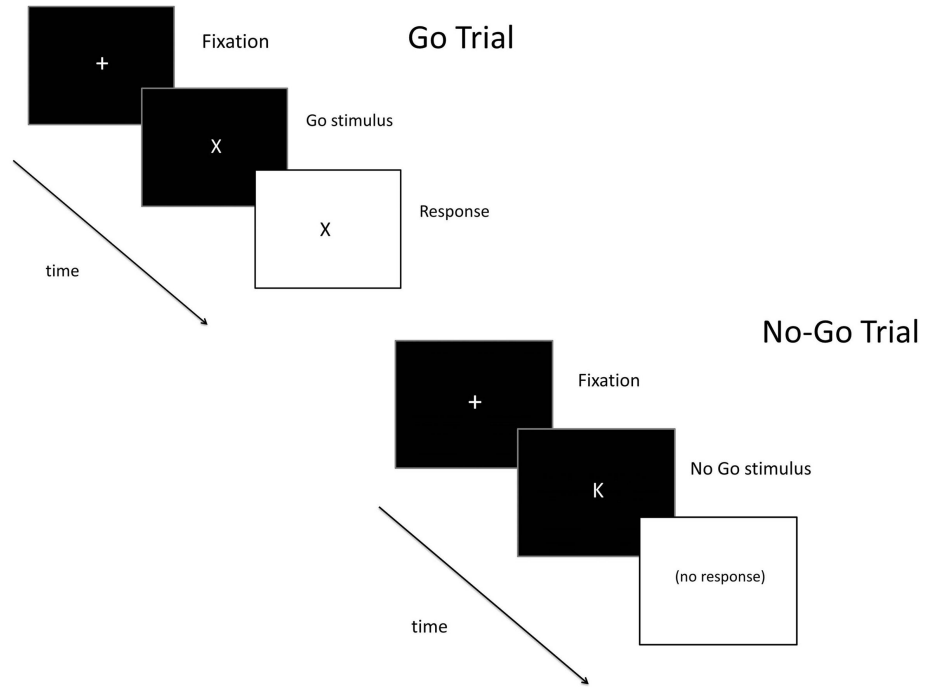

FIGURE 1 | Schematic of a go (top) and no-go (bottom) trial on the go/no-go task.

versus delayed rewards (37). This task has also been used extensively in drug abuse research, and studies have consistently shown greater discounting of delayed rewards by substance abusers (9, 11, 17). Participants made a series of choices (90 total) between a smaller amount of money (ranging from $10 to $99) delivered immediately, and a larger amount of money ($100) delivered after a delay (i.e., 1, 7, 14, 30, 60, 90, 180, or 365 days). They were told that at the end of the session a random number would be generated and if they guessed the number correctly they would receive the amount of one of their choices. Thus, subjects performed the task knowing that there was a chance they would receive one of their choices. Indifference points were calculated based on the smallest amount of money chosen over the large reward at each delay. Response consistency was calculated at each delay to ensure that participants were performing the task appropriately, and a threshold of 75% consistency was set to indicate adequate effort. The indifference points were plotted to form a discount function, and the area under the curve (AUC) of the discount function provided the dependent measure of impulsive choice (27, 38). A smaller AUC indicates a steeper discounting curve, and therefore greater impulsivity.

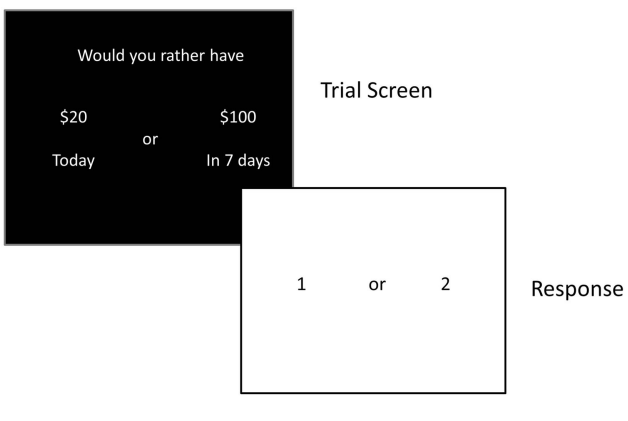

FIGURE 2 | Schematic of a trial on the delay discounting task.

Alcohol Use Disorder Identification Test

The AUDIT is a 10-item self-report measure that assesses patterns of drinking, dependence, and alcohol-related problems. Scores range from 0 (no alcohol-related problems) to 40 (most severe alcohol-related problems), and a score of 8 or greater is typically indicative of hazardous drinking (34). Accordingly, we classified participants with AUDIT scores less than 8 as "non-risk drinkers" and participants with AUDIT scores of 8 or greater as "at-risk drinkers."

Timeline Follow-Back

Participants completed a retrospective timeline calendar of their alcohol consumption for the past 28 days to assess daily patterns of drinking (39). The measure uses "anchor points" to structure and facilitate participants' recall of past drinking episodes. For each day, participants estimated the number of standard drinks they consumed. The TLFB provided two measures of drinking habits over the past 28 days: (a) drinking days (total number of days alcohol was consumed) and (b) binge days (number of days in which four or more drinks were consumed for women or five or more drinks were consumed for men). The TLFB was added to the study protocol after the study had begun, and thus data from this measure are only available from a subset of participants ($n = 457$).

Statistical Analysis

The effects of sex and at-risk drinker status on task performance were analyzed by 2 (sex: male vs. female) × 2 (group: at-risk vs. non-risk) between-groups analyses of variance (ANOVA). Significant interactions were followed by *post hoc t*-tests comparing men and women separately in the at-risk and non-risk groups.

Results

Sample Characteristics

The sample consisted of 743 healthy adults (296 men and 447 women; mean age = 22.9 years, SD = 3.2). Sample characteristics are presented in **Table 1**. In the sample as a whole, women were slightly younger than men [between-groups *t*-test: $t(741) = 2.5$, $p = 0.01$]. No other sex differences in sample demographics were observed (between-groups *t*-tests: $ps > 0.64$). The racial make-up of the sample was as follows: Asian ($n = 27$), African-American ($n = 27$), Caucasian ($n = 675$), and other ($n = 14$). The majority of participants were Caucasian as these data were collected as part of a larger genetic study.

Drinking Habits

Slightly less than one quarter of the sample ($n = 173$; 90 men and 83 women) were classified as "at-risk" drinkers (AUDIT scores ≥ 8) and the remainder ($n = 570$; 206 men and 364 women) were classified as non-risk drinkers (AUDIT scores <8). There were no risk group differences or sex × risk group interactions for any demographic variables (**Table 1**; $ps > 0.10$). Measures of drinking habits (TLFB and AUDIT) are presented in **Table 1** separately for men and women within each group. All alcohol consumption measures were greater in the at-risk compared to the non-risk group (between-groups *t*-tests: $ps < 0.001$). Men and women in the at-risk drinker group did not differ on any alcohol consumption measures ($ps > 0.05$). Among the non-risk drinkers, men had higher AUDIT scores, $t(568) = 2.9$, $p = 0.003$.

Go/No-Go Task

Valid go/no-go data were obtained for 679 participants (22 participants were missing data and 42 participants had invalid data). **Figure 3** presents mean inhibitory failures separately for men and women in the at-risk and non-risk drinker groups. The figure shows that overall women committed more inhibitory failures than men, as evidenced by a main effect of sex, $F(1, 675) = 6.53$, $p = 0.011$. Moreover, the figure shows that the sex difference was more pronounced in the at-risk drinker group compared to the non-risk group. This was confirmed by a significant sex × group interaction, $F(1, 675) = 3.88$, $p = 0.049$. Follow-up between-groups *t*-tests showed significantly more inhibitory failures in women than men in the at-risk group, $t(152) = 2.58$, $p = 0.011$, but no difference in women and men in the non-risk group, $t(523) = 0.60$, $p = 0.55$. No significant differences were observed between risk groups among men or women ($ts < 1.85$, $ps > 0.05$).

Delay Discounting Task

Valid delay discounting data were obtained for 734 participants (6 participants were missing data and 3 participants had invalid data). **Figure 4** presents mean AUC of the discounting curve separately for men and women in the at-risk and non-risk drinker groups. Neither men and women nor risk groups differed on this measure ($ps > 0.40$).

Associations Between Task Performance and Demographics

Performance on the go/no-go task was not related to delay discounting in the sample as a whole ($r = 0.01$, $p = 0.73$) or when

TABLE 1 | Demographics and drug use characteristics of participants.

	At-risk drinkers			Non-risk drinkers		
	Men ($n = 90$)	**Women ($n = 83$)**	**Total ($n = 173$)**	**Men ($n = 206$)**	**Women ($n = 364$)**	**Total ($n = 570$)**
Age (mean, SD)	23.3 (3.5)	22.0 (2.8)	22.6 (3.2)	23.3 (3.3)	22.9 (3.1)	23.0 (3.2)
Education in years (mean, SD)	15.3 (2.3)	14.9 (1.9)	15.1 (2.1)	15.4 (2.3)	15.5 (2.0)	15.5 (2.1)
Race (number, %)						
Caucasian	80 (89%)	79 (95%)	159 (92%)	187 (91%)	329 (90%)	516 (91%)
African-American	2 (2%)		2 (1%)	11 (5%)	14 (4%)	25 (4%)
Asian	7 (8%)		7 (4%)	5 (2%)	15 (4%)	20 (4%)
Other	1 (1%)	4 (5%)	5 (3%)	3 (2%)	6 (2%)	9 (1%)
IQ (mean, SD)	119.0 (10.5)	120.3 (10.3)	119.6 (10.4)	119.5 (9.4)	118.7 (9.2)	119.0 (9.3)
Alcohol use measures						
AUDIT (mean, SD)	10.5 (2.5)	10.2 (2.4)	10.3 (2.4)	4.5 (1.7)	4.1 (1.9)	4.2 (1.8)
TLFB[a] (mean, SD)						
Drinking days/month	13.0 (6.5)	11.0 (5.8)	12.2 (6.2)	8.2 (6.0)	7.4 (5.4)	7.7 (5.6)
Binges/month	4.5 (3.5)	4.4 (3.6)	4.5 (3.5)	1.2 (1.7)	1.3 (1.8)	1.3 (1.7)
Cigarettes/day (mean/SD)	1.1 (2.6)	0.6 (1.3)	0.9 (2.1)	0.6 (1.8)	0.5 (2.2)	0.5 (2.1)
Marijuana (number, %)						
None	31 (34%)	34 (41%)	65 (37%)	125 (61%)	245 (67%)	370 (65%)
Monthly	37 (41%)	37 (45%)	74 (43%)	52 (25%)	94 (26%)	146 (26%)
Weekly	17 (19%)	10 (12%)	27 (16%)	22 (11%)	24 (6.5%)	46 (8%)
Daily	5 (6%)	2 (2%)	7 (4%)	7 (3%)	1 (0.5%)	8 (1%)

[a]*Data gathered from a subset of participants (n = 457).*

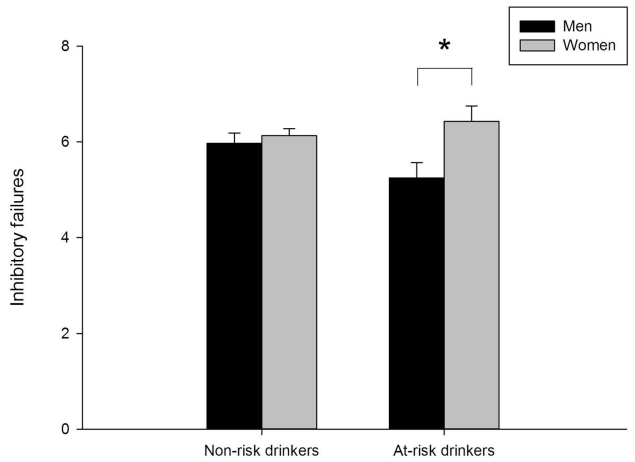

FIGURE 3 | Mean inhibitory failures on the go/no-go task for men and women in the non-risk (AUDIT scores below 8) and at-risk (AUDIT scores of 8 or above) drinker groups. In the non-risk group, men ($n = 190$) and women ($n = 335$) did not differ. In the at-risk group, women ($n = 75$) committed significantly more inhibitory failures than men ($n = 79$), $p = 0.01$. Capped vertical lines represent standard error of the mean (SEM).

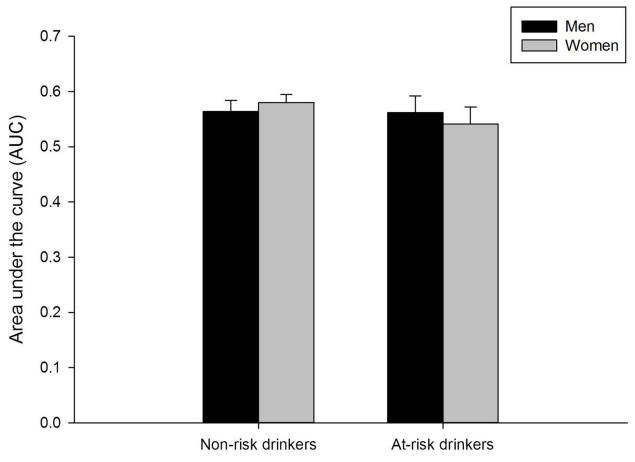

FIGURE 4 | Mean area under the curve on the delay discounting task for men and women in the non-risk (AUDIT scores below 8) and at-risk (AUDIT scores of 8 or above) drinker groups. No sex differences were observed in either group. Capped vertical lines represent standard error of the mean (SEM).

analyzed individually by sex (men: $r = -0.01$, $p = 0.84$; women: $r = 0.03$, $p = 0.54$). Inhibitory failures on the go/no-go task were negatively correlated with age ($r = -0.20$, $p < 0.001$) and education ($r = -0.08$, $p = 0.04$). AUC of the discounting curve was positively correlated with education ($r = 0.12$, $p = 0.001$) and IQ ($r = 0.22$, $p < 0.001$). As greater AUC indicates less discounting, these correlations indicate that greater impulsive choice is associated with lower IQ and less education. Sex differences in both go/no-go task performance and delay discounting were re-analyzed controlling for each of these demographic variables, and the results remained unchanged.

Discussion

This study examined sex differences in behavioral impulsivity (i.e., poor inhibitory control and impulsive choice) in at-risk and non-risk drinkers. Risk status was determined by scores on the AUDIT, a self-report measure that assesses frequency and quantity of alcohol consumption and alcohol-related problems. As hypothesized, at-risk women displayed poorer inhibitory control than at-risk men, but no sex differences were observed in the non-risk drinkers. On impulsive choice, no differences were observed in either men vs. women or by risk group.

Our findings of sex differences in inhibitory control are largely consistent with previous reports. Specifically, other studies have shown that heavy drinking women exhibit greater inhibitory deficits than heavy drinking men and light drinkers (30, 31). Further, in previous studies of women only, heavy drinking women show greater inhibitory deficits than light drinking women (40, 41). Although statistically significant differences were not observed between the at-risk and non-risk women in the current study, the direction of findings are in line with these reports and provide further support for inhibitory deficits among hazardous female drinkers. Regarding impulsive choice, the current findings are not consistent with one prior report of greater discounting among men compared to women in a sample of both alcohol-dependent individuals and controls (32). As no participants met dependence criteria in the current study, it could be that sex differences in delay discounting are more pronounced among individuals with alcohol use disorders. Taken together, these findings suggest that problematic alcohol consumption in women is strongly linked to poor inhibitory control, but not delay discounting.

Given mounting evidence of a link between disinhibition and heavy drinking in women, it is important to determine the causal direction of this association, as inhibitory deficits could be either a cause or consequence, or both, of heavy drinking. Evidence that sex-specific biological factors contribute to poor inhibition in non-alcohol abusing women would suggest that inhibitory deficits precede the onset of heavy drinking. For example, sex differences in circulating levels of gonadal hormones, including estradiol (E2), could influence inhibitory control. Indeed, Colzato et al. (20) showed that women exhibit poorer inhibition than men only when E2 levels are high, and that poorer inhibition is correlated with higher salivary measures of E2. Additionally, sex differences could exist in activation of neural circuitry underlying inhibitory control. Initial neuroimaging studies have reported that this circuitry is less strongly activated during response inhibition in women compared to men (42–45), although there are also reports of less activation in men (46), or complex differential patterns of activation in men and women (47). In sum, there is preliminary evidence of biologically based mechanisms underlying sex differences in inhibitory control, suggesting that poor inhibition may precede, and be a risk factor for, excessive and problematic alcohol use in women.

Alternately, evidence that women are more sensitive to the neurotoxic effects of alcohol would suggest that observed inhibitory deficits in women are a consequence of heavy drinking. Although findings are mixed, there is some evidence of greater adverse effects of alcohol on brain structure in adult female compared

to male alcoholics [for review, see Ref. (48)]. Further, in a sample of adolescents, Squeglia et al. (49) observed thicker cortices (indicative of less synaptic pruning) in frontal regions in binge drinking females compared to controls, as well as an association between thicker cortices and poorer inhibition in females. This group also observed decreased brain activation in female binge drinkers compared to controls during performance of a spatial working memory task, and decreased activation was associated with poorer task performance (50). Although no studies to date have examined neural activation underlying poor inhibitory control in heavy drinking female adolescents or adults, there is evidence to suggest that females may be more sensitive to the adverse effects of alcohol on inhibition-related brain structure and function.

There are several limitations to this study. First, we did not specifically recruit for heavy drinkers and excluded any potential volunteers with a history of alcohol dependence. As such, non-risk drinkers were over-represented in this sample, and this may have contributed in part to our failure to replicate well-established findings showing greater impulsive behavior in hazardous drinkers. Indeed, meta-analyses of impulsive behavior (poor inhibitory control and greater impulsive choice) report the most pronounced effects when alcohol dependent individuals are compared to healthy controls, and much weaker effects for non-dependent drinkers compared to controls (13, 17). It will be important for future studies to examine sex difference in impulsive behaviors within alcohol dependent populations, while taking into account other psychiatric symptoms that could influence sex differences, such as anhedonia (51). An additional limitation of the sample is the over-representation of women. It is important to note, however, that numbers of men and women were balanced within the at-risk drinker group. A third limitation is the lack of assessment of sex hormones. Circulating levels of gonadal hormones influence both inhibitory control (20) and impulsive choice (29, 52), and it is crucial that future studies examining sex differences in impulsive behavior account for the role of hormones in any observed differences.

In sum, this study adds to the existing literature suggesting that poor inhibitory control is strongly linked to problematic alcohol consumption in women. Future longitudinal research is needed to determine whether poor inhibitory control is a cause, or consequence, or both of heavy drinking in women. A better understanding of this association will allow for the development of sex-specific prevention and treatment efforts for alcohol abuse, with a focus on the role of poor inhibitory control.

Author Contributions

JW and JDA oversaw data acquisition and management, conducted the data analyses, and conducted the literature review and co-wrote the first draft of the paper. JW, JDA, and HdW contributed to and approved the final version of the paper.

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REVIEW
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Sex Differences in Behavioral Dyscontrol: Role in Drug Addiction and Novel Treatments

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The purpose of this review is to discuss recent findings related to sex differences in behavioral dyscontrol that lead to drug addiction, and clinical implications for humans are discussed. This review includes research conducted in animals and humans that reveals fundamental aspects of behavioral dyscontrol. The importance of sex differences in aspects of behavioral dyscontrol, such as impulsivity and compulsivity, is discussed as major determinants of drug addiction. Behavioral dyscontrol during adolescence is also an important consideration, as this is the time of onset for drug addiction. These vulnerability factors additively increase drug-abuse vulnerability, and they are integral aspects of addiction that covary and interact with sex differences. Sex differences in treatments for drug addiction are also reviewed in terms of their ability to modify the behavioral dyscontrol that underlies addictive behavior. Customized treatments to reduce behavioral dyscontrol are discussed, such as (1) using natural consequences such as non-drug rewards (e.g., exercise) to maintain abstinence, or using punishment as a consequence for drug use, (2) targeting factors that underlie behavioral dyscontrol, such as impulsivity or anxiety, by repurposing medications to relieve these underlying conditions, and (3) combining two or more novel behavioral or pharmacological treatments to produce additive reductions in drug seeking. Recent published work has indicated that factors contributing to behavioral dyscontrol are an important target for advancing our knowledge on the etiology of drug abuse, intervening with the drug addiction process and developing novel treatments.

Keywords: animal models, behavioral dyscontrol, drug addiction, food addiction, impulsivity, sweet intake, sex differences, novel treatments

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INTRODUCTION

Addiction and related impulse control disorders have an estimated cost to society of 600 billion dollars per year (1). In humans, substance abuse varies with current drug availability trends and sex differences are reported (2), but the direction of those differences is not always consistent, as it varies with current trends in substance availability and cost (3). However, in recent years, women exceed men in the abuse of prescription drugs, men use more alcohol and stimulant drugs than women, and the use of nicotine has been more equal across sexes (4). By contrast, animal studies have revealed more consistent trends in drug-seeking behavior indicating that females are more likely to initiate and maintain drug-seeking behavior, and they have a better response to treatment than males.

Sex differences in drug abuse, hormonal influences, and their implications for treatment have been extensively reviewed with regard to animal and human studies (3, 5–9). A recent finding that is important to our understanding of sex differences in drug abuse is that underlying aspects of addiction, such as compulsive and impulsive behavior (e.g., behavioral dyscontrol) are strong determinants of addiction, and differences in drug taking depend on several factors, such as type of drug, behavioral measures that are used, and sociocultural influences [e.g., Ref. (10)].

The present review focuses on elements of behavioral dyscontrol that increase vulnerability to drug abuse and add to sex differences to evaluate the importance of sex, hormonal conditions, as well as other individual differences, in developing treatments for drug addiction. In this review, findings from *laboratory animals* and *human research* will be discussed separately. We discuss major aspects of behavioral dyscontrol and how they interact with sex differences to contribute to vulnerability to drug addiction and receptivity to treatment. Behavioral dyscontrol is defined as maladaptive influences, behavior that an individual has difficulty stopping. It includes impulsivity, compulsive binge-like behavior, and it is particularly prevalent during adolescence (vs. adulthood), the time when drug addiction is most prevalent. In several reviews of factors that underlie drug addiction, these topics have emerged as the strongest contributors to addictive behavior, and there are interactions among them. The goal of this review is to bring the sex differences and behavioral dyscontrol literature together within the drug-abuse context to better understand critical vulnerability factors for drug addiction and how that knowledge may be useful in developing prevention and treatment strategies. Parallels are also drawn to other forms of addiction, such as food addiction (11–13), to illustrate that mechanisms of dyscontrol that underlie these addictive behaviors are similar. Thus, it may be instructive to target elements of dysregulation such as impulsive and compulsive behavior when developing strategies to treat drug addiction. For each of the following determinants of drug addiction, results from animal and human studies will be considered separately with respect to sex differences.

The study of sex differences in addiction has branched into several directions since our initial work of the late 1990s [see Ref. (14)]: the next section (Section 2) compares *sex differences* observed in *human and animal models* of drug abuse to understand how this factor affects addiction potential. Section 3 focuses on the *underlying processes of addiction*, such as *impulsivity that leads to drug seeking*. Thus, differences in addictive behavior in rats selected for high vs. low impulsivity (HiI vs. LoI) will be discussed and results extended to human drug addiction. Section 4 considers compulsive behavior that makes addictive behavior persist by comparing sex differences in *compulsive, binge-like characteristics of addiction* using selectively bred rat lines that were bred to binge drink a saccharin (SACC) solution (HiS) vs. rats that consume low to normal levels of SACC (LoS). These HiS and LoS rat lines are genetically predisposed to show high vs. low levels of drug seeking. These findings are discussed with respect to food addiction and its similarity to drug addiction. Section 5 compares sex differences during a *critical developmental* period (adolescents vs. adults) on measures of behavioral dyscontrol and drug addiction. Comparing different ages is a natural study in behavioral dyscontrol, as adolescence is the time when most humans express higher rates of impulsivity, compulsivity, and drug-seeking behavior compared with adults. Finally, Section 6 considers sex and individual differences in response to *treatment for behavioral dyscontrol and drug addiction*. Novel treatments are discussed, such as environmental enrichment, competing rewards/activities (e.g., exercise), and consequences (positive and negative). Pharmacological treatments are also discussed, such as medications to target underlying factors in addiction, such as impulsivity and anxiety. Self-sustaining treatments and customized treatments for addiction-prone and -resistant phenotypes are examined, as well as novel treatment combinations.

SEX AND HORMONAL INFLUENCES ON DRUG ADDICTION

Sex differences in drug addiction is an area of research that has received increased attention since it began over 15 years ago, when the early studies were first reviewed (14), to the present when research in both sexes at all levels of animal research is recommended (15), and will be mandated by NIH (16). Sex differences in drug addiction have been discussed in recent reviews of animal and human studies (3, 5–8, 17). In non-human animals, the direction of the sex differences generally favors greater avidity for drugs in females than males, and this is mainly due to hormonal differences. However, sex differences in studies of drug addiction in humans are less clear, as they are influenced by both hormonal conditions and societal factors (3). A key factor in understanding sex differences in drug addiction is that in females estrogen increases drug-seeking and drug-rewarding effects, whereas progesterone (PRO) decreases drug-seeking behaviors to the levels of males. By contrast, male hormones (e.g., testosterone) have little influence on drug addiction. The importance of sex differences and hormonal conditions in addictive behaviors in animal and human research has been recently reviewed (3, 5, 7, 8, 17–20) and is summarized in separate sections below along with suggestions of areas where future work is needed.

Laboratory Animals

Preclinical findings on vulnerability factors in drug abuse have been extensively reviewed in recent years [e.g., Ref. (5–7, 17, 18, 21–28)]. These reviews also indicate that sex differences occur in each phase of the addiction process ranging from initiation (acquisition) to maintenance, escalation, withdrawal, and relapse. In general, female animals exhibit greater vulnerability than males to drug-seeking behavior during most of these phases. An exception is that during drug withdrawal (26, 29–31), and when considering other negative or punishing effects of drugs (22, 23), males generally show more susceptibility than females to these negative drug-related effects. While sex differences in animal research occur across most phases of addiction, and they are consistent, the effects are modest in size. Observing a sex difference effect in drug addiction research is usually depend on the use of drug naive animals, low-to-moderate drug doses, and/or relatively demanding reinforcement schedules. Sex differences are not as likely to be found at high doses, or when access to the drug requires minimal effort, as ceiling effects occur.

However, there are relatively few reports of substantial sex differences in humans compared to the stronger sex-specific effects found in animals, which may be explained by environmental conditions. In experimentally naive animals, background conditions and experimental environments are minimal and typically the same for all animals, focusing on one variable, sex differences or hormonal conditions, with only minimal non-drug rewards available in the drug-taking environment (e.g., food, water). Thus, sex differences in drug seeking are more likely to emerge in animals (vs. humans) and be attributed to the rewarding effects of the drug, as the drug is a highly salient commodity. By contrast, in human studies, participants are not drug naive, there is environmental diversity (vs. uniformity), and historical factors as well as concurrently available of competing rewards can also influence self-reports of the rewarding effects of abused drugs. Another difference is that drug abuse is measured by actual drug intake in animals, whereas it is measured by self-report and choice or hypothetical choice in humans.

Humans

Sex differences in drug effects are reported in humans, and they are similar to those found in animals; females generally exceed males in drug use, although to different degrees with different types of drugs (5). For example, in recent years, women were more likely than men to use prescription drugs, such as sedatives, tranquilizers, and opioids for pain, whereas men were more likely to use illicit drugs (32). Overall, in humans, females are more avid drug seekers than males with regard to several drugs of abuse, such as alcohol (33), amphetamine (34), cannabinoids (19), cocaine (14, 20), nicotine (35), opioids (36), and phencyclidine (37). By contrast, as reported in studies with rats and monkeys, males generally show more susceptibility than females to negative drug effects, such as drug withdrawal (38).

Sex differences in drug addiction in humans are strongly influenced by biological conditions such as estrogen and PRO levels (39) and the PRO (P) to estrogen (E) ratio (P/E) (40) during different phases of the menstrual cycle that has been suggested as an index of hormonal status in humans (40). However, sex differences in drug addiction are also determined by sociological as well as biological factors (10, 17). For example, when considering sex differences in human alcohol and opioid use in the 1700s, and comparing that to alcohol, opioid use in the late 1800s to early 1900s, it is clear that as social norms and legal policy changed, drug-abuse patterns have shifted in women and men over time (17). Kornetsky (10) illustrated that due to cultural changes and changes in job opportunities, family structure, and other social factors, alcohol and opioid abuse were more common in women than men in the 1800s, but in the 1900s, men exceeded women on use of most drugs, and those patterns shifted, depending on the drug, in the late 1990s to the present.

Current Research on Sex Differences in Addiction

The study of sex differences in drug addiction did not begin in earnest until about 1998 [see Ref. (14)]. In recent years, the study of sex differences (41) and the impact of ovarian hormones (42) have expanded exponentially and taken on several new directions. For example, to better understand the differences and commonalities between sex differences in both laboratory animals and humans, animal research models have been developed to represent the human condition, such as modeling fundamental diagnostic criteria used in humans (43, 44) and modeling reduced sensitivity to treatment of drug-seeking behaviors, such as escalation (45, 46) and relapse (47, 48). The goal is not only to study sex differences in drug addiction in isolation but also to begin with the foundation of *behavioral dyscontrol* from which it arises, and consider major factors that constitute behavioral dyscontrol, such as impulsive choice and action, compulsive, binge-like drug seeking, and age (adolescence vs. adulthood). Age is especially important because adolescence and young adulthood is when the majority of drug abuse begins. It is ethically difficult to prospectively study this time period in humans; thus, it is essential to work in tandem with laboratory animal models. Biological and behavioral events that occur during this time may be crucial to finding solutions for prevention and treatment of addiction. Another novel approach of this review is to discuss sex differences in *novel treatments* that were developed in animals and tested in humans for drug addiction, and how their effects differ by sex and other vulnerability factors involving impulsive and compulsive behavior. This area has been neglected in most previous reviews, as no viable treatment strategies are currently available to adequately treat human drug addiction. However, the animal literature has begun to reveal several promising leads for prevention and treatment. Section "Sex Differences in the Effect of Novel Treatments for Behavioral Dyscontrol and Drug Addiction" will consider several novel treatments that might be self-sustaining in humans.

Thus, the present review will focus on *sex differences in behavioral dyscontrol*, highlighting key individual differences that can lead to drug addiction. These include *impulsive* drug seeking in the form of impulsive choice and action, such as *compulsive* behavior that leads to binging on drugs when extended access is available, and excessive drug seeking during abstinence that can lead to relapse. The sections that follow will examine sex differences in *impulsive* [for a detailed review, see Weafer and de Wit (49)], and other individual differences such as *compulsive*, binge-like intake of a sweetened liquid (SACC) [see reviews in Ref. (22–26, 28, 31, Carroll et al., under review)], and *age* (adolescence vs. adult) (50). Subsequently, behavioral and pharmacological interventions for reducing these forms of behavioral dyscontrol will be discussed. **Table 1** summarizes the vulnerable behaviors that will be discussed as predecessors and predictors of drug abuse, impulsivity, compulsivity, and age (adolescents vs. adults), and how treatment success varies by the vulnerability characteristic. These three vulnerability characteristics will be discussed in Sections "Sex Differences in Impulsivity and Drug Addiction," "Sex Differences in Compulsive Sweet Consumption as a Predictor of Drug Addiction," and "Sex and Age (Adolescent vs. Adult) Differences in Behavioral Dyscontrol and Drug Addiction," respectively, and compared by sex for laboratory animals and humans.

SEX DIFFERENCES IN IMPULSIVITY AND DRUG ADDICTION

Impulsivity, defined as behavior without forethought or consideration of future consequences, is a familiar form

TABLE 1 | Summary of individual differences in selected and selectively-bred rats showing trends in vulnerability to addiction, behavioral dyscontrol, reaction to aversive events, and treatment outcome as a function of sex, age (adolescent vs. adult), impulsivity (I), and sweet intake (S).

Vulnerable behaviors	Individual difference	Reaction to aversive events	Treatment outcome	Reference
Drug addiction	F > M	M > F	F > M	Anker and Carroll (6), Becker et al. (17), Carroll et al. (under review), Lynch et al. (51, 263), Perry et al. (53), Anker et al. (54), Cosgrove and Carroll (55)
	Adoles > Adult	Adult > Adoles	Adult > Adoles	Carroll and Anker (7, 263), Anker and Carroll (18), O'Dell et al. (57), Perry et al. (52), Anker and Carroll (56), Spear and Swartzwelder (50)
	Adoles > Adult		Adoles > Adult	Zlebnik et al. (58)
	HMI > LMI		HMI > LMI	Economidou et al. (71)
	HMI > LMI			Diergaarde et al. (77), Belin et al. (78), Dalley et al. (79)
	HiI = LoI HiI > LoI		LoI > HiI	Regier et al. (59) Anker et al. (54), Perry et al. (73), Poulos et al. (75), Diergaarde et al. (77)
	HiI > LoI		LoI > HiI	Broos et al. (69)
	HiS > LoS	LoS > HiS	LoS > HiS	Dess et al. (60, 61), Carroll et al. (25, 28, 62), Perry et al. (29), Anker and Carroll (56), Holtz et al. (63), Holtz and Carroll (23, 24, 64)
Impulsive action	M > F			Jentsch and Taylor (65), Bayless et al. (66), Burton and Fletcher (67)
	HiS > LoS HiI = LoI			Anker et al. (68) Broos et al. (70)
Impulsive choice	F > M			van Haaren et al. (72), Perry et al. (53), Koot et al. (74)
	F = M HMI > LMI HMI = LMI HiS > LoS		HMI > LMI	Perry et al. (73) Robinson et al. (80) Broos et al. (70) Perry et al. (52)
Sweet intake	F > M HiI > LoI			Carroll et al. (25, 28), Carroll and Holtz (22)

M, male; F, female; HiI, LoI, selected for high vs. low impulsive, delay discounting; HMI, LMI, high and low motor impulsive, 5-CSRTT; HiS, LoS, selectively bred for high vs. low saccharin intake.

of behavioral dyscontrol that has been linked to attention deficit/hyperactivity disorder (ADHD) and is a criterion for substance abuse, pathological gambling, and eating disorders [Ref. (81); see review by Fattore et al. (3)]. Impulsivity is often separated into two main forms: impulsive choice and impulsive action. *Impulsive choice* is defined as a preference for a small-immediate reward over a larger-delayed choice (82), whereas *impulsive action* is considered the inability to withhold a response until an appropriate time is signaled (83). Animal and human preclinical studies have shown that both forms of impulsivity are positively related to drug abuse [for reviews, see Ref. (27, 49, 84, 85)]. There is strong clinical evidence that greater impulsive choice is associated with the development of drug abuse (86), and lower impulsive choice is predictive of better treatment success (87). Results of studies in which both forms of impulsivity have been studied in animal and human research is discussed below.

Impulsive Choice

Impulsive choice is typically measured using procedures that assess preference for a small-immediate reward over a large-delayed reward over a range of delays to its receipt. One method to quantify impulsive choice is to determine how rapidly an individual discounts the value of the large alternative, as delays are imposed on its receipt. A steeper discounter (more impulsive) would devalue the larger or delayed alternative, and they would shift their preference to the smaller-sooner alternative at shorter delays. A shallow discounter (less impulsive) would tolerate longer delays for a larger reward. Impulsive choice (steeper discounting) is associated with drug abuse and decreased treatment success (85, 88), these findings may partially explain why animal and human females (vs. males) are more predisposed to choose drug abuse vs. healthy alternative behaviors (27, 73, 89).

Laboratory Animals

One of the first studies of sex differences in impulsive choice used a Y-maze to assess choice for immediate or delayed food in slightly food restricted rats (72), and females discounted the larger-delayed reward more than males. Subsequently, Perry et al. (52) conducted a similar study of impulsive choice for food using a two-lever operant conditioning chamber in which responding on one lever resulted in a small-immediate amount of food and responding on the other lever produced a larger-delayed amount. When this experiment was replicated with other groups of male and female rats that self-administered i.v. cocaine under a similar delay-discounting task, there were no sex differences. This was likely due to a ceiling effect since overall impulsivity for cocaine was much higher than for food (52). In a subsequent study, Perry et al. (73) compared male and female rats selected for high vs. low impulsivity (HiI vs. LoI), based on the delay-discounting task for food, on *acquisition* of cocaine self-administration, and on cocaine-primed reinstatement of cocaine seeking (a model of relapse). They found that both HiI males and females acquired cocaine self-administration faster than LoI males and females, and HiI females showed greater cocaine seeking during reinstatement than LoI females or either group of males (Hi, LoI). A similar study was conducted by Koot et al. (74) in mice that were divided into steep (more impulsive) vs. shallow (less impulsive) discounters based on a median split. Within the steep-discounter group females were more impulsive than males. Overall, while there are only a few studies of impulsive choice in animals, the results consistently support a moderately higher level of impulsivity in females than males.

Humans

In humans, sex differences in impulsive choice are more mixed. Women tend to be slightly more impulsive than men when making choices between real (lottery based) and hypothetical monetary outcomes [Ref. (90–93); but see Ref. (94)]. However, in some studies, no differences have been reported (95–100). Kirby and Maraković (94) reported that men were more impulsive than women when hypothetical money was a choice, but when real money was based on a lottery, men discounted money more steeply than women at the higher monetary values. Overall, women generally show greater impulsive choices for hypothetical rewards, but men show more impulsive choices for actual rewards.

In summary, regarding impulsive choice, results of animal studies suggest that females exhibited more impulsivity than males in the transition states of addiction, such as initiation and relapse or reinstatement of drug-seeking behavior. In humans, the methods are quite different than in animals, but women were more impulsive toward hypothetical rewards, and men were more impulsive for actual rewards [see Ref. (49)].

Impulsive Action

Impulsive action is typically considered an inability to inhibit non-productive or inappropriate responses (83), and in humans and animals, two tasks to quantify this form of impulsivity are commonly used, the stop-signal reaction time (SSRT) and Go/No-go tasks. These tasks signal periods of responding and non-responding, and failures to inhibit an inappropriate response are considered instances of impulsive action. During the SSRT, a subject must inhibit an ongoing "go" response when a "stop" signal is presented, making the task more difficult than the Go/No-go task in which the participant must respond to a "go" stimulus but inhibit a response following "no-go" stimulus. In these tasks, researchers consider *impulsive action* to be an increase in errors of commission (i.e., failures to inhibit responding to an inappropriate stimulus in SSRT, more responding during a no-go period, and longer stop-signal reaction times). These tasks are similar to the relapse aspect of drug addiction, whereby individuals are unable to withhold responding to drug-related cues (e.g., accepting a drink offer).

Laboratory Animals

In an animal study of impulsive action, male and female rats were compared on a Go/No-go task for food or i.v. cocaine infusions (68), and no differences were found in responding for food reward during the no-go period (impulsivity measure). However, females made more responses for cocaine infusions during the no-go period than males, and this was consistent with measures of impulsive choice (52). In the five-choice serial reaction time task (5-CSRTT), no sex differences were found in mice during acquisition or the challenging portion when long intertrial intervals (ITI), stress, and *ad libitum* food were tested (98). However, over repeated testing, females were more impulsive than males as indicated by premature responding (action impulsivity). In another 5-CSRTT study of young vs. adult rats, no sex or age differences were found in task acquisition, but females made more premature responses than males in the challenging task (long ITI) (67).

As in a previous study of impulsive choice (51), sex hormones were implicated in studies of impulsive action. For example, Jentsch and Taylor (65) compared intact and gonadectomized, male and female rats, in a 5-CSRTT study, and intact males made more premature responses than gonadectomized females during the acquisition and challenge (long ITI) conditions. Gonadectomy increased impulsive action in males and ovariectomy increased impulsive action in females, suggesting that both testosterone and estrogen are related to impulsive action in rats. In a recent study by Bayless et al. (66), comparing male and proestrus female rats on the 5-CSRTT, males showed greater impulsivity (premature responding) than females. Thus, there is an indication that sex and hormonal status are factors in measures of impulsive action.

Humans

In tests of impulsive action with humans, sex differences have been mixed, depending on the procedure employed. Under the Go/no-go procedure, males tended to commit more inhibitory errors than females (99, 100), but in other studies, there were no sex differences (93, 101). Similar findings occurred using a continuous performance task (CPT). In an eight-study meta-analysis of children with ADHD, boys consistently made more errors of commission (i.e., more impulsive) than girls (102), and there were similar findings in adolescent vs. adult smokers (103). However, in the SSRT, females had longer reaction times (more impulsive) than males (103–106); although, in a similar number of studies, no sex differences were found (93, 101, 106, 107). Thus, human sex differences in impulsive action may be procedure dependent. Males were more impulsive on tasks requiring inhibition of ongoing "go" responses (e.g., CPT and Go/No-go task), and females were more impulsive on the SSRT task (i.e., longer reaction times) that requires initiation of a response.

Sex differences in impulsive action also extend to drug addiction, and women drug users are more impulsive than men. Female heavy drinkers and adolescent smokers were more impulsive than males on the SSRT (103, 106) and CPT (108) tasks. Interestingly, the non-drug-seeking control males were similar or more impulsive than the female controls, suggesting a strong covariance of impulsive action and drug abuse in females vs. males. Estrogen reduced impulsive behavior in a SSRT task in humans (104), and women in the follicular phase, when estrogen levels are peaking, were more impulsive (longer reaction times) than during the luteal phase when the estrogen levels are low and PRO levels peak and decline. Overall, sex and sex hormones play a role in modulating impulsive action. Specifically, PRO reduced impulsivity (Smethells et al., under review); thus, using PRO as a treatment to target impulsivity may be effective for reducing addictive behavior (see Targeting Individual Differences with Repurposed Medications as Treatments for Addiction).

A general trend in sex differences in impulsive action in animals and humans is less clear than for impulsive choice; however, a wider range of tasks are used to assess impulsive action, and they may be accessing different elements of the behavior. In animals, males exhibit more impulsive action than females, but it is task dependent. In humans, women tend to show more impulsive action than men on several tasks [see Ref. (49)].

SEX DIFFERENCES IN COMPULSIVE SWEET CONSUMPTION AS A PREDICTOR OF DRUG ADDICTION

For many reasons (e.g., television advertising, changes in food production, and fast food access), changes in the U.S. culture over the last century have led to a condition where two-thirds of the population is overweight or obese, resulting in premature death due to metabolic syndrome, diabetes, heat disease, digestive disorders and associated cancers (109). The terms "food addiction," "hedonic overeating," and "food insecurity" (110) have been used recently to describe and explain chronic overeating leading to weight gain, and these concepts highlight underlying similarities between excessive eating and drug addiction. However, there is some disagreement that the behavioral and neurobiological mechanisms underlying this behavior are completely parallel to those involved with drug addiction [e.g., Ref. (3, 11, 12, 22, 28, 111–113)]. Nevertheless, recognizing similarities between "drug" and "food" addiction may be useful for designing treatment strategies.

Animal models have also been useful in understanding behavioral dyscontrol in food consumption as it relates to drug addiction. For example, sugar-binging rats extended this behavior to amphetamine (114), and rats selectively bred to consume large amounts of a SACC-sweetened liquid (HiS) showed faster initiation of heroin self-administration (62), with more animals per group acquiring drug use, escalating, and relapsing after forced abstinence, than rats bred for low SACC intake (LoS) (28). Other studies that model criteria for addiction in humans indicate that the HiS (vs. LoS) rats meet several DSM V (81) criteria for addiction, such as tolerance, difficulty limiting use, spending excessive time-seeking drug (29, 30), escalation of drug intake (115), impaired ability to regulate drug intake (51, 116), and continued use despite aversive consequences (117). HiS rats also showed impaired ability to regulate SACC intake (51). While sweet preference predicts all aspects of drug addiction, only a few studies in animals and humans have reported sex differences in these behaviors (28).

Laboratory Animals

One of the best examples of animal models of behavioral dysregulation in feeding that is related to drug addiction and obesity is from studies initiated by Dess and colleagues. They bred different lines of rats that ingested excessively high levels of a sweet SACC solution (HiS) or low to normal amounts of SACC (LoS). Their early studies also revealed greater sensitivity in HiS vs. LoS rats to several tastes, such as sweet, salty, and bitter (118), and they found more ethanol intake in the HiS than the LoS rats (61, 119). Subsequent studies with the HiS/LoS rat lines in our laboratory with cocaine or heroin showed that HiS rats exceeded LoS rats during all phases of drug addiction, including initiation, escalation, or binging on cocaine during long access, resistance to extinction when cocaine availability was terminated, and relapse or reinstatement of drug seeking instigated by brief exposure to cocaine, stress, or cocaine-related cues, even several weeks after cocaine self-administration had terminated [see reviews in Ref. (22, 25, 26, 28)]. In a recent study in our laboratory, the findings of SACC preference predicting drug self-administration were extended to other measures of reward, such ICSS, and HiS rats showed more cocaine-induced reward enhancement of intracranial self-stimulation than LoS rats (120). Converging results from many of these studies suggest that avidity for sweets and drug-taking behaviors are closely related, heritable, and substitutable (22, 25, 114), and they likely operate through common neural mechanisms [e.g., Ref. (121)].

A similar connection between sweet preference and drug addiction (e.g., HiS vs. LoS) was also found with outbred rats that were selected for high or low intake of SACC [e.g., Ref. (122, 123)], or other sweet substances, such as sucrose (124, 125), and opioid self-administration (126). The results were similar to those obtained in the HiS vs. LoS rat studies. The connection between drug addiction and overindulgence in food was recently modeled in a study by Yakovenko et al. (127) in which HiS rats exhibited more binge-like behaviors with access to high-fat or -sugar containing substances than LoS rats. This strong predictor of drug abuse has also been found to interact with sex. Sex differences in drug-seeking behavior were also examined in the HiS vs. LoS rats, and females exceeded males on drug seeking and intake. During the acquisition phase of drug self-administration, HiS and LoS females exceeded males in ethanol intake (119). During maintenance, females also consumed more ethanol (61, 119) and heroin (62) than males. HiS females also scored higher than LoS females on cocaine-induced locomotor activity and cocaine-induced sensitization of locomotor activity (116). Thus, HiS and female rats showed more cocaine-induced locomotor activity and sensitization than LoS and male rats.

Overall, the comparisons of HiS vs. LoS rats indicated that sex and SACC preference were additive predictors of behavioral dyscontrol in the form of drug addiction. Across several studies, the HiS females were ranked highest in drug seeking, followed by LoS females or HiS males, and then LoS males were lowest in terms of drug intake (22–25, 28). When the results of these studies were translated into DSM V (81) criteria for addiction (43), HiS rats exceeded LoS rats on several addiction criteria, such as tolerance, difficulty limiting use, excessive time-seeking drugs, impaired control over use, and despite punishment, as well as resistance to withdrawal effects [see reviews in Ref. (22–26, 28)]. Thus, the animal findings lend strong support to the conclusion that drug and food addiction have many similar characteristics.

Humans

In humans, parallels between food and drug addiction are beginning to emerge, but these areas have remained separate in the feeding literature, except for a few isolated reports. The relationship between substance abuse disorders and avidity for sweets has also been reported in human alcohol (128), cocaine (129), and opioid abusers (130). However, a more recent trend in hedonic overeating, often called "food addiction" that results in overweight and obese individuals in nearly two-thirds of the U.S. population, is nearly equally distributed in males and females (131) or worldwide, slightly more prevalent in women than in men (13). Other eating disorders, such as bulimia and anorexia

nervosa, have not been closely studied for sex differences, as most eating disorders have predominantly occurred in females [see edited volume by Avena (132)], but the lack of sex differences in the Centers for Disease Control and Prevention (131) data may be due to several factors, such as food is an essential commodity, whereas addictive drugs are optional. Nevertheless, the parallels and differences between addiction to food vs. drugs may be informative for prevention and treatment strategies. Currently, there is little human literature regarding an interchange between food and drug addiction, and how that might vary by sex. However, this interchange has been clearly demonstrated in rats, and females exceed males on both hedonic overeating and drug addiction (22, 28). The translational implications for humans are that as weight loss is effectively pursued, individuals will be at higher risk for drug addiction, and this is more likely to occur in females than males.

In summary, while animal data clearly indicate a strong connection between food- and drug-seeking behavior, and females show more drug seeking and sweet preference than males, there are not enough data available at this time to determine whether parallels in hedonic overeating and drug addiction extend to humans.

SEX AND AGE (ADOLESCENT VS. ADULT) DIFFERENCES IN BEHAVIORAL DYSCONTROL AND DRUG ADDICTION

Age (adolescence vs. adult) is an important individual factor to consider when evaluating the contribution of sex and behavioral dyscontrol to addiction, because adolescence is when biological (hormonal) and behavioral (impulsivity, risk-taking) changes emerge in animals and humans, and these are major variables contributing to drug addiction. Laboratory animal and human adolescents and adults have been compared and reviewed in several previous studies of drug addiction for their differential responding to both the rewarding and aversive aspects (136–133). Generally, adolescents are more sensitive to the rewarding effects of drugs of abuse, but they have reduced sensitivity to the aversive effects. Importantly, animal and human studies indicate that adolescents are also more sensitive than adults to other major factors included in this review that have been noted to predict drug addiction, such as impulsivity (56, 134) and compulsive sweet intake (134–136). Sex differences in the development of addictive behavior are difficult to study during the adolescent period in animals, as adolescence is only about 30 days in rodents. In humans, there is mostly epidemiological research on behavioral dyscontrol and adolescence vs. adulthood, which has been informative, but prospective studies are limited due to the difficulty of studying human adolescents. The following sections review age-dependent effects of alcohol use in animals and humans, since it is a widely abused and well studied in the adolescent population (2).

Laboratory Animals

The animal literature indicates that adolescent rats self-administer about two to three times more alcohol than adult rats [e.g., Ref. (137–139)]. Research with rats has also established that early alcohol consumption in adolescent-exposed rats produced more impulsive risky choices in adults, compared to control rats that did not have adolescent alcohol access (140, 141). Contrary to human studies, female rats tend to consume more alcohol during adulthood than adolescence [e.g., Ref. (138, 142)]. The higher intake of alcohol in male adolescent rats, compared with adults, is likely due to a reduced sensitivity to the alcohol-induced sedative/hypnotic (143), hypothermic (144, 145), motor impairing (146), anxiolytic (147), and anxiogenic effects (148). This decreased sensitivity combined with a slightly higher rate of alcohol metabolism potentially enables adolescent rats (and perhaps adolescent humans) to consume more alcohol (144, 145, 149). While adolescent rats were more vulnerable than adults to various forms of addiction (150–152), opposite age effects have been reported (133, 153). Several studies have investigated the effect of adolescent drug exposure on subsequent adult drug use in animals (56) and humans (154, 155), and the findings indicate that early exposure facilitates adult drug abuse. Few studies have compared sex differences in rat studies of adolescence and addiction. In one study, rats self-administering cocaine were exposed to physical exercise as a treatment, and it was more effective in adolescents than adults (58). More details on treatment are presented in Section "Physical Exercise."

Humans

Although few studies have compared sex and age with respect to drug addiction, one study indicated that in humans, young-adults (ages 18–25) drink more alcohol than older adults (ages 35–54) [e.g., Ref. (156)]. For instance, in the Naimi study, binge drinking (>5 drinks per sitting) occurred about two to three times more frequently in younger adults than older adults, with males far exceeding females across all age groups. Age of exposure to alcohol also interacted with other risk factors for drug use, including impulsive and risky behavior. It has been found that those whose initial alcohol problems began in adolescence (age 13–17) are more impulsive than controls. Impulsivity was observed in early drug use (157–160) and later (38–46 year olds) after drug use had become fully established (161–166). These results suggest that exposure to alcohol early in life may increase impulsive and risky behavior, and adolescence may be a critical period when drug use alters prefrontal brain development leading to increased impulsivity [Ref. (167); see reviews by Brown and Tapert (168)]. The earlier the age of initial alcohol exposure, the poorer the prognosis for alcohol abuse in adulthood, and this can result from ease of access. For example, in the case of nicotine, second-hand smoke in children and adolescents yields nicotine content similar to actual smoking (169). Thus, parental smoking can accelerate health risks from smoking in addition to smoke inhaled by adolescents who use tobacco.

Dom et al. (164) found that the age of an alcohol problem onset was important for increasing impulsive choice that is predictive of further drug use. The rate of this increase when compared to controls, however, was only significantly steeper (i.e., impulsive choice was greater) for alcoholics whose alcohol problems started earlier in life (<25 years old) but not for alcoholics whose alcohol problems started later in life (>25 years old). Given the small number of females included, sex differences could not be

determined; however, the findings suggested an age-dependent relationship between the onset of an alcohol problem onset and impulsive choice. Thus, early alcohol exposure may cause increased levels of impulsive and risky behavior later in life leading to more drug abuse.

Taken together, the animal and human research suggests that age (adolescence vs. adults) is a significant vulnerability factor that interacts with other major factors, sex and impulsivity, and since males consume more alcohol than females during adolescence, this may result in enhanced vulnerability for alcohol abuse in males later in life.

SEX DIFFERENCES IN THE EFFECT OF NOVEL TREATMENTS FOR BEHAVIORAL DYSCONTROL AND DRUG ADDICTION

In previous attempts to develop treatment for drug addiction, receptor pharmacology guided medication development. Several medications were designed to act on transmitter systems involved in drug addiction, and a consistent finding in these studies was that the treatments were more successful for female than male animals. For example, female rodents showed a greater reduction in cocaine self-administration than males when treated with kappa opioid agonists, spiralodine (170), bremazocine (171), a $GABA_B$ agonist, baclofen (172), a corticosterone synthesis inhibitor, and ketoconazole (173). In more recent studies with rats modafinil (an analeptic drug) decreased methamphetamine (METH) induced reinstatement (relapse) in both males and females. Other studies compared treatment effects bremazocine, a kappa opioid receptor agonist, in female and male monkeys self-administering orally delivered PCP (55), while females consumed more drug than males (milligram per kilogram), they reduced their drug intake more than males with bremazocine (171) treatment (see **Table 1**). However, most of those treatments failed to show efficacy or had undesirable side effects when translated to humans.

Despite these previous innovative treatment attempts and their success in animals, there are currently no safe, non-addictive, effective treatments for reducing the morbidity and mortality of drug addiction that are useful in humans, except for agonist therapies (e.g., methadone, buprenorphine) and drugs that have modest effects on relapse to smoking (e.g., varenicline – Chantix) or alcohol abuse (e.g., naltrexone). This is indicated by epidemiological reports that the rates of most forms of addictive behavior have remained steady or increased over the last decade, and there are endless new forms of addiction (e.g., designer drugs, bath salts, etc.) that defy treatment (32). Thus, development of treatments for drug addiction is a high priority. Of the studies that show some promising initial findings, very few have compared males and females. A review of 280 treatment studies for substance abuse disorders in men and women that were published between 1975 and 2005 indicated better treatment outcomes for women than men (174). However, their later analysis of the multi-site combined pharmacotherapy and behavioral interventions for alcohol dependence program (COMBINE), including 1383 men and women, reported that while there were sex differences in those seeking treatment for alcoholism, there were no sex differences in the combined treatment condition. Women responded to naltrexone treatment combined with a medical management control condition similar to men (175).

A novel approach to designing new treatment strategies is to target factors that underly drug addiction. For example, behavioral dyscontrol is common to many forms of addiction; thus, treatment models can be designed to remedy this underlying aspect of drug abuse. The reinstatement (relapse) model has been useful for this purpose, as it portrays several aspects of the drug addiction process that occurs in humans, such as *acquisition* or initiation of drug self-administration, steady *maintenance* intake, *escalation or binge-like* intake of drugs, persistence of drug seeking (drug-lever responding) during *extinction* or *abstinence* when the drug is no longer available (*compulsive drug seeking)*, *reinstatement* or *relapse* of drug seeking following experimenter-administered injections of the drug or presentation of drug-related cues or stress stimuli, and *incubation of craving* (a time-dependent increase in drug seeking) that accelerates drug craving and leads to relapse after extended periods of abstinence (176, 177). Earlier studies with rats and rhesus monkeys indicated that behavioral interventions as well as medications have had some success in reducing drug-motivated behavior, and some of these studies indicated that females were more responsive to treatment than males [see review by Carroll and Holtz (22)].

Much of the animal findings regarding medications for drug addiction have generally not translated to effective treatments for drug abuse in humans. Thus, recent animal studies have focused on novel treatments for drug addiction that could be self-sustaining in humans. These include (1) *using natural consequences* such as *non-drug rewards* or positive events (environmental enrichment) that a drug-abusing individual might encounter in the environment that would compete with drug use (e.g., social interaction, exercise). Also, negative consequences, such as punishment for drug use are naturally built into the environment and can be programed to reduce drug use. (2) *Targeting factors that underlie behavioral dyscontrol*, such as *impulsivity or anxiety* by repurposing medications designed to relieve these underlying behaviors that can drive drug addiction. For example, PRO [e.g., Ref. (40)] or atomoxetine (ATO) could be used for anxiety, impulsivity, or other forms of behavioral dyscontrol that are associated with ADHD, and (3) combining two or more novel behavioral and pharmacological treatments.

Environmental Enrichment

A widely studied and promising approach for reducing or preventing the development drug addiction (as a form of behavioral dyscontrol) has been to enrich the environment with non-drug rewards [see reviews in Ref. (27, 28, 178, 179)]. This has been a successful treatment method for reducing many aspects of drug addiction, and it is well supported by extensive preclinical and clinical evidence. However, this method has not been widely studied with respect to individual differences, such as sex. In earlier studies, a commonly used method of environmental enrichment for reducing drug-seeking behavior was to use preferred foods (180), or place animals after weaning in a larger social environment (vs. isolated) that contains novel objects and activities (181). Non-caloric sweet substances (e.g., SACC) were also effective as competing rewards to reduce drug seeking in rats [e.g., Ref. (55)]

and rhesus monkeys [e.g., Ref. (182, Carroll et al., under review)]. In these environmental enrichment studies, females reduced drug taking more than males when they had sweet substances concurrently available [see reviews in Ref. (22, 25)], or when they had prior access to a sweet substance (183, 184). Studies with female and male monkeys self-administering orally delivered PCP (55) or cocaine (Carroll et al., under review) indicated that females consumed more drug than males (milligram per kilogram), but females also reduced their drug intake more than males when treated with access to a non-drug reward, SACC (see **Table 1**). While these therapeutic advances were effective and providing palatable substances was a powerful intervention for drug abuse [see Ref. (22–25, 28)], more recent studies have sought to provide a healthier environmental enrichment alternative, focusing on social and physical elements of the environment.

Social

Taking drugs in a social environment is important for humans and non-human primates. In behavioral economic terms, some drugs and social rewards work together as complements, and each increases the other, such as drinking and smoking at a social gathering, or smoking while talking on the phone. However, in other cases, social stimuli and drug-taking work as substitutes, whereby one reward may replace the other (173, 185). Thus, the rewards of social interaction can be used as substitutes to reduce drug taking (181).

Laboratory Animals

Rearing environment is an important factor in the development of drug self-administration. To examine this, rats were raised in enriched conditions (EC) with a large environment, several cage mates, and a variety of toys and exercise devices, whereas rats raised in the isolated condition (IC) were singley housed in smaller standard rat cages. As adults, rats were allowed to self-administer drugs, and EC rats self-administered less amphetamine than the IC rats (181). Lower rates of responding in EC rats (vs. IC) indicated that the enriched environment reduced motivation for amphetamine (lower break point on a progressive ratio schedule) (186). The EC rats were also less impulsive during the acquisition of an impulsive action task compared to IC rats (187), and they were less impulsive than IC rats on an impulsive choice procedure (73). These findings suggest that early exposure to an enriched environment may alter sensitivity to drugs of abuse and blunt the development of drug abuse in adulthood; however, sex differences were not often considered in these studies.

Humans

In humans, non-drug rewards delivered in a contingency management (CM) format successfully reduced drug dependence [for a review see Ref. (188)]. In general, CM programs promote drug abstinence through a combination of positive reinforcement for drug-free urine samples. For instance, voucher-based reinforcement therapy in which medication compliance, therapy session attendance, and negative drug screenings reinforced with vouchers to local business (e.g., movie theater, restaurants, etc.) directly reinforces drug abstinence, provides competing reinforcers, enriches the environment, and it is a robust treatment across a broad range of abused drugs (189). Another example of using social rewards to reduce drug addiction was given in the Naimi et al. (156) study, comparing younger and older adults, who reported that enhancing non-alcohol-related campus social programing had decreased alcohol use.

In summary, both animal and human studies indicate that environmental enrichment is an important intervention that moderates the development and progression of drug addiction. There is little information regarding sex differences in social reward at present; however, once drug use patterns have developed, non-drug rewards, such as social interaction, have the advantage of being self-sustaining and are effective in both sexes.

Physical Exercise

There is accelerating evidence that physical exercise is a useful treatment for preventing and reducing drug addiction [see reviews in Ref. (28, 178, 190, 191)]. In some individuals, exercise has its own rewarding effects, and a behavioral economic interaction may occur, such that physical and social rewards of exercise can substitute for the rewarding effects of drug abuse. Exercise has also been a valuable treatment for slowing cognitive decline in patients with dementia [e.g., Ref. (192)], health-related problems in obesity [e.g., Ref. (193)], and in psychiatric disorders, such as anxiety (194), depression (195), and schizophrenia (196). The value of this form of treatment for drug addiction in laboratory animals and humans is that exercise, if it can substitute for the rewarding effects of drugs, could be self-maintained over an extended period of time. Work to date in laboratory animals [for review, see Ref. (191)] and humans [for review, see Ref. (178)] regarding exercise as a treatment for drug addiction supports this hypothesis.

Laboratory Animals

Recent animal studies have consistently reported that exercise reduces drug-seeking behavior in both self-administration and conditioned place preference (CPP) studies [see reviews in Ref. (28, 178, 190, 191)]. In rat studies, exercise in the form of wheel running decreased cocaine-seeking behavior in males and females across all phases of the drug addiction, including acquisition (197), maintenance (58, 198–201), escalation/binging (58, 201, 202), extinction (203–205), and reinstatement/relapse (203–207), including extended relapse or incubation of cocaine-cue-induced reinstatement (craving) over extended time periods (208). Voluntary running is also effective if it is provided in the home cage environment, and drug-seeking behavior is tested separately in an operant chamber [e.g., Ref. (203, 204, 206, 208)].

There have been few studies directly comparing sex differences on the effects of exercise as a treatment to reduce drug-seeking behavior [see review by Zhou et al. (190)]; however, limited evidence shows that concurrent access to a running wheel (vs. a locked wheel) reduced cocaine self-administration more in female than male rats (198). Few studies have compared sex and age in treatment studies with rats. However, in rats self-administering cocaine, physical exercise was more effective in adolescents than adults (58). Exercise may be a more suitable treatment than pharmacological interventions in adolescents who are undergoing critical phases of development and brain maturation (209, 210). In animal studies, both concurrent exposure to exercise (198, 211)

and prior exposure and/or exposure in a different environment (200, 201, 203, 204, 212–215) effectively reduced drug seeking.

While both *concurrent* and *sequential* approaches are effective, these data show actual reductions in drug intake (vs. drug seeking) with *concurrent* access to exercise (198, 211) and other non-drug rewards (28), while previous studies using *sequential* access to exercise report that initiation of drug self-administration (213) or drug-seeking behavior during extinction from former access (relapse) is suppressed [e.g., Ref. (212)]. While concurrent and sequential access to drug and exercise has not been directly compared in rat studies, there may be an advantage to allowing concurrent access or at least presenting both in a contiguous time frame. For example, a previous within-subjects study using treatment with a non-drug reward (SACC) in monkeys, with both concurrent and sequential access, verified a more robust reduction in drug intake with *concurrent* access to SACC than sequential access (183). Thus, comparing concurrent vs. sequential access, and contingent access [e.g., Ref. (188)] with exercise as a treatment is an important area for future research.

Recent studies in rats have examined sex differences on the effect of previous exercise exposure in a different environment on subsequent drug seeking during different parts of the drug addiction process. Ehringer et al. (199) indicated that females significantly lowered their alcohol consumption compared to males when a running wheel was available, but not during the reinstatement (relapse) component. Smith et al. (204) did not find a sex difference in the effect of wheel running on cocaine self-administration or reinstatement, but they found that females decreased drug seeking more than the males during the first few extinction sessions when a running wheel was available. However, two studies directly compared the effect of exercise in male and female rats self-administering cocaine (198) or on cocaine-primed reinstatement (216), and both found a better effect of exercise in reducing drug seeking in females than males. In other studies, wheel running reduced cocaine (206) and nicotine acquisition (213) and nicotine seeking during reinstatement (212). Nevertheless, in the cocaine study (206), males' cocaine seeking was also reduced more than females' by entry into the locked wheel control condition, and an opposite sex difference was found in the nicotine study (212) whereby females' nicotine seeking was reduced more than males by entry into the locked wheel control condition. In contrast, Smith et al. (204) did not find a sex difference in the effect of wheel running on cocaine self-administration or reinstatement, but they found that females had decreased extinction responding compared to males. Results of these and other initial studies [e.g., Ref. (58, 198, 205, 216, 217)] suggest that the effects of exercise are strongest when exercise is available during the critical phases of addiction (acquisition, maintenance, escalation, or drug-primed reinstatement), and sex differences (F > M) are found. More work is needed with both males and females during all phases of addiction to identify the most effective treatment strategy. While numerous studies exercise as a treatment for addiction have been conducted with both male and female rodents [see Ref. (191); **Table 1**] using both drug self-administration and CPP models, approximately 80% of the work has been done with males. It was encouraging that in most of the studies reviewed, exercise had an advantageous effect on preventing or treating CPP for the environment where drug exposure occurred.

In general, existing studies suggest that physical exercise is an effective deterrent to drug seeking and abuse, and it offers a healthy, self-sustaining treatment for drug abuse. However, more work is needed to evaluate the potential for this treatment in both males and females and its effect on individuals with other vulnerabilities for drug abuse. Moderate use of this treatment may be the key to its success. For example, non-drug rewards such as excessive amounts of sweet drinks also reduce drug addiction in animal models (185), but they can also become addictive (112, 218) and lead to other unhealthy consequences. Similarly, while it is uncommon, too much exercise could result in health issues, such as exercise addiction and exercise-induced anorexia (3, 219).

In summary, emerging evidence from the animal literature indicates that exercise is a healthy candidate for treating drug abuse, but not enough data are available to make a strong prediction regarding sex differences in treatment efficacy or the best strategy for delivering this treatment, whether it is concurrent with drug access, sequential, or contingent upon non-use of drug [e.g., Ref. (188)]. In previous rat, monkey, and human studies, concurrent and/or contingent access to drug and non-drug rewards have been the most effective strategies for reducing drug abuse [see Ref. (173, 178, 185, 188)].

Humans

Compared to the large number of laboratory animal studies that have prospectively examined physical exercise as a potential treatment for drug abuse [see Ref. (191)], human studies are few, and the results are not as definitive. Most of the human data are cross-sectional, but importantly they involve cigarette smoking, which is easier to study than illicit drugs because large sample sizes are available and it is a legal drug. However, in a recent review of the clinical literature, Linke and Ussher (220) concluded that there is a lack of prospective randomized clinical trials (RCT) that are needed to study the effects of exercise not only nicotine, tobacco, and alcohol abuse but also for other drugs that have a high rate of abuse, such as METH. For example, in several studies, higher abstinence rates were reported at 3 months (195, 221, 222), 6 months (223), and 12 months (221) after an exercise regimen; however, other studies found no significant effects of exercise on abstinence (220, 224). In a recent review of the literature on physical activity and drug abuse, Bardo and Compton (178) noted that the impact of physical activity on the reduction of drug intake in humans has also been shown mainly in observational studies, both cross-sectional and prospective. Survey research has also indicated that higher levels of physical activity are associated with lower alcohol, tobacco, and marijuana use (225).

Reviews of these correlational studies emphasize a need for RCT in alcohol, tobacco, and marijuana addiction, and initial studies on the use of exercise programs for treatment tobacco use have shown improvement for smoking cessation [e.g., Ref. (223)]. However, others have shown no benefit, possibly because they were underpowered. There are efforts to promote physical activity as an adjunct for smoking cessation, especially among women (224), but key parameters, such as type and intensity (dose) of

physical activity, have not been determined. Aside from the few studies on tobacco and alcohol, there are no reports of RTC studies showing improvements in outcomes on drug addiction using exercise as an inpatient treatment. However, a RTC study was recently reported by Rawson et al. (226), whereby they used 8 weeks of exercise as a post-residential treatment for METH addiction, showed a significant reduction in use (confirmed by urine screens) in participants who had been using meth 18 days or less a month. Earlier reports from this group showed that exercise also resulted in improvements in fitness and heart rate measures (227, 228). In another human study on cigarette smoking, it was reported that individuals were more successful in maintaining abstinence if they continued their exercise program on their own after the experimental intervention ended (221).

Animal and human research on physical exercise as a treatment for stimulant addiction indicates that this is one of the most promising treatments on the horizon. However, there are few studies of sex differences in outcome of this form of treatment. Initial animal work suggests that females and adolescents are more responsive to this form of treatment than males; however, further animal work and extension to human RTCs is needed.

Negative Environmental Consequences

For drug abusers, punishment exists in natural settings, in the form of natural consequences for drug use, such as loss of friends, jobs, money, and to promote survival. It has seldom been proposed for treating drug abuse in humans, although treatment methods for alcoholism, such as antabuse, re-setting voucher amounts in VBRT after positive urine samples, and revocation professional licenses for drug addition, are forms of punishment that human drug abusers encounter. While treatments based on negative environmental consequences have not been systematically explored in humans, animal studies indicate that negative consequences for drug use may be an important aspect of treatment to consider. However, only a few animal studies have modeled the effect of punishment on drug seeking and drug self-administration, and results indicate that mild forms of punishment are effective and enduring. For example, after several months of ethanol intake, rats continued to drink alcohol despite the consequences of footshock (229) or bitter tasting quinine (230), and this aversion-resistant alcohol intake is considered to be a model of compulsive drug abuse in humans [e.g., Ref. (231)]. However, in some animals, these aversive pairings with drug self-administration reduce drug intake. The extent to which rats have reduced sensitivity to aversive effects of drugs interacts with individual differences, such as sex, age (adolescent vs. adult), sweet preference (HiS, LoS), and impulsivity (HiI, LoI). Given the individual differences in vulnerability to addiction (see **Table 1**), and response to treatment effects in rats and monkeys with biologically and behaviorally mediated differences (male/female, HiI/LoI, HiS/LoS and adolescent/adult), recent animal studies have considered individual differences in response to punishment as a treatment for drug abuse. Histamine was used as a chronic, aversive condition to validate a model of punished drug seeking that would represent the negative emotional and physical symptoms (hangovers, anxiety, anhedonia, and irritability) experienced by humans. Histamine (i.v.) was added to the i.v. cocaine self-administration in groups of male vs. female HiS vs. LoS, HiI vs. LoI, and adolescent vs. adult rats (23, 117). All groups suppressed responding for cocaine when histamine was added. Female and LoS rats showed a significantly slower (5–15 days) return to baseline levels of cocaine self-administration after histamine was terminated, and HiI and LoI rats showed no differences throughout the experimental phases (117). However, while adult rats also showed a greater punishment effect than adolescent rats when histamine was present in the cocaine solution, adults and adolescents recovered to baseline at the same rate (23).

Consistent with the histamine findings, in other studies, adult rats had more severe withdrawal effects than adolescent rats (232, 233). This was in contrast to findings that adolescent rats self-administering cocaine were more sensitive to the rewarding effects of drug (52, 120) and showed more severe relapse effects than adult rats (18). These findings highlight opposite effects that can occur in groups of rats when considering the rewarding vs. aversive effects as previously discussed by Riley (234), and they emphasize the importance of considering individual differences in vulnerability to drug abuse and response to treatment. These results with differentially vulnerable groups concur with recent treatment studies with baclofen, an agent that reduces cocaine-induced dopamine increase in the nucleus accumbens. Baclofen treatment reduced cocaine self-administration in the less vulnerable LoS animals, and potentiated it in the more vulnerable HiS animals (63). Similar effects were found with PRO that reduced escalation of cocaine self-administration in LoS rats and increased it in HiS rats (56). These studies highlight the importance of considering novel treatment mechanisms and individual differences in response to different treatments.

Targeting Individual Differences with Repurposed Medications as Treatments for Addiction

In recent studies, proposed novel treatments have addressed factors that underlie behavioral dyscontrol. For example, (1) impulsivity has been shown to be positively related to drug addiction, and repurposing medications that reduce impulsivity to treat underlying problems had initial success in treating drug addiction, as both male and female humans report that it reduces anxiety. For instance, ATO that is used to treat ADHD, and it reduced impulsivity in rats (235). (2) Hormonal conditions are known to increase (estrogen) or decrease (PRO) cocaine and nicotine-seeking behavior, especially in females, and PRO has emerged in animal and human studies as a promising medication that could be repurposed for drug addiction, as both male and females report that it reduces anxiety. For example, PRO is used in some oral contraceptives to treat problems with the female reproductive system, but when used for drug-abuse treatment, it counteracts the facilitatory effects of estrogen and reduces drug relapse [see Ref. (9)]. PRO also has anxiolytic effects that reduce drug seeking [e.g., Ref. (40, 236)]. (3) An additional strategy has been to combine two or more novel approaches, such as

medication (e.g., ATO, PRO) or behavioral treatments, that often has a greater impact than monotherapy in animals and humans.

In summary, research in animals has begun to target specific behaviors or hormonal conditions that are associated with addictive behavior, such as anxiety, depression, and impulsivity. In this section, we discuss two repurposed medications, ATO and PRO, as they have shown efficacy for treatment in rodent studies. Thus far, the results support the hypothesis that treating the underlying behaviors associated with drug abuse, with PRO and ATO, has potential for treating human drug abuse, and as discussed in Section "Treatment Combinations," adding these treatments (ATO or PRO) to a behavioral treatment in rats, such as physical exercise, results in an enhanced treatment effect. However, initial studies with these novel treatments have not fully examined sex differences, and sex is an important factor in drug abuse and its treatment.

Atomoxetine

Atomoxetine is a selective norepinephrine (NE) reuptake inhibitor that is used in humans for ADHD, inattention, and impulsivity associated with ADHD (237). These properties also make it a candidate therapy for psychostimulant addiction [for a review see Ref. (243)]. Like cocaine, ATO functions as a selective NE reuptake inhibitor that increases NE and dopamine in the prefrontal cortex (238, 239), but it does not have the abuse liability of other stimulants such as methylphenidate and desipramine (240).

Laboratory Animals

The relationship between ATO and impulsive behavior has been shown using several behavioral tasks in animals, such as the 5-CSRTT (76, 241), the SSRT task (76), and delay discounting (76, 235), but in other studies, ATO did not modify impulsivity (70, 241). In animal models of addictive behavior, ATO treatment was not effective at reducing cocaine self-administration in rats (71, 242–244). However, in combination with wheel running (245), ATO reduced cue-primed cocaine seeking in rats. It also reduced the strength of conditioned stimuli associated with nicotine in rats (246), attenuated nicotine withdrawal symptoms in mice (247), and reduced impulsive responding for i.v. cocaine in female rats (Smethells et al., under review). In our series of animal studies, we have modeled the combination approach with animals using some of the novel treatments described above. For instance, when combined with physical exercise ATO attenuated cocaine extinction, and cocaine-primed reinstatement in females but not in males (245). In a recent study, ATO was studied in rats responding for i.v. cocaine under a delay-discounting schedule with a small amount of cocaine available immediately, or a larger amount after a delay, treatment with ATO or ATO combined with PRO shifted the choice from the impulsive choice of a smaller-immediate cocaine delivery to the less impulsive choice of a larger-delayed cocaine delivery (248). However, the combined ATO–PRO treatment did not reduce impulsive cocaine seeking any further than either treatment alone. These animal studies suggest that ATO may be an effective treatment for psychostimulant addiction and for reducing impulsive behavior that underlies drug seeking.

Humans

Little data are available from human studies to confirm the potential for ATO to treat drug cocaine or other stimulant addiction. Some clinical investigations have not demonstrated a therapeutic effect of ATO on cocaine use (243, 244) or on the subjective effects of METH (249). However, Sofuoglu and Mooney (250) reported that ATO attenuated physiological and subjective effects of D-amphetamine. Others have shown fewer days of heavy alcohol drinking, less alcohol craving with ATO and longer abstinence from alcohol use with ATO treatment than with counseling by itself (251, 252).

Progesterone

Progesterone is used therapeutically in humans and for other primates for contraception, endometriosis, and maintaining pregnancies. It has also been shown in animal studies to indicate impulsive drug seeking and anxiety-like behaviors (248, 253, 254). PRO plays an important role in reducing drug seeking in rats [for review, see Ref. (6)], monkeys (255–257), and humans [for review, see Ref. (8)].

Laboratory Animals

In preclinical models, exogenously administered PRO and its primary metabolite, ALLO, attenuated acquisition, escalation of cocaine self-administration, and cocaine-primed reinstatement (54, 258) of cocaine seeking in rats (259, 260). Sex differences in the effects of ALLO have been reported with METH-primed reinstatement (64), and reinstatement was significantly reduced in female rats when they were treated with ALLO. However, ALLO had no effect on male rats [see Ref. (6) for a complete review]. In rats self-administering cocaine, concurrent running-wheel access was combined with PRO treatment, and the combination reduced extinction responding and cocaine-primed reinstatement in females but not males (216). However, in treatment-resistant males, the wheel access and PRO combination were more effective than wheel access or PRO alone. Studies of the effects of PRO on the rewarding effects of drugs show that rhesus monkeys maintained higher breakpoints for cocaine during the follicular than the luteal phase [Ref. (255); lowest dose only]. Also, rats self-administered more cocaine during the estrus phase of the estrous cycle, when estrogen levels are rising, than during proestrous, when PRO is relatively high (51, 259, 261–264).

Humans

In humans, during the follicular phase, when estrogen peaks, women report that cocaine is subjectively more rewarding than during the luteal phase, when PRO levels are have peaked [Ref. (265–267); see also Ref. (268)]. Human laboratory studies also indicate that PRO has an important role in nicotine addiction. For example, in a study of sensitivity to alcohol in women with premenstrual dysphoric disorder (PMDD), women reported a blunted physiological response and less intoxication after an alcohol infusion in the late luteal phase (high P/E) compared to the mid-follicular phase (low P/E) of the menstrual cycle indicating that PRO reduced the intoxicating effects of alcohol (269). In a recent study with both men and women, the effects of i.v. nicotine

were assessed as a function of sex and menstrual cycle phase, and men reported greater subjective reactivity to nicotine, but women showed more physiological reactions (39). In women, this effect was diminished during the luteal phase (higher P/E ratio) compared to the follicular phase of the cycle. Women reported less nicotine reactivity, fewer negative symptoms, and better task performance during the luteal compared to the follicular phase suggesting that a higher P/E ratio may have alleviated nicotine's negative effects. However, this sex difference finding was inconsistent with previous studies of the same i.v. nicotine infusion (250), oral intake (270), intranasal (271), and transdermal (272) nicotine administration, although phase of menstrual cycle was not a factor in these studies. The finding of greater subjective nicotine sensitivity in men vs. women was consistent with previous reports using intranasal nicotine (273) and smoked cocaine. Physiological findings of nicotine administration were consistent with the heart rate response (272) and diastolic blood pressure seen by others (274), but not with studies of nicotine and heart rate or blood pressure (250, 275).

In a recent smoking treatment study with either varenicline vs. placebo or nicotine patch vs. placebo patch in women, PRO levels were measured and compared to treatment outcome. This was the first study to identify a relationship between increasing levels of PRO and better abstinence outcomes in freely cycling women (236). The additive effect of rising PRO levels and treatment success was mainly found with the nicotine patch (vs. varenicline). There was a 23% increase in the odds of being abstinent within each of the 4 weeks of treatment in the luteal (PRO) + patch group. Based on animal research findings, clinical and preclinical researchers have examined the effects of exogenously administered PRO as a treatment for cocaine abuse. Comparable findings were obtained in humans who were treated with PRO. They showed reduced physiological and subjective rewarding effects of cocaine or cue-induced cocaine craving (8, 272, 276–279). Also, in clinical trials, PRO treatment reduced cocaine use in post-partum women in (280). Overall, there is strong accumulating evidence in human and animal studies, suggesting that, at least in females, PRO may serve as an efficacious pharmacological intervention for nicotine and cocaine addiction.

Treatment Combinations

Human studies suggest that combined therapies produce additive reductions in drug addiction compared to single treatment, and effects may vary with individual differences, such as male vs. female. For example, a review of 280 treatment studies for substance abuse disorders in men and women, published between 1975 and 2005, revealed better treatment outcomes for women than men (174). However, recent analysis of the multi-site COMBINE project, including 1383 men and women, reported that while there were sex differences in those seeking treatment for alcoholism and in those reporting alcohol treatment, there were no sex differences in the combined behavioral + naltrexone intervention, and the combination did not produce a better outcome than the individual treatments. Furthermore, women responded to naltrexone treatment and naltrexone + the control condition, medical management, similar to men (175). A recent review of combined pharmacotherapies (vs. single) for stimulant use disorder provided little evidence for an advantage of combined vs. monotherapies (281). Thus, further clinical work is needed with combined behavioral and pharmacological treatments for stimulant addiction to extend the promising results with laboratory animals to humans.

A recent study in rhesus monkeys showed reduced oral cocaine self-administration in female rhesus monkeys during the luteal phase of the menstrual cycle when PRO peaks compared with the follicular phase when estrogen peaks (Carroll et al., under review). In this study, monkeys received SACC concurrently with access to cocaine (0.4 mg/ml) under FR 4 schedules, and cocaine intake (milligram per kilogram) was compared in males and females during the follicular vs. the luteal phase of the menstrual cycle. When concurrent water was available with cocaine, females in the follicular phase consumed more cocaine than luteal females or males, an effect attributed to the lower PRO levels. Treatment with concurrent access to SACC along with cocaine resulted in reduced cocaine intake in both males and in females in both their follicular and luteal phases. An additive effect of PRO and SACC may have been occluded by a floor effect of SACC. However, a comparison of females across phases indicated a reduction in cocaine intake due to higher PRO (luteal phase) and to the additive effectiveness of PRO and SACC.

SUMMARY/CONCLUSION

Sex differences in behavioral dyscontrol were discussed in relation to drug addiction, as well as other factors that interact with sex differences to influence addictive behavior, such as impulsivity, compulsive binge intake of sweet substances, and age (adolescence). Each of these vulnerability factors has a substantial influence on behavioral dyscontrol and drug addiction. Not only do these individual differences explain the propensity for addiction in some individuals and not others but they also can be additive, presenting serious challenges to prevention and treatment once drug addiction has developed. Furthermore, these factors explain the propensity for addiction in some individuals and not others, which is instructive for designing prevention and treatment strategies. In addition, recent findings suggest that drug-prone individuals vs. those that are less sensitive to the aversive effects of drugs, further enhancing their vulnerability to addiction. Challenges in designing treatment for individuals with these addiction-prone characteristics are addressed by proposing novel treatments that take into account impulsive behavior and other forms of behavioral dyscontrol, such as excessive reward seeking, as well as sex, and hormonal conditions. Promising treatment strategies include behavioral manipulations, such as environmental enrichment (social and physical), such as exercise, or brief exposure to negative environmental consequences (e.g., punishment), and targeting individual differences with medications repurposed to address specific vulnerability factors, such as hormonal status (PRO), anxiety, or impulsivity (ATO), and combined behavioral and pharmacological therapies. Overall, the present review emphasizes that sex differences are intertwined with other major

personality (or age-related) differences (e.g., anxiety, impulsivity, compulsive binging), and these factors are inseparable from sex differences when considering promising treatments for addiction. Thus, when considering development of treatments for drug abuse, sex is important, but other factors, such as a tendency for compulsive or impulsive behavior and anxiety, are equally as influential. Initial preclinical work has indicated that targeting these personality factors and sex differences has resulted in successful treatments for addiction.

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Factors predicting cybersex use and difficulties in forming intimate relationships among male and female users of cybersex

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Sexual addiction otherwise known as compulsive sexual behavior is associated with serious psychosocial problems and risk-taking behavior. This study used the Cybersex addiction test, Craving for pornography questionnaire, and a Questionnaire on intimacy among 267 participants (192 males and 75 females) mean age for males 28.16 (SD = 6.8) and for females 25.5 (SD = 5.13) who were recruited from special sites that are dedicated to pornography and cybersex on the Internet. Results of regression analysis indicated that pornography, gender, and cybersex significantly predicted difficulties in intimacy and it accounted for 66.1% of the variance of rating on the intimacy questionnaire. Second, regression analysis also indicated that craving for pornography, gender, and difficulties in forming intimate relationships significantly predicted frequency of cybersex use and it accounted for 83.7% of the variance in ratings of cybersex use. Third, men had higher scores of frequency of using cybersex than women [$t(2,224) = 1.97$, $p < 0.05$] and higher scores of craving for pornography than women [$t(2,265) = 3.26$, $p < 0.01$] and no higher scores on the questionnaire measuring difficulties in forming intimate relationship than women [$t(2,224) = 1$, $p = 0.32$]. These findings support previous evidence for sex differences in compulsive sexual behavior.

Keywords: sex addiction, pornography, cybersex, intimacy, craving

INTRODUCTION

Sex addiction otherwise known as Compulsive sexual behavior, has been associated with serious psychosocial problems and risk-taking behaviors. This behavior has not been recognized as a disorder that merits inclusion in the DSM (1) see Ref. (2–4) for recent reviews. Despite different views about pathological characteristics of sexual addiction there is an agreement that this is a progressive relapsing condition, which does not merely refer to sexual lifestyle that is socially deviant (2–4). Recently, the American Psychiatric Association Board of Trustees rejected several proposals for the new disorder and therefore sexual addiction does not appear in the DSM-5. Even though clinicians have been treating the disorder, the Board of Trustees estimated that there was not enough research to consider adding the disorder to Section 3 (disorders that require further research) of the DSM-5 (5).

Sex addiction is associated with behaviors such as constantly seeking new sexual partners, having frequent sexual encounters, engaging in compulsive masturbation, and frequently using pornography. Despite of efforts to reduce or stop excessive sexual behaviors individuals with sex addiction find it difficult to stop and they engage in risky sexual activities, pay for sexual services, and resist behavioral changes to avert risk of HIV (6–9). Cognitive and emotional symptoms include obsessive thoughts of sex, feelings of guilt about excessive sexual behavior, the desire to escape from or suppress unpleasant emotions, loneliness, boredom, low self-esteem, shame, secrecy regarding sexual behaviors, rationalization about the continuation of sexual behaviors, indifference toward a regular sexual partner, a preference for anonymous sex, a tendency to disconnect intimacy from sex, and an absence of control in many aspects of life (7, 8, 10, 11). Finally, some studies find that sexual addiction is associated with or in response to dysphoric affect (9, 12–16) or stressful life events (17).

Pornography has a decisive role in establishing basic assumptions about identity, sexuality, women's worth, nature of relationships, and their long-term addictive effects. The easy availability to pornographic content on the Internet go beyond human imagination and fantasy and enables graphic interactive encounters that fulfill urges for nudity and sexual encounters with available women always for pleasure with minimal implications and temporary encounters. Online sexual activity includes viewing and downloading pornography, visiting sex shops for sexual aids and toys, advertising or hiring sex workers on the Internet, seeking sex education information, locating sex contacts, and interacting with sexual subcultures or communities (18). Exposure to pornography results in reduced self-esteem and body image satisfaction, increased sense of vulnerability to violence, and an increased sense of defenselessness in women, and in men in reward for displays of hyper masculinity and trivializing or excusing violence against women (19). These effects are seen not only in men's perceptions of women but also in women's own perceptions of themselves. Pornographic norms for gender relationships and sexuality infuse many forms of media, such as music videos, reality television

shows, even children's toys. Thus, it becomes difficult to distinguish pornography's specific effects from those of the general climate of gender inequality in the culture of pornography (20).

Cybersex usually involves watching, downloading, and online trading of pornography or connecting to chat rooms using role plays and fantasy for men (21) and this space enables people to explore and investigate their sexual urges and private fantasies online (22). Cybersex addicts tend to suffer from poor impulse control and often have a history of multiple addictions to alcohol, tobacco, drugs, gambling, food, or sex. If an online user already suffers from a history of sexual addiction, cybersex serves as another outlet for gratification that feeds a previous problem. However, new research has found that over 65% of cybersex addicts have no history of sexual addiction (23). There are studies showing that cybersex negatively affects the patient, the spouse, and the family (24, 25). Other studies have found that males use cybersex for mood management (26, 27). Although cybersex can be used as an outlet for sexual activity there is therefore no evidence that those who use it are sexually addicted. It is important to investigate the relationship between pornography and cybersex and to ascertain their effects on the ability to form intimate relationships in men and women.

Recent studies by Laier and Brand (28, 29) explain the use of pornography and cybersex as means of sexual arousal and gratification. Furthermore, Laier and Brand (30), described a model on the development and maintenance of cybersex addiction which is based on the model for Internet addiction introduced by Brand et al. (31). These models support the arguments for the link between pornography and cybersex.

Consistent with previous studies and models on sex addiction (28–31), we have investigated the frequency of cybersex use, craving for pornography and the ability to form intimate relationships among men and women who use pornography and cybersex on the Internet. In accordance with findings of previous research, we have predicted that frequency of using cybersex, craving for pornography would predict difficulty in intimacy in men and women who use cybersex. Second, we have predicted that sex, craving for pornography and difficulties in intimacy would predict frequency of cybersex use. Third, we have predicted that there would be sex differences in the frequency of use of cybersex and craving for pornography.

PROCEDURE

PARTICIPANTS

The participants of this study were recruited from forums on the Internet that are dedicated to pornography and cybersex in order to satisfy sexual curiosity and arousal.

Men and women were approached on the websites and were asked to fill in questionnaires and send them by mail to the investigators. Questionnaires were anonymous and there were no means for assessing deception by the participants. Inclusion criteria for compulsive sexual behavior were males and females who use the Internet for sex purpose. From the original sample of 272, five participants did not meet inclusion criteria and were removed from the sample and 267 participants remained. The sample included 192 men (72%) and 75 women (28%) with mean age for males 28 years and 2 months (SD = 6.8) and for females 25 years and 6 months (SD = 5.13). Men were significantly older than women in this sample [$t(2,265) = 3.61$; $p < 0.01$]. Education attainments were 6.7% with university Master's degree, 40.4% with university Bachelor degree, 27.7% high school education, 23.6% further education after high school, 1.5% with elementary school education. Employment status of the participants included 40.4% full-time employment, 35.6% part-time employment, and 24% unemployed. Marital status was 14.2% married, 57.7% bachelors, 23.6% in relationship but not married, 4% separated, 4.1% divorced. Most of the participants lived in the city (83.5%) and 16.5% lived in rural areas. Most of the participants were Jewish (91%), 2.2% Muslims, 4% Christians, and 2.8% others.

QUESTIONNAIRES

(1) *Demographic questionnaire* including items on age, sex, education, employment status, marital status, type of living (urban or rural), and religion.

(2) *Cybersex addiction test* (23), which consists of 20 questions about cybersex addiction including pornography. For example, rate the frequency that you neglect your duties in order to spend more time in cybersex, the frequency that you prefer cybersex on intimacy with your partner, the frequency that you spend time in chat rooms and private conversations in order to find partners for cybersex, the frequency that people complain about the time that you spend online, etc.

The scale is from 0 to 5 where 0 is "not applicable" and 5 is "always." The Cronbach measure of internal validity of the questionnaire was $\alpha = 0.95$. Participants were divided into four groups non-addicted (score 0–30), moderately addicted (31–49), medium addiction (50–79), and severely addicted (80–100).

(3) *Craving for pornography questionnaire* (32), which consists of 20 questions about perceived control in using pornography, changes in mood, psychophysiological activity, and intention for using pornography. The scale is from 1 ("do not agree at all") to 7 ("agree very much"). The questionnaire was validated by Kraus (32) on US students and it has a Cronbach internal reliability of $\alpha = 0.94$. Scores vary from low levels of craving for pornography (0–20) and high craving for pornography (100–140).

(4) *Questionnaire on difficulties in intimacy* (33), which consists of 12 questions including 4 questions on fear of abandonment, 4 on fear of exposure, and 4 on shame and fear of rejection. The questionnaire has been widely used for research on psychosocial intimacy and for couple treatment. The scale is from 0 ("does not describe me") to 4 ("definitely describes me"). The questionnaire has a Cronbach internal reliability of $\alpha = 0.85$. Scores vary between 0 = no problems in intimacy and 44 = lots of problems in intimacy.

PROCEDURE

The questionnaires were filled in online using a form that was created through Google Drive and was sent as a link on email messages to members in groups and forums on pornography and cybersex. Those who responded filled in the questionnaires and informed consent forms while privacy and anonymity were maintained. The study was approved by the Institutional Review Board (IRB-Helsinki committee) of the University of Ariel in Israel.

STATISTICAL ANALYSIS

(1) Descriptive statistics of male and female participants on the questionnaires measuring frequency of cybersex, craving for pornography and difficulties in intimacy was performed.
(2) Regression analysis:
A stepwise regression analysis was performed with measures of intimacy as a dependent variable. In the first step, craving for pornography was entered; in the second step, gender was entered; and in the third step, frequency of cybersex use entered as independent variables.
(3) Comparison of questionnaire measures according to gender and level of use of cybersex:
   (1) Male and female participants were compared on measures of the questionnaires measuring frequency of cybersex, craving for pornography, and difficulties in intimacy.
   (2) All participants were divided into three groups according to their level of frequency of cybersex use "high," "medium," and "low." An analysis of variance (ANOVA) of the factors of frequency of cybersex, craving for pornography, ratings of intimacy, and gender was performed. *Post hoc* comparisons of questionnaire measures in all groups were performed with Bonferroni corrections for multiple comparisons.
(4) A Pearson correlational analysis between frequency of using cybersex, craving for pornography, and difficulties in forming intimate relationship scores was performed in all participants also separate in men and women.

RESULTS

DESCRIPTIVE STATISTICS

Overall, mean scores on the frequency of cybersex questionnaire ($n = 226$) were 22.65 (SD = 19.38) (score range 0–100), craving for pornography ($n = 267$) 52.47 (SD = 26.9) (score range 20–140), and questionnaire on difficulties in intimacy ($n = 267$) were 14.59 (SD = 9.22) (score range 0–44).

REGRESSION ANALYSIS OF ALL VARIABLES

The results of the regression analysis using intimacy ratings as a dependent variable, indicated that the three variables of pornography, gender, and cybersex were significant and they all accounted for 66.1% of the variance of ratings on the intimacy questionnaire. Craving for pornography accounted for 29.3% of the variance, frequency of cybersex accounted for 20% of the variance, and gender accounted for 16.8% of the variance.

The results of the regression analysis using cybersex frequency as a dependent variable, indicated that the three variables of pornography, gender, and cybersex were significant and they all accounted for 83% of the variance of the intimacy questionnaire. Craving for pornography accounted for 58.8% of the variance, intimacy accounted for 13.4% of the variance, and gender accounted for 11.5% of the variance.

See **Table 1** for results of the regression analyses.

COMPARISON OF QUESTIONNAIRE MEASURES ACCORDING TO GENDER

(1) A comparison of scores of frequency of using cybersex between men and women found that men had a higher score (Mean = 24.02, SD = 19.25) than women (Mean = 17.98, SD = 19.31); $t(2,224) = 1.97$, $p < 0.05$.
(2) A comparison of craving for pornography scores between men and women found that men had a higher score (Mean = 55.77, SD = 27.35) than women (Mean = 44.03, SD = 23.86); $t(2,265) = 3.26$, $p < 0.01$.
(3) A comparison of the questionnaire on difficulties in forming intimate relationship between men and women found no significant difference between scores of men (Mean = 15.56, SD = 8.86) and women (Mean = 13.85, SD = 9.45); $t(2,224) = 1$, $p = 0.32$.

Table 1 | (A) Regression analysis of the effects of pornography, gender, and cybersex addiction scores on intimacy in all participants ($n = 267$); (B) regression analysis of the effects of pornography, gender, and intimacy on cybersex addiction scores in all participants ($n = 267$).

Variable	*B*	SE	β	*t* Value	*p* Value
(A)[a]					
Pornography	0.100	0.02	0.29	3.96	0.0001
Gender	3.43	1.16	0.16	2.95	0.01
Cybersex	0.09	0.03	0.20	2.68	0.01
(B)[b]					
Pornography	0.43	0.04	0.59	11.62	0.0001
Gender	-5.013	2.03	-0.12	-2.46	0.01
Intimacy	0.284	0.11	0.13	2.69	0.01

[a] $F(3,263) = 21.5$, $p < 0.001$, $R^2 = 0.197$.
[b] $F(3,263) = 75.65$, $p < 0.0001$, $R^2 = 0.463$.

Table 2 | Means and (SD) of males and females on all questionnaires.

	Cybersex	Pornography	Intimacy
Men	Mean = 24.02, SD = 19.25	Mean = 55.77, SD = 27.35	Mean = 15.56, SD = 8.86
Women	Mean = 17.98, SD = 19.31	Mean = 44.03, SD = 23.86	Mean = 13.85, SD = 9.45
Comparison	$t(2,224) = 1.97$, $p < 0.05$	$t(2,265) = 3.26$, $p < 0.01$	$t(2,224) = 1$, $p = 0.32$

Table 2 shows means and (SD) of males and females on all questionnaires and comparisons between men and women using *t*-tests on all measures.

Figure 1 shows differences between men and women on measures of addiction to cybersex, craving for pornography, and difficulty in forming intimate relationships.

AN ANALYSIS OF QUESTIONNAIRE MEASURES ACCORDING TO LEVEL OF CYBERSEX USE

All participants were divided into three groups according to their level of frequency of cybersex use: participants with 1 standard deviation above mean cybersex score were included in the "high frequency cybersex group" ($n = 54$ score above 36), participants with <1 SD above mean cybersex score and more than 1 SD below mean cybersex score were included in the "medium

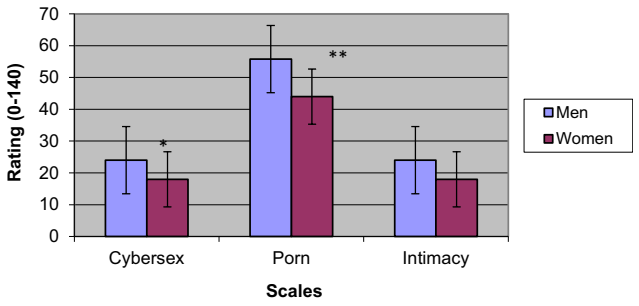

FIGURE 1 | Questionnaire ratings of cybersex, porn and intimacy – a comparison between men and women. $*p < 0.05$; $**p < 0.01$; $***p < 0.001$.

frequency cybersex group" ($n = 172 < 1$ score < 36) and participants with <1 SD below mean cybersex score were included in the "low-frequency cybersex group" ($n = 41$ $0 <$ score < 1).

An ANOVA of the factors of frequency of cybersex, craving for pornography, ratings of difficulties intimacy, and gender was performed. The analysis showed a significant frequency of cybersex effect $F(2,266) = 314.84$; $p < 0.001$, $F(2,266) = 76.28$; $p < 0.001$ and difficulties in intimacy effect $F(1,266) = 12.18$; $p < 0.001$. *Post hoc* comparisons of questionnaire measures in all groups were performed. The analysis showed that participants who had a high score on cybersex frequency had higher scores of craving for pornography and higher rates of difficulties in forming intimate relationship than those with low frequency of using cybersex.

Table 3 shows mean questionnaire ratings and comparisons using *t*-tests of ratings of cybersex, pornography, and difficulty in intimacy according to levels of use of cyberspace (low-frequency users compared with medium frequency users and high frequency).

Figure 2 demonstrates that higher levels of use of cyberspace were associated with higher levels of use of pornography and higher rates of difficulties in forming intimate relationships.

A Pearson correlational analysis between frequency of using cybersex, craving for pornography, and difficulties in forming intimate relationship scores was performed and it was found that frequency of using cybersex was positively correlated with craving for pornography ($r = 0.68$, $p < 0.01$). Second, frequency of using cybersex was positively correlated with difficulties in forming intimate relationship ($r = 0.33$, $p < 0.01$). Third, craving for pornography was positively correlated with difficulties in forming intimate relationship ($r = 0.39$, $p < 0.01$).

In men, ratings of difficulties in intimacy was positively correlated with cybersex ratings $r = 0.47$, $p < 0.01$ and with pornography ratings $r = 0.48$, $p < 0.01$ whereas in women, ratings of difficulties in intimacy was not correlated with cybersex ratings $r = 0.11$, $p =$ N.S and with pornography ratings it only showed a trend of a positive correlation $r = 0.22$, $p = 0.06$.

Table 4 shows correlations on all questionnaires in all participants.

Table 3 | Questionnaire Ratings according to levels of use of cyberspace (non-users, light users, moderate users, and heavy users).

	Ratings on frequency on the cybersex questionnaire	**Comparison with low frequency cybersex group**
"Low-frequency cybersex group" ($n = 54$)	0.74 (2.4)	
"Medium frequency cybersex group" (n = 172)	16.44 (10.6)	$t(1,52) = 8.74$; $p < 0.001$
"High frequency cybersex group" (n = 41)	54.95 (16)	$t(1,39) = 21.27$; $p < 0.001$
	Ratings on craving for pornography questionnaire	**Comparison with non-users**
"Low-frequency cybersex group" ($n = 54$)	37.35 (17.6)	
"Medium frequency cybersex group" ($n = 172$)	48.45 (27.5)	$t(1,52) = 1.56$; $p = 0.125$
"High frequency cybersex group" ($n = 41$)	89.22 (26.8)	$t(1,39) = 9.22$; $p < 0.001$
	Ratings on intimacy questionnaire	**Comparison with non-users**
"Low-frequency cybersex group" ($n = 54$)	10.78 (7.6)	
"Medium frequency cybersex group" ($n = 172$)	14.54 (8.6)	$t(1,52) = 2.36$; $p < 0.05$
"High frequency cybersex group" ($n = 41$)	19.83 (10.98)	$t(1,39) = 5.05$; $p < 0.001$

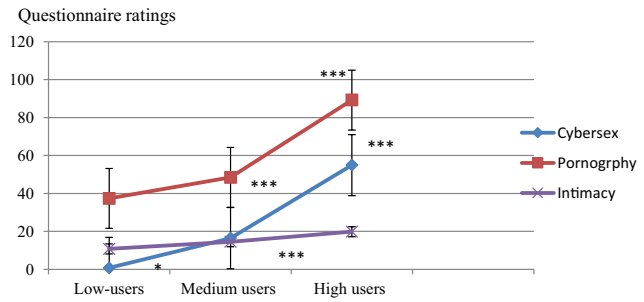

FIGURE 2 | Questionnaire ratings of frequency of use of cybersex, craving for pornography, and difficulties in intimacy in all participants. $*p < 0.05$; $**p < 0.01$; $***p < 0.001$.

DISCUSSION

The results of this study showed that men had higher scores on measures of craving for pornography and frequency of using cybersex than women. These findings support previous evidence for sex differences in the use of pornography and online sexual behaviors between men and women see Ref. (30, 34) for review.

Previous research has found that both women and men use all types of online sexual activities but women were more interested in interactive online sexual activity while men were more interested in visual oriented online sexual activity (21, 35–38). In general, women found this use of sexual media acceptable or

Table 4 | (A) Pearson's correlations on all questionnaires in all participants; (B) Pearson's correlations on all questionnaires in men; (C) Pearson's correlations on all questionnaires in women.

	Cybersex	Pornography
(A)		
Cybersex		
Pornography	$r = 0.68$, $p < 0.01$	
Intimacy	$r = 0.33$, $p < 0.01$	$r = 0.39$, $p < 0.01$
(B)		
Cybersex		
Pornography	$r = 0.63$, $p < 0.0001$	
Intimacy	$r = 0.47$, $p < 0.01$	$r = 0.48$, $p < 0.01$
(C)		
Cybersex		
Pornography	$r = 0.69$, $p < 0.0001$	
Intimacy	$r = 0.11$, $p =$ N.S	$r = 0.22$, $p = 0.06$

positive when associated with shared sexual activity. However, men reported more sexual enjoyment when pornography use was solitary; in those cases, women reported a partner's solitary use was taking something away from the relationship (39, 40).

Gender has been found to be an important indicator of sexual attitudes and behaviors related to sexual explicit material found online (21, 41–44). Males were more likely than females to view erotic material online and offline and males go online at an earlier age to view sexual materials (45–48). Males most often report sexually explicit materials online to be arousing. While some females found these materials to be arousing, more reported the sexually explicit materials to be disturbing and disgusting (48). Women reported that the primary reason they used sexual media is as part of lovemaking with their partners or in response to requests by their partner. In general, women found this use of sexual media acceptable or positive when associated with a shared sexual activity. However, men reported more sexual enjoyment when pornography use was solitary; in those cases women reported a partner's solitary use was taking something away from the relationship (39, 40). Females also reported feeling anger about online sexual materials (42), negatively compare themselves with online images (22), and often reported feelings of betrayal by their partners (49). The difference in reported frequency of using cybersex between men and women in our study may be since women feel fear of disclosure and feeling uncomfortable about admitting such activity. Second, since intimacy is an essential ingredient in cybersex which unlike pornography in general it is also characterized by chatting with a partner, participants may be jealously keeping discretion about this activity from their partner.

There could be several reasons why craving for pornography was higher in men than women in this study. Women prefer romantic fantasies and also look for intimacy and connection that is not provided by pornography whereas men look for short-term visual and graphic triggers for sexual arousal and prefer pornography. This pattern is supported by recent brain imaging studies that have demonstrated the differences between men and women in sexual arousal (50, 51). Hamann (51) examined brain activity with fMRI in men and women while they viewed sexually arousing photographs and neutral photographs. The primary finding was that the amygdala and hypothalamus exhibited substantially more activation in men than in women when viewing the same sexually arousing visual stimuli, presumably due to a stronger appetitive motivation or desire elicited by visual sexual stimuli. Furthermore, sexual activity in men is strongly related to psychological problems in daily life (28). Brand et al. (28) have found that in heterosexual males self-reported problems in daily life were linked to online sexual activities and these were predicted by subjective sexual arousal ratings of the pornographic material, global severity of psychological symptoms, and the number of sex applications used when being on Internet sex sites in daily life. Laier et al. (29) have also found that indicators of sexual arousal and craving to Internet pornographic cues predicted tendencies toward cybersex. Problematic cybersex users reported greater sexual arousal and craving reactions in response to pornographic cue presentation. However, the number and the quality with real-life sexual contacts were not associated to cybersex addiction. Finally, craving, sexual arousal rating of pictures, sensitivity to sexual excitation, problematic sexual behavior, and severity of psychological symptoms predicted tendencies toward cybersex addiction in Internet pornography users whereas being in a relationship, number of sexual contacts, satisfaction with sexual contacts, and use of interactive cybersex were not associated with cybersex addiction (30).

The finding of an association between craving for pornography and frequency of using cybersex is evident since those who started watching pornography have moved on to cybersex and vice versa and those websites advertise together both forms of sex media. The use of pornography is associated with difficulty in forming intimate relationship since pornography fills up a gap in the real world, and creates a virtual reality in which women always get satisfied and never complain. Cybersex enables those who have problems in attachment and avoid intimacy to form virtual relationships where warmth and affection and commitment are not required. An appealing feature of cybersex is that there is no requirement to perform the sexual act together so one does not fear performance anxiety. The use of sexual activity on the Internet affects sexual activity offline and there is evidence that some Internet users had abandoned or decreased their offline pornography consumption, while sexual compulsive users were found to increase their offline pornography consumption to a greater extent than did non-sexually compulsives (52).

Finally, sexual activity online negatively affected the relationship between men and women. Many studies showed that the consumption of Internet pornography threatens the economic, emotional, and relational stability of marriages and families (40, 53–61) see Ref. (25) for review. These studies indicated that pornography consumption, including cybersex, was significantly associated with decreased marital sexual satisfaction and sexual intimacy. Men and women perceived online sexual activity as threatening to a marriage as offline infidelity (56, 62).

The discovery that one of the partners is involved in sexual activity online leads to a re-evaluation of the relationship. A study conducted a web-based survey of 100 women whose partners used pornography showed that nearly one-third reported moderate to high levels of distress about their partner's use of such material (53). They reported feeling as though their partners were not interested in making love to them, but during sexual intercourse

were picturing the women they had seen in the pornography. They also felt their partners were less trustworthy, usually because he would keep the use a secret from them (even when they did not object to it). Nearly three-quarters reported feeling that the use negatively affected their self-esteem. Some felt they had failed their partners sexually; if they had been better sexual partners, their partners never would have had to turn to such material for sexual satisfaction. In this way sex on the Internet is quite often a mirror for dysfunctional sexual relationships at home and online as well (63). Schneider (24) has described how sexual addiction and compulsivity affected the patients, the spouse and the whole family. The survey respondents (93 women and 3 men) felt hurt, betrayal, rejection, abandonment, devastation, loneliness, shame, isolation, humiliation, jealousy, and anger, as well as loss of self-esteem. Being lied to repeatedly was a major cause of distress. Furthermore, cybersex addiction was a major contributing factor to separation and divorce of couples in this survey. Regarding the indirect impact on children of living in a home where a parent uses pornography, there is evidence that it increases the child's risk of exposure to sexually explicit content and/or behavior (57). Children and youth who consume or encounter Internet pornography can have traumatic, distorting, abusive, and/or addictive effects. The consumption of Internet pornography and/or involvement in sexualized Internet chat can harm the social and sexual development of youth and undermine the likelihood of success in future intimate relationships (57). Schneider (24) has also reported adverse effects on the children including exposure to cyber porn and to objectification of women, involvement in parental conflicts, lack of attention because of one parent's involvement with the computer and the other parent's preoccupation with the cybersex addict, breakup of the marriage. In view of this abundant evidence for the damage of online pornography and cyberspace to couple and family life further research merits investigation on how to treat this modern outlet for sexual behavior.

LIMITATIONS

Limitations, this study relied on ratings of subjective questionnaires which may result in variance of responses. Despite the promise of anonymity and confidentiality it is plausible that some of the responders have not fully disclosed the full information. Second, there may be other factors that are important in determining the effects of pornography and sex on intimacy and cybersex addiction that have not been investigated in this study. Thirdly, there was an unequal number of men and women with age difference between samples and this could limit the generalizability of the results. Finally, the Questionnaire on difficulties in intimacy by Marenco (33) has been widely used for research on psychosocial intimacy and for couple treatment but it needs further validation of reliability and validity in larger studies.

CONCLUSION

In conclusion, the results of this study showed sex differences between men and women in their craving for pornography and frequency of using cybersex and that both craving for pornography and frequency of cybersex were associated with difficulty in forming intimate relationship. The reasons why people turn into cybersex are important, whether it is since passion has subsided over the years, or whether it is convenience, disappointment from past romantic relationships that lead into isolation and more. It is also important to know the reasons why people switched from pornography to cybersex and vice versa, whether it is the need for a partner or a need for stronger stimulation and arousal. A following study could also look at sexual preferences of men and women that may explain why for example some men or women use cybersex to fulfill homosexual activity. Finally, these studies have implications for treatment and sex therapy since a thorough understanding of the mechanisms and processes underlying compulsive sexual behavior are important for treating this disorder.

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APPENDIX

INTIMACY QUESTIONNAIRE

Assign a number that best describes how you feel concerning each of the following statements. Base your answers on what has been true for you for the greater part of your life. What comes most quickly to your mind is usually the best answer.

0 = definitely not me, 1 = mildly disagree, 2 = neutral, 3 = mildly agree, 4 = definitely me.

1. You are concerned that if you truly reveal yourself to another person, s/he will leave
2. You fear that if someone really knew you that s/he would not like you
3. You have an uneasy feeling that people will smother you if you get too close
4. A parent physically or emotionally abandoned you in your childhood
5. You were teased or shamed for your feelings or needs when you were younger
6. You feel that one of your parents or significant caretakers was overly involved in your life
7. You would feel a sense of panic if you had a conflict with your partner and s/he pulled away
8. You would want to hide if your partner did a background check on you that was really on the mark
9. You find yourself needing more space in relationships once another person tells you that s/he really cares about you
10. You get angry when the person you've been involved with for six months says that s/he's taking a vacation with friends that does not include you
11. You are comfortable showing your checkbook to your partner
12. You feel smothered when in the first few weeks of a relationship your partner wants you to call every day

SCORING

1. Fear of abandonment (add your scores for questions 1, 4, 7, and 10) Total
2. Fear of exposure (add your scores for questions 2, 5, 8, and 11) Total
3. Fear of engulfment (add your scores for questions 3, 6, 9, and 12)

If you score higher than 10 on any of the three areas, this is a strong indication that this could be creating a block that prevents you from becoming more fully intimate with others.

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Attention-deficit/hyperactivity disorder in relation to addictive behaviors: a moderated-mediation analysis of personality-risk factors and sex

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Introduction: Research has shown that those with attention-deficit/hyperactivity disorder (ADHD) have an increased risk for addiction disorders like alcoholism and substance abuse. What is less clear is the mechanism(s) whereby ADHD gives rise to increased engagement in addictive behaviors, and whether there are sex differences in the ADHD-addiction propensity. Both ADHD and addictions have also been associated with personality traits such as impulsivity, reward seeking, anxiousness, and negative affect. In this study, we tested a moderator-mediation model, which predicted that both sex and ADHD-symptom status would make independent contributions to the variance in personality risk and in addictive behaviors, with males, and those with diagnosed ADHD, scoring higher on both dependent variables. Our model also predicted that the effect of sex and ADHD-symptom status on addictive behaviors would be via the mediating or intervening influence of personality-risk factors.

Methods: A community-based sample of young men and women took part in the study. Among these individuals, 46 had received a lifetime diagnosis of ADHD. The non-diagnosed participants were dichotomized into a high-ADHD-symptom group ($n = 83$) and a low-symptom group ($n = 84$).

Results: We found that a high-risk personality profile may, in part, account for the relationship between ADHD symptomatology and the use/abuse of a broad range of addictive behaviors. However, we found no sex differences in personality risk for addiction or in the use of addictive behaviors; nor did sex moderate the relationships we assessed.

Conclusion: While ADHD status showed a strong relationship with both dependent variables in the model, we found no difference between those who had been diagnosed with ADHD and treated with stimulants, and their high-symptom non-diagnosed/non-treated counterparts. These results add support to claims that the treatment of ADHD with stimulant medication neither protects nor fosters the risk for substance abuse disorders.

Keywords: attention deficit/hyperactivity disorder, addictive behaviors, personality, sex

INTRODUCTION

Attention-deficit /hyperactivity disorder (ADHD) is a highly heritable (≈70%) neuropsychiatric disorder with typical onset in childhood (1). Furthermore, in a substantial proportion (≈75%) of cases, ADHD symptoms do not remit in childhood/adolescence and continue into adulthood (2). It appears, however, that genetic factors account for a lower heritability in adults with ADHD (≈30–40%) than in children with this disorder (3, 4). The psychosocial and behavioral impairments that characterize ADHD are associated with a number of deleterious outcomes. Perhaps most notably is the increased risk of substance use and abuse – evidence, which derives largely from follow-up studies of children and adolescence with ADHD [e.g., Ref. (5, 6)]. It also seems that this co-morbid risk is exacerbated in girls (7), and that a common underlying bio-behavioral process influences both the risk for ADHD and for substance and alcohol dependence (8). In addition, in a recent long-term follow-up study, results were relatively consistent with most previous studies in finding that substance and alcohol abuse were about six times more likely in cases with ADHD than in controls, and that females had a significantly higher risk than males (9).

The ADHD-drug use/abuse link is also evident from the reverse perspective. It has been estimated that up to 50% of adolescents and adults with substance abuse disorders have a lifetime diagnosis of ADHD (5, 10). For example, ADHD was significantly more prevalent in methamphetamine abusers compared to control participants, especially in those with a persistence of symptoms into adulthood (11). Research also indicates that the comorbidity of

substance use disorders and ADHD is associated with a more severe progression from use to abuse, and with greater social and psychiatric impairment (12).

In a recent 15-year, longitudinal, population-based ADHD study, the prevalence of substance abuse/dependence was substantially higher (≈31%), however, for nicotine than for other drugs like alcohol, cannabis, and cocaine (13). It also appears that the choice of addictive substance may be affected by the medication status of the user as seen in a case–control study of medication-compliant (i.e., methylphenidate or atomoxetine) adolescents. As anticipated, the ADHD probands were more likely than the controls to be daily smokers (14). However, contrary to expectation, the control participants reported heavier and more regular use of alcohol. A weaker link between ADHD symptoms and alcohol use, compared to that between ADHD and nicotine use, has also been found in other research (15). Such substance-related differences were explained, in part, by previous evidence that alcohol has a synergistic effect on methylphenidate by increasing its potency and causing feelings of dizziness and discomfort – effects that might discourage alcohol consumption in some individuals taking this medication (16).

MEDICATION STATUS AND RISK FOR SUBSTANCE USE/ABUSE

Stimulant medication for ADHD continues to be the first-line treatment for this disorder in most clinical settings, despite lingering concerns about its potential for abuse and whether it may sensitize individuals to later problematic substance use (17). Drugs like methylphenidate and amphetamines block or inhibit the dopamine and the norepinephrine transporters thereby increasing extracellular levels of these neurotransmitters. Amphetamines also gain access to the presynaptic terminals and foster the release of these catecholamines (18). As with all pharmacotherapies, however, efficacy of the drug varies across individuals and is influenced by brain neurochemistry and physiology. For instance, in two human studies, it was found that low levels of the dopamine D2 receptor in the striatum were associated with greater reinforcing responses to methylphenidate – a factor, which may predispose individuals with a hypo-functioning dopamine system to the risk of stimulant drug abuse (19, 20).

In an early meta-analysis of six stimulant-treatment outcome studies, Wilens and colleagues (21) concluded that pharmacotherapy for ADHD in childhood actually reduced the likelihood of later problem drug and alcohol use. However, a more rigorous review, of a larger body of empirical evidence a decade later, found no support for the "sensitization hypothesis" of stimulant treatment. Indeed, neither did it find that stimulant treatment conferred a protective effect on later substance abuse (17). Recent preclinical research suggests that inconsistencies in the putative relationship between stimulant treatment and risk for substance abuse may be explained by the moderating effects of emotional factors. For instance, juvenile rats chronically treated with methylphenidate showed a greater intake of, and preference for, alcohol in adulthood, but only in those who were socially isolated by being caged in solitary housing – an environment known to increase stress and anxiety in these animals (22).

Sex and age appear to be other factors that moderate the ADHD-drug use relationship. In a clinical population-based, birth-cohort study, it was found that childhood ADHD cases were 6.2 times more likely to have an alcohol/drug use disorder than non-ADHD controls from the same cohort, and that stimulant treatment tended to be a protective factor, but *only* in boys (23). In a more recent prospective arm of the same study, from the same birth cohort, it was confirmed that ADHD cases diagnosed in adolescence were more likely to have alcohol or drug dependence in adulthood (24). In other words, as ADHD cases grew to maturity, they were more likely to use drugs and were more likely to develop new-onset drug dependence than controls. Importantly, however, this study found that ADHD cases who had received treatment (for at least 6 months) after the age of 13 were at greater risk than those who received treatment before that age. Similarly, Dalsgaard et al. (9) found that both boys and girls with ADHD were at increased risk for substance abuse in adulthood, but that early initiation of stimulant treatment in children resulted in reduced risk compared to cases with later treatment onset. Nevertheless, there is still not complete agreement on the relationship between treatment with psychomotor stimulants and the risk for developing a drug addiction, nor the causal direction of such a putative association. Some of the outcome inconsistencies may be due to the relatively short length of follow-up and the high rates of attrition in earlier studies [e.g., Ref. (25, 26)].

MECHANISMS LINKING ADHD AND SUBSTANCE USE/ABUSE

Although links between ADHD symptomatology and substance (ab)use are well-documented, there has been little information about mechanisms that might foster this connection. One approach has been to examine the influence of personality traits associated with both ADHD and substance users in the general population. In this regard, the very limited ADHD research has focused largely on facets of impulsivity and their association with alcohol consumption in this clinical cohort [e.g., Ref. (27)]. Other research has indicated that the positive relationship between nicotine and marijuana use and ADHD-symptom dimensions may also be mediated by aspects of impulsivity (28). In addition, related investigations have found that an aversion to delayed gratification and an abnormal sensitivity to individual instances of reward are mediating links between symptoms of ADHD and addictive behaviors (29). These authors have suggested that a high reward drive might imply that "dopamine timing is off" in those with ADHD. Indeed, the pathophysiology of ADHD has mostly been ascribed to dopamine dysfunctions in the mesocorticolimbic pathway (30). Imaging studies have shown, for example, that ADHD patients display in increased availability of the dopamine transporter in this brain region relative to their healthy counterparts [see Ref. (31) for a review]. While there is other evidence that ADHD is associated with reduced functionality of the dopamine system – due in part to reduced receptor densities in various brain regions compared to non-affected individuals [see Ref. (32, 33)] – findings are not entirely consistent. For example, some studies suggest that ADHD is associated with a hyperactive dopamine system due either to an elevated efflux of dopamine or a reduced decrease in the reuptake of dopamine (34).

Results of recent longitudinal research have also shown that the development of internalizing problems such as depression and anxiety – largely through peer rejection – mediates the relationship

between ADHD symptoms and risk for substance use and abuse (15). Indeed, several studies have reported that depression and anxiety disorders are the most frequently reported psychiatric comorbidities in those with ADHD [see Ref. (35)]. Such data suggest that substance use, and other addictive behaviors, may be a form of "self-medication" in the absence of adequate social support, and as a means to cope with stressful events in adolescence. Together these studies mesh with evidence that high-risk profiles for substance misuse include anxiety sensitivity, impulsivity, and high sensation-seeking tendencies (36).

In the quest to better understand the mechanisms linking ADHD symptoms to addictive behaviors, no mediational research has examined whether stimulant-medication treatment for ADHD affects the hypothesized associations among the variables of interest. Moreover, the possible role of sex differences in moderating these associations is untested. To address these issues, the current study has employed a case-double-control design. Examining undiagnosed individuals with high-ADHD symptoms in the general community, as well as stimulant-treated clinical cases of ADHD, in relation to addictive behaviors removes the potential confounding effects of medication status on outcome.

THE CURRENT STUDY

In this study, a moderated-mediation analysis was used to test our prediction that a composite index of personality risk – including impulsivity traits, reward sensitivity, and anxiety proneness – mediates the relationship between ADHD symptomatology on the one hand, and a general tendency toward engaging in addictive behaviors on the other. We also predicted that sex would moderate these relationships with males showing higher scores on all the measured variables compared to females (see **Figure 1**). These associations were assessed in three groups of young adult men and women: those with a previous or current diagnosis of ADHD who had been (or were currently being) treated with a stimulant medication (e.g., methylphenidate); a high-ADHD-symptom group; and, a low-ADHD-symptom group, both with no lifetime diagnosis of, or stimulant treatment for, ADHD. It was anticipated that the cases would have higher scores on all the measured variables in the analyses compared to the high-symptom control group, who, in turn, would have higher scores than the low-symptom controls.

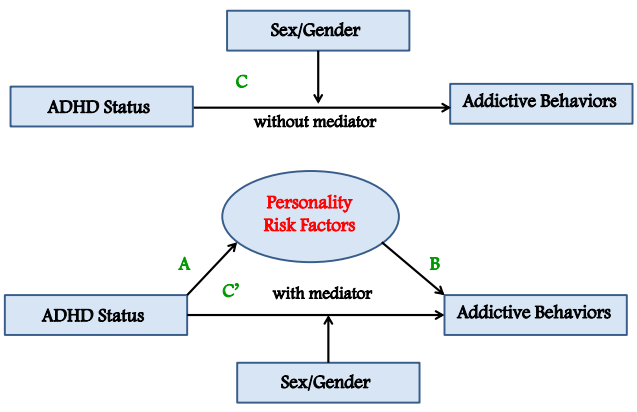

FIGURE 1 | Moderated-mediation model predicting that a personality-risk index mediates the relationship between ADHD status and a composite measure of addictive behaviors, and that sex moderates these associations.

MATERIALS AND METHODS

PARTICIPANTS

A sample of young men ($n = 98$) and women ($n = 116$) between the ages of 17 and 32 years were recruited from the community of a large Canadian university (student enrollment is ≈55,000, with an additional 7000 faculty and staff employed on campus). Mean ages (and SD) of the participants were 22.5 (3.3) and 22.2 (3.3) years, for males and females, respectively. Among these individuals, 46 (men = 25; women = 21) had received a diagnosis of ADHD, and were either currently being treated with stimulant medications or had been in the past. The prescribed medications were Concerta, Ritalin, Vyvanse, Adderall, and Dexedrine. Participants were required to be fluent in written and spoken English and to have lived in North America since childhood. Exclusion criteria included a current diagnosis of an addiction disorder and a current or lifetime diagnosis of a psychotic disorder using an abbreviated (non-patient) version of the *structured clinical interview for DSM-IV* (SCID).

MEASURES

ADHD status

ADHD status was established by participant self-report, each of whom was asked whether they had ever had a medical diagnosis of ADHD. If they answered in the affirmative, they were asked at what age the diagnosis took place and whether they were ever prescribed (and took) stimulant medication as part of their treatment protocol. If stimulants were taken, the participant was asked for the length and dates of the treatment, and for the name of the prescribed medication. Approximately half of the ADHD group was still on stimulant medication at the time of study participation, while the other half had a prior history of pharmacotherapy with stimulants, but was no longer receiving treatment at the time of recruitment. The non-diagnosed participants were dichotomized into a high-ADHD-symptom group ($n = 83$: females = 53) and a low-symptom group ($n = 84$: females = 41) based on a median split of their scores on the well-validated *Connors Adult ADHD Rating Scale* (CAARS) (37). The self-report measure was employed, which evaluates the presence and severity of ADHD symptoms. The scale comprises 30 items that are rated on a four-point scale based on the frequency and severity of ADHD inattentive and hyperactive/impulsive symptoms (0 = not at all, 1 = just a little, 2 = pretty much, and 3 = very much). In the present study, the total score was used and a median split of the data from the non-ADHD participants was used to define the low- and high-symptom groups.

Personality risk

Personality risk was modeled as a latent variable comprising three personality factors associated with impulsive and rash responding, and with anxiety proneness: (i) *Impulsivity* was assessed by the well-validated 30-item *Barratt Impulsivity Scale* (BIS) (38), which identifies facets of impulsivity such as the non-planning aspects

of this construct, as well as the tendency to act rashly and to make quick decisions. The alpha coefficient in this study was 0.77; (ii) *Reward Sensitivity* was assessed by the Reward subscale (RS) of the *Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ)* (39). This scale comprises 24 forced-choice items reflecting the respondent's approach responses under various conditions of reward. This scale was developed to assess the behavioral activation system (BAS) of Gray's psychobiological model of personality (40, 41). The alpha coefficient for the present study was 0.78; and (iii) *Addictive Personality Traits* were assessed by the 32-item *Addiction Scale* (AS) of the *Eysenck Personality Questionnaire-Revised* (EPQ-R) (42). This scale was derived empirically by identifying those items of the EPQ-R, at or beyond the 0.001 level of significance – and irrespective of subscale – which differentiated male drug addicts from normal controls (43). In addition to studies with drug addicts (44), this scale has been validated with groups of problem drinkers (45), pathological gamblers (46), and those with anorexia nervosa, bulimia nervosa, and binge eating disorder (47, 48). The scale items are weighed toward the impulsive traits, as well as anxiousness and negative affect. The alpha coefficient in the present study was 0.81.

The three variables described above were moderately correlated, as expected (r between 0.33 and 0.41; all p-values <0.0001). A composite score was therefore calculated using principal component analysis, as described in the Section "Results."

Addictive behaviors

Addictive behaviors were assessed by the *Shorter PROMIS Questionnaire* (49), a self-report instrument for the concurrent measurement of 16 addictive and/or excessive behaviors. Each subscale comprises 10 statements that the respondent endorses on a 6-point scale from 0 ("not like me") to 5 ("like me"). The items for each scale reflect the common characteristics of addictive behaviors, such as use for effect, protection of supply, preoccupation, using more than intended and increased capacity or tolerance. For the purpose of the current study, a total score was created by summing the items for the following seven subscales: caffeine, recreational drugs, sex, nicotine, food binging, shopping/spending, and alcohol. Other subscales such as "compulsive helping – dominant/submissive" and "relationship – dominant/submissive" were deemed insufficiently related to conventional addiction disorders to be included in the aggregate score.

PROCEDURES

Participants were recruited by posters placed around the university campus, by newspaper advertisements, and by means of targeted announcements in online student forums. An initial screening took place during a short telephone interview. An appointment was made for a 1-h meeting in the university research laboratory of the first author for participants who appeared to meet the eligibility criteria. One the day of testing, informed consent and all relevant demographic and clinical information was obtained during a face-to-face interview. After the questionnaire package was completed, height and weight were measured with the participant standing in stocking feet and wearing light indoor clothing. At the completion of the study, each participant was paid $15.00 to cover out-of-pocket expenses. All study procedures were carried out according to the Declaration of Helsinki.

STATISTICAL ANALYSES

The moderated-mediation model described in the Section "Introduction" was analyzed using the four-step procedures described by Baron and Kenny (50). According to this approach, mediation is present when the following conditions are met: (i) the independent categorical variable (ADHD status) is significantly related to the proposed mediator (personality risk), shown as path A in the model (see **Figure 1**); (ii) the proposed mediator (personality risk) is significantly related to the dependent variable (addictive behaviors), shown as path B in the model; (iii) the independent variable (ADHD status) is significantly related to the dependent variable (addictive behaviors), shown as path C in the model; and (iv) the relationship between ADHD status and addictive behaviors is substantially minimized – or becomes non-significant – when the proposed mediator (personality risk) is added as a covariate in the analysis of variance (ANOVA) analysis described in the third step. Sex was included as a potential moderator variable in the first, third, and fourth ANOVA analyses described above. Moderation is found if the ADHD status × sex interaction is statistically significant.

RESULTS

As a preliminary analysis, independent t-tests were used to assess group differences between the currently medicated and the previously medicated ADHD participants on all the quantitative variables used in this study. Since there were no significant differences between the groups, they were combined into a single group for all subsequent analyses.

Table 1 presents the means and SD for all quantitative variables included in the analyses, as well as for age and BMI, listed separately for the three ADHD-status groups (i.e., those with a diagnosis of ADHD, the high-symptom control group, and the low-symptom control group). The groups did not differ from each other on BMI. However, the low-symptom group was significantly older than the high-symptom ($p = 0.033$) and the ADHD ($p = 0.008$) groups, who did not differ from each other. Although statistically significant in our sample, an age difference of 1–2 years in young

Table 1 | Means and SD for all quantitative variables listed separately for the three ADHD status groups.

Variable	ADHD		High-symptom		Low-symptom	
	Mean	SD	Mean	SD	Mean	SD
Age	21.5	2.7	22.0	3.3	23.1	3.3
BMI	25.8	4.4	25.4	6.7	24.2	4.7
CAARS total score	41.4	20.6	40.0	11.3	15.3	6.4
Barrett impulsivity scale	71.3	14.9	67.3	11.5	55.7	7.8
Reward sensitivity	12.5	4.3	13.5	4.2	10.4	4.3
Addictive personality traits	13.3	6.2	14.5	4.7	9.8	4.4
Addictive behaviors	71.0	60.0	64.0	35.2	42.8	29.5

adulthood was not considered clinically relevant in the context of our research. With respect to the classification variable for the control groups (viz. symptom scores as assessed by the CAARS), the ADHD group had significantly higher scores than the low-symptom group ($p < 0.0001$). Surprisingly, there was no difference between the ADHD groups and the high-symptom control group ($p = 0.456$).

In order to create a latent variable reflecting personality risk, a composite score was calculated for the three personality variables (BIS, RS, and AS) using a principal component analysis. The extracted component accounted for 58% of the variance in the three personality scales, and all three loaded strongly on this factor (loadings ranged from 0.73 to 0.79).

MODEL TESTING

Path A

Path A was tested using a 3 (ADHD status) × 2 (Sex) ANOVA with personality risk as the dependent variable. There was a significant main effect for ADHD status. *Post hoc* comparisons using the *least significant difference* (LSD) test indicated that the low-symptom group had significantly lower personality-risk scores than the ADHD group ($p < 0.0001$) and the high-symptom group ($p < 0.0001$), which did not differ from each other ($p = 0.634$). Neither the main effect for sex nor the AHDH status × sex interaction was statistically significant. **Table 2** presents the summary statistics for these analyses.

Path B

Path B was tested by regressing addictive behaviors on the personality-risk factor score, and results indicated a significant positive association between the two variables (see **Table 3**).

Path C

Path C (without the mediating variable) was tested using a 3 (ADHD status) × 2 (sex) ANOVA with addictive behaviors as the dependent variable. There was a significant main effect for ADHD status. *Post hoc* comparisons using the LSD test again indicated that the low-symptom group had significantly lower scores on the addictive-behaviors variable than the ADHD group ($p < 0.0001$) and the high-symptom group ($p = 0.001$), which did not differ from each other ($p = 0.348$). Neither the main effect for sex nor the AHDH status × sex interaction was statistically significant. **Table 4** presents the summary statistics for these analyses.

Path C′

In the final step, *Path C′* was tested by repeating the analysis described in Section "Path C"; however, this time the proposed mediator (personality risk) was included as a covariate in the model. Results indicated that personality risk was a highly significant predictor in the model, but that the ADHD status main effect no longer contributed significantly to the variance in addictive behaviors. There was no main effect for sex, nor was the ADHD status × sex interaction statistically significant (**Table 5**).

SUPPLEMENTARY ANALYSES

Although we selected an aggregate index in this study to reflect a *general* proclivity for addictive behaviors, we also expect that some readers may be interested in the statistical outcome for each individual addictive behavior. The following provides a summary of these results, and should be viewed as information supplementary to the original hypothesis-driven analyses. **Table 6** presents the means and SD for each of the seven addictive behaviors, listed separately for the ADHD status groups and for men and women. To assess group differences, we employed a 3 (ADHD status) by 2 (sex) multivariate analysis of variance (MANOVA) with the individual addictive variables as dependent variables.

Table 2 | Summary statistics for the 3 × 2 ANOVA with the personality-risk factor score as the dependent variable.

Source	df	Mean squares	*F*	*p*-value
Intercept	1	0.7	0.89	0.346
ADHD status	2	23.7	31.80	**<0.0001**
Sex	1	0.3	0.45	0.502
ADHD status × sex	2	1.0	1.40	0.249
Error	203	0.7		
Total	209			

Table 3 | Unstandardized coefficients for the regression analysis with addictive behaviors as the dependent variable and the personality-risk factor score as the independent variable.

Variable	*B*	SE	$t(H_o)$	*p*
Intercept	57.4	2.3	25.11	**<0.0001**
Personality risk	25.5	2.3	11.14	**<0.0001**

$R^2 = 0.38$.

Table 4 | Summary statistics for the 3 × 2 ANOVA with the addictive behaviors as the dependent variable.

Source	df	Mean squares	*F*	*p*-value
Intercept	1	664358.0	418.34	<0.0001
ADHD status	2	13642.9	8.59	**<0.0001**
Sex	1	2292.1	1.44	0.231
ADHD status × sex	2	1073.1	0.68	0.510
Error	206	1588.1		
Total	212			

Table 5 | Summary statistics for the 3 × 2 ANOVA with addictive behaviors as the dependent variable and the personality-risk factor score as a covariate in the model.

Source	df	Mean squares	*F*	*p*-value
Intercept	1	614323.1	569.3	<0.0001
Personality risk	1	107627.9	99.34	**<0.0001**
ADHD status	2	1352.7	1.2	0.288
Sex	1	984.3	0.91	0.341
ADHD status × sex	2	2571.5	2.38	0.095
Error	201	1079.12		
Total	208			

Table 6 | Means and SD for seven addictive-behaviors subscales of the PROMIS questionnaire, listed separately for the three ADHD status groups and for sex.

Variable	ADHD		High-symptom		Low-symptom	
	Mean	SD	Mean	SD	Mean	SD
Female						
Caffeine	3.9	5.1	3.9	4.6	1.5	2.8
Recreational drugs	12.9	18.5	3.3	7.1	2.3	5.6
Sexual activities	7.2	13.9	3.8	8.6	2.3	6.1
Nicotine	8.6	14.6	2.6	8.4	1.9	6.1
Food binging	13.2	13.6	16.0	9.8	12.3	6.1
Alcohol	9.0	10.4	9.7	10.7	8.3	9.3
Shopping/spending	13.9	12.5	17.0	9.9	13.6	9.4
Male						
Caffeine	4.7	7.8	5.9	7.4	4.9	6.9
Recreational drugs	12.4	15.4	7.2	10.7	3.8	7.4
Sexual activities	10.3	13.7	9.9	9.5	6.4	8.2
Nicotine	8.2	15.4	6.6	11.7	2.1	6.2
Food binging	10.0	10.0	14.9	8.1	6.8	6.1
Alcohol	15.4	11.4	15.4	11.0	11.2	8.8
Shopping/spending	10.8	9.8	11.5	8.6	8.3	7.2

The multivariable Wilks' Lambda F ratios were statistical significant for ADHD status and for sex ($F_{14,400} = 3.33$; $p < 0.0001$, and $F_{7,200} = 7.12$; $p < 0.0001$, respectively). However, the main-effects interaction term did not reach statistical significance. Results of the univariate results are provided below.

Caffeine intake, alcohol consumption, and shopping/spending

For these three variables, there were no main effects for ADHD status. However, males had a higher frequency of caffeine ($p = 0.01$) and alcohol ($p = 0.01$) consumption compared to females, while females were more prone to compulsive shopping ($p = 0.001$).

Recreational drugs and nicotine

In contrast, for these two addictive behaviors there were no main effects for sex. There were, however, significant main effects for ADHD status ($p < 0.0001$ and 0.002, respectively). *Post hoc* comparisons using the LSD procedure indicated that for recreation drug use, the ADHD group had significantly higher scores than both the low- and the high-symptom groups ($p < 0.0001$ in each case), who did not differ significantly from each other. With respect to nicotine, similar results were found with the ADHD group having higher scores than the high-symptom ($p = 0.026$) and the low-symptom ($p < 0.0001$) groups, who again were not different from each other.

Food binging and sexual activity

For these two variables, there was a significant additive effect of ADHD status ($p = 0.001$ and 0.045, respectively) and sex ($p = 0.025$ and 0.002, respectively). Not surprisingly, woman had higher scores on food binging than men, while the reverse was found for sexual activity. Concerning food binging, the high-symptom group had more elevated scores than either the low-symptom ($p = 0.001$) or the ADHD groups ($p = 0.027$), who did not differ from each other. And finally, the low-symptom group had reduced scores on the sexual-activity variable compared to the high-symptom ($p = 0.037$) and the ADHD ($p = 0.004$) groups, who were not significantly different from each other.

DISCUSSION

Results of our moderated-mediation analysis suggest that a composite index of personality risk – reflecting aspects of impulsivity and reward drive, as well as neurotic and anxiousness traits – may mediate the positive relationship between ADHD symptomatology and addictive behaviors. In other words, these findings suggest that the personality traits frequently found in those with ADHD may be the underlying mechanism driving their preference for, and proneness to engage in, activities with immediately reinforcing qualities and outcomes. Unexpectedly, however, there were no differences between the ADHD group and the high-symptom participants on the composite measure of addictive behaviors, although both groups had significantly higher scores than the low-symptom group[1]. We also found that the ADHD and the high-symptom group had virtually identical scores on the ADHD-symptom variable (viz. the CAARS), which is used clinically as a diagnostic tool, and was employed in this study to dichotomize the sample into high- and low-symptom control groups. The findings described here suggest that stimulant medication (either current or past) does not appear to enhance or diminish the general likelihood of engaging in addictive activities. In essence, these results appear to be in accord with recent research showing no evidence of a "sensitization" effect of stimulant treatment in those with a lifetime diagnosis of ADHD (17). Such conclusions, however, must be interpreted with caution since the sample of participants with ADHD was not of sufficient size to control for factors such as length of stimulant treatment, age of onset, and medication dosage.

The absence of clinically relevant symptom differences between the ADHD and the high-symptoms groups may suggest that the former was more high-functioning than is typical of the general population of young adults with ADHD (or a history thereof). Indeed, this possibility gains credibility since most of the ADHD participants in our study were recruited from the student body of a local university. On the other hand, a recent survey of childhood impairments in those with and without ADHD – based on retrospective adult recall – found that while the ADHD group reported

[1]When each addictive behavior was considered separately – as seen in the Section "Supplementary Analyses" – recreational drug use and cigarette smoking were significantly higher in the ADHD group than in either of the control groups, who did not differ from each other. Moreover, there were no group differences regarding alcohol consumption. It is interesting to note that the nicotine and alcohol results in the current study are in close accord with previous findings reported in the Section "Introduction" (14, 15). With regard to food binging, the finding that the high-symptom group had significantly elevated scores, compared to the ADHD or low-symptoms groups, is difficult to explain. Given that half of the ADHD group was currently on stimulant medication, and in light of recent evidence that stimulants are effective in reducing binge-eating episodes (51), it may be that the relatively low scores in the ADHD group were the result of medication effects. Importantly, however, and similar to results with the addictive-behaviors composite score, there was no ADHD status × sex interaction for any of the individual variables.

more school difficulties compared to controls, there were no differences in their respective levels of educational attainment (35). Such data imply, therefore, that university recruitment does not necessarily create a biased sample in relation to the severity of ADHD symptomatology. Another possible explanation for the absence of differences between the ADHD and the high-symptom groups is that stimulant treatment for the former may have ameliorated their symptom severity. On the other hand, the absence of differences may also indicate that ADHD is relatively under-diagnosed among apparently healthy adults who have high-ADHD symptoms.

It was of considerable interest to find no differences in the magnitude of the personality-risk index between those with AHDH and the high-symptom group, although again both had significantly higher scores than the low-symptom group. The composite personality variable – created for the current study as a marker of risk for addictive behaviors – is not only validated empirically by our results but also complements previous research in this area. For instance, both novelty seeking and harm avoidance were significantly greater in a large group of patients with opiate addiction and/or alcohol dependence compared to normal controls (52). Individuals with a compulsive buying disorder also had more symptoms of ADHD, as well as lifetime mood, anxiety, and impulse control disorders, compared to an appropriate control group (53). Additionally, the compulsive buyers had more pronounced personality traits related to depression, impulsivity, and novelty seeking (an aspect of high-reward sensitivity).

Contrary to expectations, and after controlling for ADHD status in our analyses, there were no male–female differences in personality risk, nor in the use of addictive behaviors; neither did sex moderate the relationships tested in our mediation model. Concerning the addictive-behaviors variable – and in light of our findings that individual differences in risk were not sex-specific – it may be that sex differences were washed out because we operationalized addictive behaviors as an aggregate index of several activities, both substance and non-substance related. Some addictive behaviors, like compulsive buying (54) and binge eating (55), are more frequently found in women, while others like hypersexual behaviors tend to be more common in men (56)[2].

In conclusion, strengths of this study are the inclusion of a non-diagnosed and non-treated group of young adults with high-ADHD symptom severity equivalent to the group of clinically diagnosed ADHD participants. In addition, we also included a low-symptom control group, thereby providing a double control for the clinical cases. Our focus on both mediating and moderating factors in connection to the ADHD-addictive behaviors link is another strong point of this research. The use of a composite dependent-variable index of addictive behaviors also provided a more comprehensive approach than one which examined each addictive activity separately (although these data have been provided as supplementary information). This strategy is particularly relevant since preferences for specific addictive activities are known to vary across sociocultural groups (59–61). In addition, while other studies have examined personality correlates of ADHD – in particular, those also associated with risk for addiction – as reviewed in the Section "Introduction," this body of work has largely investigated constructs related to impulsive responding. The current study has extended this research by using a multivariate approach to operationalize personality risk by forming of composite latent variable including facets of impulsivity, reward sensitivity, and anxiousness. We have also moved beyond the investigation of simple relationships by employing moderated-mediation procedures in our data analyses.

However, despite the merits of our current research, it is also important to address the limitations of the study. Foremost is the fact that the ADHD participants comprised two distinct subgroups – those who were currently on stimulant medication and those who had been, but were no longer, taking these drugs. While our data indicated that the two groups did not differ on the variables included in this study, these analyses may have been under-powered by virtue of relatively small sample sizes. Another constraint of the study is that the associations we observed were based on cross-sectional data, thereby limiting our ability to infer directional relationships between symptoms and behaviors. While it is intuitive, for example, to suppose that ADHD symptoms contribute to the use and abuse of addictive behaviors, it is also known that chronic use of addictive substances/activities can foster some of the symptoms that define ADHD such as poor impulse control (62). Only longitudinal research will be able to establish causal mechanisms between ADHD symptoms and addiction, and the mediating role of personality-risk factors.

To summarize, we found that a high-risk personality profile may, in part, account for the relationship between ADHD symptomatology and the use/abuse of a broad range of addictive behaviors. We also found no evidence that current or past treatment of ADHD symptoms with stimulant medication increases the probability of engaging in potentially addictive activities. While there is good evidence that ADHD is more prevalent in males than in females (63), we found no sex differences in personality risk for addiction or in the use of addictive behaviors; nor did sex moderate the relationships we assessed. The mediational impact of personality-risk factors found in our study has important clinical implications, especially in light of recent evidence from a randomized control trial, demonstrating that a personality-targeted prevention program for adolescence was significantly more effective in reducing alcohol use and misuse than a standard and statutory drug-education program (36).

[2]Indeed, results from the *post hoc* Supplementary Analyses did demonstrate that women had higher scores than men on the binge-eating and compulsive-shopping variables, as seen in previous research (54, 55). We also found, as others have, that men had higher scores than women on sexual addiction (56) and alcohol consumption (57). With respect to caffeine, our findings showed that men also had higher scores than women. While very few studies have examined sex/gender differences in caffeine consumption, one early report indicated that adolescent boys found the reinforcing effects of caffeine greater than girls did, suggesting that the former may be more prone to consume caffeinated beverages (58). Important, however, is that sex did not moderate the relationship between ADHD status and addictive behaviors whether we used the composite index or the individual sub-scale scores.

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REVIEW
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A positive affective neuroendocrinology approach to reward and behavioral dysregulation

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Emerging lines of research suggest that both testosterone and maladaptive reward processing can modulate behavioral dysregulation. Yet, to date, no integrative account has been provided that systematically explains neuroendocrine function, dysregulation of reward, and behavioral dysregulation in a unified perspective. This is particularly important given specific neuroendocrine systems are potential mechanisms underlying and giving rise to reward-relevant behaviors. In this review, we propose a forward-thinking approach to study the mechanisms of reward and behavioral dysregulation from a positive affective neuroendocrinology (PANE) perspective. This approach holds that testosterone increases reward processing and motivation, which increase the likelihood of behavioral dysregulation. Additionally, the PANE framework holds that reward processing mediates the effects of testosterone on behavioral dysregulation. We also explore sources of potential sex differences and the roles of age, cortisol, and individual differences within the PANE framework. Finally, we discuss future prospects for research questions and methodology in the emerging field of affective neuroendocrinology.

Keywords: testosterone, cortisol, emotion, affect, reward, self-regulation, sex differences

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Introduction

In recent decades, separate lines of research have investigated the psychological, neural, and neuroendocrine mechanisms of behavioral dysregulation, defined here as appetitive, risky behaviors, such as sexual risk-taking (e.g., unprotected sex), dangerous driving, risky financial decision making, and substance use. Two bodies of research of relevance have independently examined the hormonal mechanisms of behavioral dysregulation. One perspective investigates the hormonal predictors and mechanisms (particularly testosterone), while another has focused on reward dysregulation, defined by researchers as the pursuit of pleasurable feelings and stimuli and heightened responsiveness to positive, reward-related stimuli [e.g., Ref. (1–3)]. As we argue, these systems share overlapping psychological and physiological mechanisms, yet have not been simultaneously deployed to understand behavioral dysregulation. Thus, there is a need to integrate these disparate lines of work into a common theoretical framework. This framework should not only be consistent with extant findings but also make novel predictions to be tested in future research.

In this paper, we propose a forward-thinking approach to study reward motivation and behavioral dysregulation, referred to as the positive affective neuroendocrinology (PANE) approach. The PANE approach incorporates existing research in the hormonal mechanisms of behavioral dysregulation with research on reward dysregulation and related positive affectivity. This approach suggests that reward

dysregulation underlies the established links between testosterone and behavioral dysregulation. The PANE approach also holds that testosterone increases reward processing – or neural activity in the reward-relevant regions of the brain – and reward motivation, which in turn increase the likelihood of behavioral dysregulation. More specifically, this framework posits that increases in reward mediate the effects of testosterone on behavioral dysregulation. In this paper, we provide a focused review of the roles of testosterone in modulating behavioral dysregulation and then discuss how reward dysregulation represents a crucial mechanism in this relationship. We also explore the potential sources of sex differences and the effects of age, cortisol, and individual differences within a PANE perspective. Finally, we close with a discussion of future research prospects in the emerging field of affective neuroendocrinology.

Evidence for PANE

What is the evidence for the PANE framework of reward and behavioral dysregulation? In the following sections, we discuss the evidence from three areas for why the association between testosterone and behavioral dysregulation may be mediated by elevated reward dysregulation: (1) evidence showing that testosterone is a predictor and mechanism of behavioral dysregulation, (2) evidence for how reward dysregulation is a critical mechanism of behavioral dysregulation, and (3) evidence that testosterone increases reward dysregulation.

Testosterone and Behavioral Dysregulation

Testosterone, a steroid hormone and end-product of the hypothalamic–pituitary–gonadal (HPG) axis, is of prime relevance to behavioral dysregulation. In men, testosterone is primarily produced in the testes, while women's testosterone is produced in smaller quantities by the ovaries and adrenal cortex (4). Testosterone also has a diurnal cycle, where testosterone is highest upon waking and decreases across the day, flattening in the afternoon (5). Researchers often distinguish between organizational effects of testosterone – the "permanent modification of brain structure and function during prenatal and early postnatal life due to exposure to testosterone" [Ref. (6), p. 15268] – and activational effects of testosterone – temporary, non-developmental moment-to-moment effects of testosterone that modulate affect, cognition, and behavior upon administration or release of testosterone.

Research on the dysregulatory behavioral effects and correlates of testosterone confirms both stable and dynamic, contextual psychological effects of the HPG axis. Studying the stable, trait-like elements of testosterone involves inferring stable levels of testosterone from either multiple samples at the same time of day [e.g., Ref. (7)], or taking a sample at one time of the day for all participants, after a period of neutral activity (8). Support for this approach comes from reports that testosterone concentrations are relatively stable when measured at the same time of day (9). Thus, baseline testosterone can be considered a trait-like index of testosterone. Large-scale studies have linked baseline testosterone to several dysregulatory behaviors in army veterans, such as substance use, previous juvenile delinquency, and law breaking [e.g., Ref. (10)]. Baseline testosterone is also positively associated with risky financial decision making and preferences [see Ref. (11), for a review; e.g., Ref. (12, 13)].

Collectively, there is a weak positive association between stable, trait-like testosterone concentrations and risk-taking, with some inconsistent findings. For instance, Stanton et al. (14) report a non-linear relationship between testosterone and risk-taking, suggesting that risk-taking is elevated in low and high testosterone individuals, but not those with middle-range testosterone concentrations. Additionally, Sapienza et al. (6) report a positive association between testosterone and risk-taking in women, but not men. Furthermore, Schipper (15) found a negative association between testosterone and risk-aversion for gains, but not losses, in men.

The lack of strong effects of baseline testosterone on risk-taking in humans may be due to the potential for testosterone concentrations to alter in response to social events. Although baseline testosterone may predict how individuals generally respond and act across a wide variety of contexts and self-reported psychological traits, a more fine-tuned assessment of testosterone may be needed for assessing situation-specific behaviors. For example, previous work has examined the behavioral effects of testosterone responses to competitions (16–19), opposite sex interactions (20), men's interactions with women (21, 22), social exclusion (23), holding dominant vs. submissive postures (24), and aggressive provocation (25). These dynamic effects of testosterone are theorized to be more robustly associated with context-specific social behaviors than baseline testosterone (26), and this notion is supported by several emerging studies [e.g., Ref. (16, 27, 28)] showing robust effects of testosterone changes predicting aggressive behavior in social contexts. This work is also bolstered by a recent study showing that acute changes in testosterone in response to monetary wins and losses also are associated with increased financial risk-taking in men (29). Collectively, these studies suggest that both baseline and dynamic changes in testosterone are positively related to a range of dysregulatory behaviors, particularly risk-taking.

Reward-Seeking and Behavioral Dysregulation

Theories of behavioral dysregulation (e.g., risk-taking) have distinguished between appetitive, approach-oriented, reward motivations based on achieving satisfaction and avoidance motivations based on reducing or avoiding negative consequences, such as pain, punishment, or losses [e.g., Ref. (30–32)]. Affective and motivational accounts of risk-taking specify reward dysregulation as a critical component [e.g., Ref. (33)]. Additionally, elevations in reward-seeking facilitate the heightened risk-taking behaviors associated with adolescence [see Ref. (34), for review] and underlie a host of dysregulatory behaviors, such as addictive gambling (35), substance abuse (36), traffic violations (37), and childhood obesity (38). In this work, both the elevated experience of positive emotions and the experience of excessive reward motivation are critical components to behavioral dysregulation.

The deleterious effects of reward motivation and excessive positive emotion also emerge in clinical disorders. Disorders associated with risk-taking behavior, such as bipolar disorder (BD), are characterized by elevated and abnormally persistent positive emotions (39), excessive reward pursuit and deficits in reward-related learning [e.g., Ref. (40)], and deficits in positive

emotion regulation [e.g., Ref. (41–43)]. BD is often characterized by elevated risk-taking behaviors and impulsivity (44, 45), such as substance use (46), impulsive gambling behavior (47), aggressive behavior (48), and harmful substance use (46). Broadly, deficits in the behavioral approach system (BAS) are thought to characterize BD and elevated behavioral dysregulation (49).

The effects of positive emotion regulation and elevated, persistent positive affect on behavioral dysregulation are becoming increasingly known. When experiencing urgent positive emotions, people are more likely to engage in a variety of dysregulatory behaviors, such as substance use and risky-sexual behavior (50, 51). Elevated reward processing and positive affect have a robust association with risk-taking (52). Additionally, dysregulatory behaviors such as substance use, binge eating, and risky-sexual behavior, are more likely to occur in the context of positive emotions (50, 51). Elevated reward processing and positive affect have a robust association with risk-taking (52). Additionally, elevated reward-sensitivity uniquely characterizes a subpopulation of drug addicts that are motivated toward drug addiction through the presence of potential for rewards (53, 54).

Research on clinical disorders has also provided insights into the fundamental affective mechanisms of behavioral dysregulation. This research suggests that reward dysregulation is a critical component of behavioral dysregulation. Affective accounts of risk-taking specify reward dysregulation as a critical component [e.g., Ref. (33)]. Clinical disorders associated with risk-taking behavior, such as BD, are characterized by elevated and abnormally persistent positive emotions (39), excessive reward pursuits and deficits in reward-related learning [e.g., Ref. (40)], and deficits in positive emotion regulation [e.g., Ref. (3, 41, 42)]. BD is often characterized by elevated risk-taking behaviors and impulsivity (44, 45), such as substance use (46), impulsive gambling behavior (47), aggressive behavior (48), and harmful substance use (46). In addition to excessive positive emotion, this heightened irritability may also potentiate behavioral dysregulation, such as impulsive aggression (55).

Reward-Related Neural Function and Behavioral Dysregulation

In addition to elevated positive affect and reward motivation, neural structures related to positive affect and reward also predict behavioral dysregulation. The reward system has been broadly thought to be the neural basis of the BAS, which operates via the mesolimbic dopaminergic network (56, 57). Connectivity between these dopaminergic regions is theorized to form the basis of the neural circuits of reward and appetitive behavior [see Ref. (58) for a review]. Broadly, this reward system of the brain utilizes several key dopamine-linked structures, such as the ventral tegmental area (VTA) and nucleus accumbens (NAcc), the latter of which is nested in the ventral striatum (59–61). Within these regions, the VTA has numerous dopaminergic pathways with output to the hippocampus, amygdala, medial pre-frontal cortex (PFC) ventral pallidum, and of prime relevance, the NAcc [Ref. (62), for a review]. For example, dopaminergic neuron activation in the VTA that stimulates the NAcc aids in reinforcing responses to food and drugs used in substance abuse [see Ref. (63), for a review], as well as reward cues (64). The NAcc also plays a critical role in affect and appetitive motivation, reaction to novel stimuli, reward-related learning, responses to delayed reward, controlling feeding, and hedonic taste preferences [e.g., Ref. (65–70)]. More broadly, dopamine release in the ventral striatum is associated with self-reported euphoria in humans [e.g., Ref. (71)] and is thought to be a critical modulator of reward anticipation in mammals (72).

Dysregulation in the dopaminergic system has attracted considerable attention in researching behavioral dysregulation and related psychiatric disorders [see Ref. (59, 73), for a review]. For instance, the dopaminergic reward system and dopamine receptor polymorphisms have been linked to the crucial rewarding effects of substance abuse and addiction (74) and pathological gambling [e.g., Ref. (75–77)]. The dopamine system and receptors also modulate increased risky-decision making in humans [e.g., Ref. (78, 79)] and impulsive behavior in rodents [e.g., Ref. (80)]. Furthermore, neural theories of self-regulation (81, 82) hold that self-control is a function of the balance of activation and connectivity between the mesolimbic dopaminergic regions and regions of the PFC – a putative mechanism of self-control, inhibiting craving, and emotional control (74, 83–85). As we will discuss, testosterone modulates activity in these regions (see **Figure 1**).

Testosterone and Reward

Our evidence for testosterone's role in reward-seeking comes from three areas of research: testosterone and reward-seeking behavior, testosterone and reward-related affect, and testosterone and the neural circuitry of reward.

Testosterone and Reward-Seeking Behavior and Traits

Without involving affective and neural processes, testosterone is associated with increased reward-focused traits, sensation seeking, and impulsive behaviors in humans and animals [e.g., Ref. (86–92)]. Additionally, previous work suggests that exogenous testosterone administration can shift sensitivity from punishment

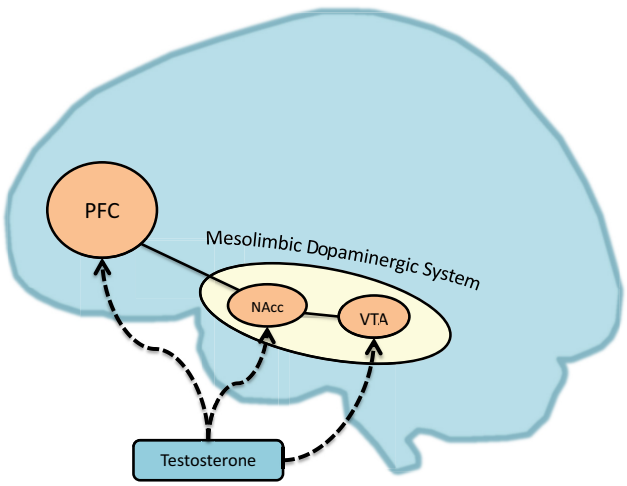

FIGURE 1 | Testosterone's effects on brain regions associated with reward dysregulation. PFC, prefrontal cortex; NAcc, nucleus accumbens; VTA, ventral tegmental area.

to reward dependency (93). Testosterone changes are also associated with increased monetary gains in stock traders (94). Broadly, this work suggests that testosterone increases motivation to seek rewards.

Testosterone and Reward-Related Affect

Testosterone may be related to reward-seeking behaviors, but is it associated with reward-related affect? Work using exogenously administered testosterone suggests that testosterone may shift focus away from withdrawal-related emotions to approach-related, reward-focused aggression (95, 96), and increase subjective and physiological measures of sexual-arousal (97). Testosterone may also be associated with approach-related positive affect. Indeed, testosterone increases are correlated with increased enjoyment of competition in decisive victories (98). Additionally, there is a well-established negative correlation between testosterone and depressive symptoms [see Ref. (99), for a review]. Previous work also suggests that exogenously administered testosterone can also decrease depression (100, 101) and increase manic symptoms (102). Furthermore, in women with BD, testosterone concentrations positively predict the number of manic episodes and suicide attempts (103).

Testosterone and Reward-Related Neural Function

Broadly, both testosterone's organizational and activational effects on the brain are associated with neural regions linked to increased dominance, reward, and approach behaviors [see Ref. (26, 104–106) for reviews; Ref. (107)]. Relevant to the current framework, an expansive literature suggests that testosterone is linked to reward-related neural function, both within animal and human literature. We summarize these associations in **Figure 1**. Animal research suggests testosterone modulates the dopaminergic system (108–110) and dopamine-linked sexual behaviors in rodents [e.g., Ref. (111, 112)], and has rewarding effects via the mesolimbic dopaminergic system [see Ref. (113), for a review]. For instance, rats show conditioned place preference for regions where they received testosterone injections, and this effect is mediated by dopamine function in the ventral striatum and NAcc (114, 115). Supporting this idea, research in hamsters also suggests testosterone can facilitate dopaminergic activity in the NAcc (116). Furthermore, research with California mice suggests testosterone increases in response to victories facilitate future aggression through the expression of androgen receptors in the ventral striatum (117), potentially through dopaminergic activity.

The association between testosterone and reward-related neural activity parallels that of rodent research. In humans, adolescents' hormonal changes in puberty have also been theorized to increase appetitive motivation by influencing reward-linked brain structures and dopaminergic pathways (118–122). In humans, testosterone administration increases functional connectivity in neural circuits linked with reduced depression (123). Additionally, exogenous testosterone administrations in humans increase ventral striatal responses to financial reward cues in adolescents and adults receiving monetary rewards (124, 125).

In summary, testosterone may increase reward motivation by acting directly on dopaminergic neural structures in the BAS. However, less work has focused on the effects of testosterone and the BAS beyond dopamine-dependent regions. Although some work suggests, for instance, that testosterone is associated with elevated dorsolateral pre-frontal cortex (DLPFC) activation during an anger control induction (126), other work has not revealed associations between testosterone and the DLPFC during aggressive interactions (127). Future research is needed to extend the specificity of the effects of testosterone beyond reward function to the BAS.

Reciprocal Associations Between Reward and Testosterone

Overall, the literature reviewed above suggests that testosterone can increase reward processing and dysregulation. However, there also may be a reciprocal effect of reward on testosterone increases. Reciprocal associations are consistent with existing neuroendocrine theories that posit hormones and behavior reciprocally affect each other through feedback loops [e.g., Ref. (128)]. Broadly, contexts that modulate testosterone responses, such as competitive outcomes and sexually attractive individuals, have rewarding properties. For instance, testosterone responses to competitive victories that facilitate aggressive and risk-taking behavior may occur because winning a competition is an enjoyable experience. Research supporting this possibility suggests a positive association between testosterone responses in winners of competitions and enjoyment of the competition (98). Additionally, the dynamic increases in testosterone following winning a competition and decreases following losing have been thought to facilitate changes in reward-dependent learning (129). However, to fully test this hypothesis, research experimentally manipulates reward in multiple contexts while measuring the effects on testosterone fluctuations is needed.

Critical Moderators

In the following section, we highlight potential critical moderators for within the PANE framework, including cortisol, sex, age, and individual differences linked to reward sensitivity and motivation.

Interactive Effects with Cortisol

Within the PANE framework, testosterone may interact with other hormones to predict behavioral dysregulation. Emerging work also suggests that cortisol – a glucocorticoid steroid hormone released as the end-product of the HPG axis – interacts with testosterone to modulate dysregulatory behavior [see Ref. (130), for a review]. From a neurobiological perspective, cortisol downregulates androgen receptors, inhibits HPG activity, and inhibits the effects of testosterone on specific tissues [e.g., Ref. (131–134)]. Additionally, the HPG and HPA axes are thought to have mutually inhibitory effects on each other (135). Therefore, it is possible that cortisol may also moderate the psychological and behavioral effects of testosterone. This notion is supported by psychological literature, finding that when cortisol levels are low, but not high, testosterone levels are positively associated with dominance (136), risk-taking (137), perceived status (138), violent crime (139, 140), and externalizing psychopathology in adolescents (141), although others did not find similar associations (10, 142). Recent research also suggests that acute testosterone changes are positively related to earnings in bargaining contexts when cortisol levels decrease, but not increase (143). In summary,

not only do cortisol and testosterone have independent effects on costly behavioral dysregulation but these hormones may also co-regulate risk-taking behavior and impulsive traits. Future research is needed to further investigate the extent to which testosterone and cortisol jointly influence self-control related behaviors (144).

Sex Differences in the Psychoneuroendocrinology of Behavioral Dysregulation

A large literature suggests men are more impulsive, punishment insensitive, and sensation seeking than women [see Ref. (145), for a meta-analysis; Ref. (146)], and are on average, more risk-taking (147), although the effect sizes are small (148). Men also typically die earlier than women (149, 150), are more likely to die from violent deaths (151), are more aggressive [e.g., Ref. (152–155)], and are more likely to abuse alcohol (156). Additionally, relative to women, men have more psychopathological traits and disorders linked increased impulsivity (39, 157–160).

Sex differences in testosterone are thought to account for sex differences in risk-taking (6). Work by Sapienza and colleagues indicates that both the organizational functions of testosterone in prenatal development – indexed by the ratio of the second to fourth finger digits (161, 162) – and circulating levels of testosterone account for sex differences in risky-decision making. On the level of prenatal exposure to testosterone, previous work has found physiological indicators of prenatal testosterone exposure can alter children's social and empathic abilities (163). Although numerous cultural and social factors explain gender differences in behavioral dysregulation, both organizational and activational effects of testosterone likely explain a portion of this variability. It is important, however, not to rule out social and cultural factors facilitating differences in behavioral dysregulation between men and women. Gender roles often guide behavior through social pressures and conformity [see Ref. (164, 165), for reviews]. To explain sex differences in dysregulatory impulsivity and risk-taking, it is necessary to account for not only both the nature and nurture, but the interaction between the two (164–166).

The effects of dynamic changes in testosterone on behavior may be specific to men. For example, Carré et al. (16) find that testosterone reactivity mediates the effect of competitive outcomes on aggressive behavior specifically in men but not women. Although several studies investigating the effects of testosterone reactivity on dysregulatory behaviors have primarily focused on samples of men [e.g., Ref. (23, 28)], future research is needed to establish whether the dynamic effects of testosterone on dysregulatory behavior are sex-specific. This work does not imply, however, that testosterone cannot have behavioral and psychological effects in women. Several testosterone administration studies, for example, have produced behavioral and psychological effects of testosterone in samples of exclusively women [e.g., Ref. (167–170)]. Additionally, previous work has identified interactive effects of testosterone and cortisol in samples of both men and women (136, 137).

Several factors may additionally explain smaller psychological and behavioral effects of testosterone in women. First, animal research suggests that females may have less androgen sensitivity compared to males. Although exogenous androgens can influence sexual mounting behaviors in female hamsters, female hamsters are less responsive to the effects of androgens on neuroendocrine function and sexual behavior than males (171, 172). Females have also been found to have decreased androgen receptor immunoreactivity and density compared to males in several regions of the brain (173). Second, compared men, women produce far less testosterone and have less variability in testosterone. This restricted range reduces the statistical power to detect testosterone's psychological and behavioral effects (174) and this may hinder the detection of these effects in women. Additionally, the type of methodology used to measure testosterone can have sensitivity at different ranges (175) and may not always be well-suited for measuring the decreased concentrations of testosterone in women.

In summary, testosterone explains both intersex and intrasex variability in dysregulatory behavior. Researchers have several obstacles in measuring testosterone, which hopefully will be curtailed with the advent of greater precision in measurement and the accumulation of more data. Further exploring the role of testosterone in reward dysregulation within men and women would advance the study of the psychological effects of testosterone.

Age

Another potential moderator of the PANE framework is age. Post-adolescence aging coincides with decreases in testosterone [e.g., Ref. (176)], decline in neural reward-related function [e.g., Ref. (177)], increased preferences for delayed rewards (178), and decreased risk-taking behavior [e.g., Ref. (147)]. Furthermore, developmental researchers have proposed that pubertal increases in sex hormones including testosterone are linked to elevated risk-taking in adolescents (179, 180). Additionally, research on risk-taking suggest that both male and female adolescents engage in more risk-taking compared to adults [e.g., Ref. (181, 182)], leaving greater potential for testosterone to explain risk-taking in adolescents compared to adults. Thus, it is possible that age may moderate associations in the PANE framework and also modulate differences in the mechanisms of testosterone, reward function, and behavioral dysregulation.

Individual Differences

Although work on individual differences moderators of testosterone, reward, and behavioral dysregulation is preliminary, the associations in the PANE framework may be modulated by individual differences. For instance, Norman et al. (183) found that trait anxiety moderates the association between testosterone dynamics and impulsive aggression, while Schultheiss and colleagues (184, 185) report that implicit power motive can modulate testosterone responses to competitive contexts. Additionally, the mechanisms in PANE may also be affected by other individual differences related to reward motivation, such as the behavioral inhibition and activation scales [BIS/BAS; (186)] or regulatory focus (187).

The PANE Framework – A Summary

The PANE framework provides an organizing framework of existing research showing that the association between testosterone and behavioral dysregulation is mediated by increased reward motivation and reward dysregulation (see **Figure 2**). Specifically, the PANE approach primarily holds that both stable, trait-like levels and moment-to-moment dynamic changes in testosterone

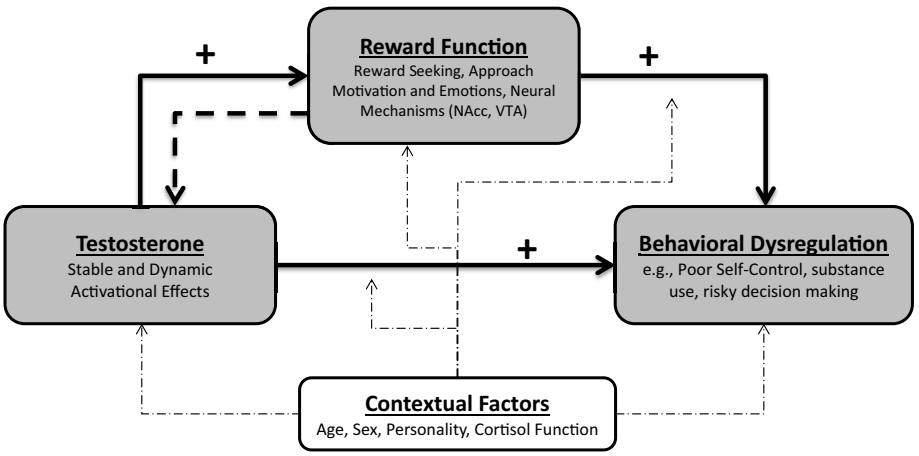

FIGURE 2 | The PANE framework of reward and behavioral dysregulation. The PANE framework specifies that elevated stable levels and dynamic increases of testosterone facilitate increased reward function. This increased reward function then facilitates behavioral dysregulation and behaviors indicative of excessive reward pursuit. This perspective also allows for the possibility that reward function can increase testosterone.

can increase reward dysregulation. Enhanced reward processing – a psychological and neural mechanism of behavioral dysregulation – then increases the likelihood of behavioral dysregulation. Because reward function is affected by testosterone and also serves as a key mechanism of behavioral dysregulation, we argue that reward function is a prime candidate for a mediator of the association between testosterone and behavioral dysregulation. Consistent with contemporary accounts of mediation (188), by specifying reward function as a mediator of the association between testosterone and behavioral dysregulation, we mean that reward function is a causal mechanism in this association. As we review above, testosterone and reward function and motivation modulate a common set of reward-dependent behaviors, and well-established causal directions among testosterone, reward, and behavioral dysregulation suggest that this network of relations is mediated.

The PANE approach is currently at a preliminary state in understanding neuroendocrine function, reward-dysfunction, and behavioral dysregulation. The current paper provides a rationale for why reward function may mediate the association between testosterone and behavioral dysregulation. However, as a whole, this mediation is untested by empirical articles. Future work is needed for researchers to test the overall mediation proposed by the PANE framework. This framework can be measured and tested in numerous forms and contexts, including using both human and animal samples, experimental manipulations of reward, pharmacological testosterone manipulations, testosterone modulating experimental paradigms (e.g., competitive outcomes), and multiple measures of behavioral dysregulation (e.g., poor financial decision making, substance abuse, risky-sexual behaviors). This flexibility allows for the PANE model to be tested and applied by researchers from many backgrounds.

It is necessary to note where the PANE approach differs from other neuroendocrine accounts of behavior. Previous accounts of testosterone and social behavior often indicate testosterone as a biomarker and mechanism of dominance and reproductive behaviors [e.g., Ref. (189, 190)], while recent research has also linked testosterone to threat-based neural function [e.g., Ref. (191)]. It is clear that testosterone modulates these psychological functions in addition to purely reward-related function. However, the literature we review suggests that dominance and sexual behavior are not the only variables regulated by testosterone. As we reviewed, testosterone is related to reward-related neural function, affect, and behaviors, as well as multiple phenotypes of behavioral dysregulation more distal to sexual behavior and dominance, such as substance use, risky-decision making, and sensation seeking. Thus, these behaviors are unlikely to be guided completely by the dominance and sexual behavior-related functions of testosterone. It is possible, instead, that rewards of status-seeking and sexual behavior may actually be a function of the reward-related function of testosterone, but future work is needed to test this possibility. At this point, the PANE framework is designed to be an additive perspective of the effects of testosterone on behavior in addition to other existing accounts.

Future Directions for Research on Reward Dysregulation, Testosterone, and Behavioral Dysregulation

Although the PANE approach proposes that reward function is a critical mediator in the association of testosterone and dysregulatory behaviors, this research can be developed in several ways. In the following sections, we also propose additional ways the PANE perspective can be expanded: (1) the role of social functioning, (2) translational work in psychiatric populations, (3) integration with neuroendocrine models of aggressive behavior, (4) the positive effects of behavioral dysregulation, and (5) integration with other systems of behavioral dysregulation.

Decreased Social Functioning

Testosterone may also increase risk-taking by decreasing social connections with others. It has been long known that socially isolated or disconnected individuals are more likely to engage

in reckless behaviors, such as aggression, violence, and drug use (192, 193). This idea is consistent with recent reports suggesting a robust association between having social connections and decreased risk-taking. For instance, having better quality peer and family relationships is associated with decreased risk-taking in adolescents (194, 195) and higher levels of social support are linked with decreased risk-taking in stigmatized sexual minorities [e.g., Ref. (196, 197)]. Additionally, self-regulation has been found to be impaired by social exclusion (198). Socially excluded people are also more likely to engage in financial risk-taking (199).

How might testosterone decrease social relationship quality? Broadly, low testosterone is associated with nurturant, pro-social, relationship-promoting behavior (200–202). Basal testosterone is positively associated with having an avoidant, disconnected interpersonal approach, and greater loneliness (203). Testosterone is also positively related to decreased relationship satisfaction and commitment in couples, in both individuals and their romantic partners (204). Additionally, exogenous testosterone can decrease empathy and trust (168, 205), which may impair social relations. Furthermore, the increased risk-taking associated with testosterone function may also in turn decrease relationship quality, further impairing this process.

In summary, by decreasing the quality of social relationships, testosterone may increase the likelihood individuals engage in dysregulatory behaviors, such as maladaptive substance use to cope with poor social relationships [e.g., Ref. (206)]. We additionally suggest this association may be mediated by other processes we previously reviewed. For instance, research suggests having more meaningful family relationships can decrease risk-taking through neural activation indicative of decreased reward sensitivity and increased cognitive control [dorsolateral pre-frontal cortex, Ref. (194)]. Likewise, decreased empathy – an emergent property of reward and positive emotions (207, 208) – may also be related to the association between testosterone and reward processing.

Translational Implications for Psychiatric Illnesses

Numerous psychological disorders are characterized by trait impulsivity and behavioral dysregulation, such as BD, borderline personality disorder, and attention deficit hyperactivity disorder (39). From the PANE perspective, targeting hormones and affective states leading to behavioral dysregulation presents a novel, translational approach to understanding and treating these disorders. In particular, BD is a prime candidate to investigate the PANE approach. BD is characterized by increased reward sensitivity and difficulties down-regulating reward (2, 41), which may be of particular interest and application for the PANE approach. A chronic, severe, and often fatal psychiatric illness, BD ranks in the top 10 leading causes of worldwide disability by the World Health Organization. The core diagnostic criterion for BD involves periods of abnormally and persistently elevated positive mood (39) and impairments in reward processing have been proposed as a putative endophenotype for BD (209).

Three lines of evidence suggest that BD is a target population for studying testosterone and reward function. First, BD is associated with increased reward sensitivity. For example, people with BD exhibit increased reward reactivity (2, 210, 211), excessive pursuits aimed at obtaining rewards (1, 212), and impairments in reward-related learning (213). Second, empirical models of BD stress the importance of reward dysregulation in the causes and course of the disorder (1, 2, 210–212). Troubles with reward processing persist in BD, even during periods of symptom remission. For example, remitted BD patients report trouble decreasing or down-regulating reward (42), and engage in maladaptive strategies that amplify reward-relevant responses (43, 214), compared with healthy controls. Third, increased reward sensitivity is associated with clinical impairment in BD. Sensitivity to reward predicts increases in manic symptoms over time in BD (215).

Preliminary evidence also suggests that testosterone is important factor for understanding the course and symptom severity in BD. For instance, heightened testosterone levels are associated with significant increases in mania symptoms and severity in BD (103, 216), and oral administration of testosterone has been causally linked to the onset of manic symptoms (102). Future research is needed to understand the hormonal and reward-related mechanisms of BD and other disorders.

Integration with Theories of Aggressive Behavior

Much of research and theory links aggressive behavior to negative affective systems and threat processing [e.g., Ref. (217–221); see Ref. (26), for a review]. However, the reward systems are also implicated in aggressive behavior [e.g., Ref. (117, 222)]. A model of aggressive behavior accounting for reward and threat-processing may help explain mixed evidence for testosterone and aggressive behavior in neuroendocrine research. Although threat-function and negative affective systems undoubtedly play a critical role in facilitating aggressive behavior, a PANE approach to aggression may help enhance neuroendocrine models of aggressive behavior beyond just accounting for negative affect.

Exploring the "Light Side" of Behavioral Dysregulation

So far, the primary discussion of the PANE approach to impulsive behavioral dysregulation has focused on impulsive behaviors. However, just as calculated, non-impulsive behaviors can have antisocial consequences, not all impulsive acts have negative effects and many can be generous or pro-social to others [e.g., Ref. (223, 224)]. Emerging research suggests testosterone is positively associated with pro-social acts of fairness, cooperation, and reciprocity (205, 225, 226). Because positive emotionality has been found to be linked to pro-social behavior and because neural systems linked to reward are also related to pro-social behavior (227), the PANE approach may also explain the how testosterone can increase pro-social behaviors through positive emotions and reward motivation. Future research is needed to uncover further associations between testosterone, positive emotions, and pro-social behavior.

Integration with Other Systems of Behavioral Dysregulation

Although the PANE perspective specifies reward processing as a central mediator to the association between testosterone and behavioral dysregulation, reward is likely not the only mechanism. For example, one potential mechanism of increased risk-taking and impulsive behavior implicated are the pre-frontal regions of

the brain linked to impulse control and self-regulation, such as the orbitofrontal cortex (OFC), which is related to risky-decision making [Ref. (228); see Ref. (179), for a review]. Although the literature suggesting testosterone can modulate the OFC is not as expansive as the testosterone-reward literature, the association testosterone has with aggression and risk-taking has been in part explained by decreased OFC activation (127) and volume in males (179). Furthermore, research suggests testosterone decreases connectivity between the OFC and subcortical areas like the amygdala (229, 230).

The effects of testosterone on the reward and self-control systems fit well with established dual-systems models of self-control. Hofmann et al. (231) specify that two systems modulate self-control: an impulsive associate system that automatically triggers impulsive responses to the environment and a reflective system providing executive control of overriding impulses and implementing strategic plans for goal pursuit. Based on what is known of the neural effects of testosterone, testosterone changes may modulate the activation of both impulsive and reflective systems. As more research emerges, one broad goal of the PANE perspective and surrounding research will be to integrate more with other mechanisms and perspectives of behavioral dysregulation, such as the dual-systems approach.

Conclusion

The PANE perspective is designed to organize the work on testosterone, reward dysregulation, and behavioral dysregulation into one coherent framework to stimulate research on behavioral dysregulation. The endocrine mechanisms discussed in this paper may also influence behavioral dysregulation through other mechanisms than reward [such as self-control systems and the OFC, Ref. (127)]. However, the evidence is clear that reward dysregulation is a principal mechanism modulating dysregulatory behaviors and it is necessary to unify this work into a larger framework. Broadly, researchers need to identify mediating psychological and neural mechanisms for the association between testosterone and behavioral dysregulation, and to unify these processes in an elegant, unified model. Together, both neuroendocrine and reward motivation accounts of behavioral dysregulation may hold promise in explaining poor self-control and impulsive behaviors across a wide range of clinical, health, and social contexts.

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Importance of sex differences in impulse control and addictions

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Historically, sex- or gender-related differences in addictions have been understudied. When neglected, both sexes may not receive the full benefit of medical research. Although hormone fluctuations in women are rarely investigated with respect to treatments, levels of estrogen and progesterone may have large impacts on the efficacies of behavioral or pharmaceutical interventions (1–7). The National Institutes of Health (NIH) have been advocating for investigating gender-related differences and hormonal influences (8), including with respect to impulse control and its contributions to addictions. Despite the importance of studying sex differences, the standard integration of sex-difference considerations, including in preclinical research using cell lines and animals, has yet to occur.

Sex differences are present in personality traits and behaviors, such as impulsivity, that have been associated with addictions (both substance and non-substance). Impulsivity has been defined as a tendency to act with little foresight or little consideration of future consequences (9, 10). Impulsivity is a complex construct that may be separated into specific factors; two main domains that can be measured in the laboratory include impulsive action and impulsive choice (11). Both impulsive action and choice have been associated with drug use, in both a predictive fashion and as a result of drug use (12, 13). Work investigating sex differences in impulsive action in both animals and humans has shown mixed results (14). The mixed findings may in part relate to sex hormones, with females displaying fluctuating levels of impulsivity dependent on cycle phase and estrogen levels (14).

Impulsive choice has been measured in the laboratory using delay-discounting tasks (13, 15–17). While multiple studies suggest that men may be more impulsive than women, careful investigation of specific facets suggest otherwise. Women may display greater discounting rates than men (i.e., greater choice impulsivity); however, reward type is relevant as men have been found to discount real money more rapidly than women, with women discounting hypothetical rewards more rapidly than men (18). Among adolescents, female smokers appear more impulsive than male smokers, but male control subjects appear more impulsive than female control subjects (19). Consistent with findings from Kirby and Marakovic (18); Heyman and Gibb (20) found that female smokers also tend to discount the value of hypothetical rewards more rapidly than do males.

Among heavy drinkers, women exhibit poorer inhibitory control than men (21, 22). A study investigating the neural correlates of impulsivity in non-abusing individuals who were family-history positive for alcohol abuse found that those who are family-history positive show greater recruitment of brain regions involved in addiction, inhibitory control, and executive function compared to those without family histories of alcoholism; however, this effect was driven by males (23). Had gender differences not been built into the experimental design, such a finding would not have been identified. Although there exist strong associations between drug use and impulsivity in both humans and animals, with impulsivity increasing the propensity for drug use and vice-versa (12, 13, 24, 25), few studies have investigated sex differences, particularly in preclinical work. The possible roles for cycle phase or circulating hormones in delay-discounting-task performance warrant further study.

Impulsivity and behavioral performance in impulsivity tasks does not always differ between men and women; however, that does not mean that both sexes are achieving similar performance in the same way. Even when men and women perform comparably in inhibitory tasks, different neurobiologies may underlie the behaviors. For example, in a recent study of gender-related differences in neural factors associated with performance of the stop-signal task, men tended to show more activation in the lentiform nucleus, parahippocampal gyrus, posterior and anterior cingulate cortices, middle and medial frontal cortices, and thalamus, compared to women, despite similar performance on the task (26). In general, men and women display different brain connectivity patterns, both in adolescence and adulthood. One study found that men show greater within-hemispheric connectivity and women show greater across-hemispheric activity, suggesting that male brains may be better suited to facilitate connectivity between perception and coordinated action, whereas female brains may be better suited to facilitate communication between analytical and intuitive processes (27). As neurobiological differences in males and females start in early stages of development (28, 29), it may be difficult to

determine which differences are the result of genetics, which are influenced by cycling hormones and which may arise through interactions and other processes. Some differences may arise from how similarly conserved genes across the sexes are translated and expressed differently depending on sex (30).

Although men and women may use the same drugs and display the same behavioral addictions, frequencies may vary by drugs and behaviors (31). Furthermore, addictions may present differently, have different courses and patterns of comorbidity, be driven by different motivations, and have different factors leading to relapse (14, 32, 33). Males typically have higher rates of drug use and are more likely to develop dependence or abuse; however, women may have transition from initial use to dependence more quickly. Preclinical and clinical data suggest an enhanced vulnerability to drug use with greater acquisition of drug self-administration in females as compared to males (32, 34–40).

Given apparent sex differences in susceptibilities to drug use, sex differences in the approach to treating drug use and drug-use disorders are important to consider in order to optimize interventions for each sex. A recent study investigating sex differences in the efficacy of disulfiram in cocaine and alcohol dependence found that women, compared to men, had poorer treatment outcomes on several measures of cocaine use during treatment and at post-treatment follow-up, which was primarily accounted for by disulfiram being less effective in women than men (41). Gonadal hormones may influence relationships with treatment outcomes as estrogen may enhance the rewarding properties of drugs whereas progesterone may be more protective and attenuate drug-rewarding effects (5, 7, 42). Severity of withdrawal symptoms may vary based on menstrual-cycle phase (1–4). Moreover, estrogen interactions with dopamine transmission or the hypothalamic-pituitary-adrenal (HPA) axis may partially underlie facilitative effects (43–45). For example, females may be more affected by stress and report stress as a reason for drug use and relapse; therefore, greater activation of the HPA axis through stress has the potential to interact with circulating estrogen and monoamine neurotransmitters such as dopamine and serotonin (both implicated in rewarding and motivational aspects of drug use and impulse control) (34, 46, 47).

Women may be more likely to engage in addictive behaviors for negative reinforcement reasons (e.g., escape from stress) whereas men may be more likely to engage in addictive behaviors for positive reinforcement reasons (e.g., seeking a high), and these motivational differences may reflect different biologies and/or result in different clinical presentations. For example, studies link differences in cortico-striato-limbic activations in cocaine dependence to stress cues in women and drug cues in men (48). Additionally, women more frequently than men present with other mental health issues, such as trauma and depression, that co-occur with addictions (33).

Sex differences may extend to non-substance or behavioral addictions like gambling disorder. Women with gambling problems often display a "telescoping" effect similar to women with substance addictions, whereby females often initiate recreational behavior at a later age than men but progress more quickly into problematic gambling (49, 50). Males tend to develop problems with "face-to-face" forms of gambling (e.g., poker or blackjack), whereas females are more likely to develop problems with less personally interactive forms [e.g., bingo, keno, electronic-gambling (slot) machines], with differences appearing to relate to impaired control over gender-related behavioral preferences evident in recreational gamblers (49, 51). Taken together, data suggest important gender-related differences exist that warrant consideration in optimizing policy, prevention, and treatment initiatives.

When investigating the relationships between sex, hormones, impulsivity, and addictions, it will be important to consider research designs. Impulsivity is a multifaceted construct and therefore using tasks assessing specific aspects of impulsivity is important (52, 53). Additionally, the reinforcer presented may also be an important variable as males and females may have different motivations relating to consumption of specific reinforcers, and women may discount more quickly than men when rewards are hypothetical. In rodents, no differences were found between males and females in premature responding when the reward was food; however, when the reward was cocaine, female rats made significantly more premature responses (54). It is unclear whether the increase in premature responding in female rats for cocaine was related to cycle phase. High estrogen levels may attenuate impulsive action and depleting male rats of testosterone may decrease impulsive action (55), but high estrogen levels have also been associated with increased sensitivity to cocaine (56). Therefore, it is important to determine whether there are fluctuating levels of impulsivity across different cycle phases and how these might relate to addictions. Additionally, understanding and studying genetic differences (and similarities) between men and women that may underlie behavior and neural activity is important. One way to disentangle potential roles of hormones and genetic factors relating to impulsivity and addiction involves manipulating hormone levels by administering or blocking cycling hormones and using hormone replacement therapy, particularly in females who are in menopause. Moreover, in preclinical models, the use of ovariectomized animals and controlled administration or release of various hormones is possible. Preclinical studies may effectively disentangle influences of genotype (XX, XY) from gonadal phenotype (ovaries, testes) with respect to impulsivity-related and addiction-related behaviors (57). Applying these techniques in longitudinal studies across the life-span in both females and males could provide important insight into developmental sex differences in impulsivity and addiction, and these findings may inform human research and efforts to develop more effective policy, prevention, and treatment interventions.

In summary, data demonstrate the importance of studying sex differences in addictions and impulsivity and their interactions. While research has progressed in these areas, there remains a deficit in understanding sex differences. While NIH has promoted the study of males and females in clinical populations, sex differences are not uniformly and systematically investigated and influences of circulating hormones are not routinely documented. Therefore, it is difficult to determine which differences may link to hormones and which may link to genetic

differences between the sexes. In preclinical research, sex differences are often neglected, which may limit the translation of preclinical findings into clinical settings. Routine considerations of sex differences in preclinical and clinical research settings will help advance translational efforts and improve prevention, treatment, and policy initiatives.

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Is it important to consider sex and gender in neurocognitive studies?

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Is it important to consider sex and gender in neurocognitive, neurobiological, and clinical studies? I refer here to "sex" as a biological variable related mainly to sex chromosomes and sex steroid hormones, while "gender" stands for a psychosociocultural construct related to gender role socialization, levels of masculinity and femininity, and stress related to adhesion to gender stereotypes. It is a rhetorical question and I hope that an overwhelming majority of readers would answer: "yes, of course!" However, despite the fact that more attention has been devoted over the past decade to delineating differences between men and women in their neuroanatomy, neurophysiology, and cognitive and emotional processing (1, 2), a substantial number of researchers (basic and clinical) continue ignoring "the second sex" and study exclusively males. The reasons are multiple and range from an unawareness, through a lack of sufficient funding to examine both sexes, to the argument that the studies, to date, have not found any significant sex differences in a given paradigm or disorder and therefore there is no need to include both males and females in a study. Finally, there is a group of theorists who sees this line of inquiry (i.e., investigating sex differences in the brain and cognition) as inherently biased, thus contributing to some harmful stereotypes that may lead to increasing gender inequalities [e.g., Ref. (3, 4)].

It is hard to argue with the lack of funds and indeed there are cognitive and clinical domains where we have not seen any indication of potential sex or gender differences. Nevertheless, our technology has improved and we possess more sensitive instrumentation, which may detect subtle differences that were not previously apparent. Moreover, we must remember that men and women of today are different from men and women of two or three decades ago. We are not only socialized differently, due to changed family values and education, more competitive job market and prominence of social media, but also exposed to more environmental toxins, including endocrine disruptors, which may affect our physical and mental health (5, 6). As to the harmful effects of some studies of the neurobiological and cognitive sex differences, I agree that data are sometimes interpreted in a biased manner and may contribute to propagation of damaging gender stereotypes. However, I also believe that excluding women is much more dangerous. We have seen the harm done with several drugs released for treatment of various disorders without proper testing or consideration of women's physiology (e.g., Posicor, approved for the treatment of hypertension and angina, slowed or stopped the heart rate especially in elderly women; antihistamines such as Seldane and Hismanal induced cardiac arrhythmias disproportionally more frequently in women), but thankfully the situation is changing (7, 8).

While it is true that men and women are much more alike than different and it actually makes more sense to talk about sex and gender similarities (be it in brain structure or cognitive function), there are those subtle differences that may provide clues to disentangling etiology of some neurological and neuropsychiatric disorders, such as multiple sclerosis, autism, mood, and anxiety disorders, or shed a new light on treatment of these conditions. In short, "vive la similarité, but let's explore differences!" I would like to use two clinical examples that I am most familiar with, to illustrate my point – schizophrenia and drug addiction.

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Schizophrenia

The existence of sex differences in the prevalence, development, and progression of schizophrenia was noted already by Kraepelin and Bleuler who conceptualized and meticulously described the disorder at the beginning of the twentieth century (9, 10). Possibly because the prevalence of schizophrenia is greater in men than in women during the first half of life (until about 40 years of age), most studies forgot about women altogether – this despite the fact that there is a second peak of new cases in women around the age of menopause when they catch up with men in the prevalence (11, 12). I was unaware of this bias when I started investigating neural correlates of cognitive function in schizophrenia during my graduate school years, but very soon afterwards, as an independent researcher, it became clear that existing theories and treatment of schizophrenia were based almost entirely on data from male subjects (human and animal). This realization hit me when I came across two intriguing research studies, which found a neuroanatomical reversal of normal sexual dimorphism in the anterior cingulate (13), amygdala, and orbitofrontal cortex (OFC) (14). Due to my research familiarity with functional magnetic resonance imaging (fMRI), I began to search for any fMRI studies of emotion processing in schizophrenia since the anterior cingulate, amygdala, and OFC are all part of the corticolimbic system heavily implicated in the experience and expression of affect. I found numerous studies that met my search criteria, but none of them examined sex differences as they included either exclusively men, or the number of women was too small to allow for any comparisons. This was almost a decade ago and it has motivated our group to make an extra effort to recruit women diagnosed with schizophrenia to our studies. We have conducted several fMRI studies; some revealed reversal of normal sexual dimorphism [e.g., during mental rotation task; (15)], others did not find any sex or sex-specific differences [e.g., during passive viewing of emotional stimuli; (16)], while a few found significant relationship between brain activations and sex steroid hormones [e.g., Ref. (17, 18)]. This line of research suggested to us that there might be a subtype of schizophrenia patients where symptoms and related brain dysfunction is partly fostered by hormonal imbalance during organizational and/or activational stage of neurodevelopment.

Thankfully, over the past decade the situation in the field has changed; sex differences in schizophrenia are more widely acknowledged and females (both animal and human) are more frequently studied or at least included in the protocols. It is also recognized that women might require lower doses of antipsychotic medications during their reproductive years (due to interactions between antipsychotic medications and estradiol) and that they may benefit from low doses of estradiol or selective estrogen receptor modulators (SERMs) (19). It is possible that factors contributing to the development of schizophrenia and related psychosis are slightly different in men and women or that these factors interact differently with the sexes. For example, perturbation in the organizational effects of testosterone *in utero* could affect male and female fetuses differently, and exposure to environmental toxins could affect endocrine systems of males and females differently.

Drug Addiction

Drug addiction is another condition characterized by important differences between men and women, and demonstrates how research has changed over the past few decades. Somewhat similarly to schizophrenia, traditionally drug abuse and dependence have been considered a "male problem." However, while the prevalence of alcohol and cannabis dependence is still greater among men, gender differences in the abuse of stimulants and prescription drugs seem to have disappeared in the Western world (20). In addition, women appear to be more prone to develop drug dependence, suffer more severe physical and psychological consequences of drug abuse, and have a more difficult time "kicking the habit" (21). The reasons for this gender gap include a mixture of biological and psychosocial factors. For example, while a larger proportion of men initiate drug use to induce feelings of elation, energy or focus, women frequently start taking drugs to alleviate pre-existing mental health problems, including depression and anxiety (22). This maladaptive self-medication strategy often results in a faster transition to a habitual drug use and eventually a more severe dependence (23, 24). In addition, the socio-cultural norms, particularly in the Western society, have changed dramatically over the past few decades. Thus, while there is still a more severe stigma and prejudice against women who use drugs, especially if they are pregnant or have children, overall there is greater acceptance of women's drug use than it was several decades ago (25). Moreover, women have much greater access to various drugs of abuse than they used to have. Finally, over the past couple of decades, new research has suggested some neurobiological factors that could also contribute to sex differences in drug addiction. For example, there is evidence that the dopamine system, which for decades has been strongly implicated in drug reinforcement, is sexually dimorphic. The number of dopaminergic neurons, the density of the dopaminergic terminals, as well as responsiveness of the dopaminergic system to drugs of abuse, have been shown to differ between males and females and they have been shown to be modulated by sex steroid hormones, especially estrogen (22, 26, 27). All these psychological, socio-cultural, and biological factors that contribute to sex differences in drug use and drug dependence should be considered while evaluating and treating individuals with drug addiction problems.

Our research has focused specifically on addiction to nicotine partly because it is a significant problem in schizophrenia. In the general population, still more men than women smoke cigarettes, but this gap is decreasing steadily. Moreover, studies show that women become dependent faster and have more difficulties quitting the habit than men (28). The difficulty quitting and the higher relapse rates have been linked to greater levels of drug craving, although evidence is still equivocal. For example, we examined sex differences in cue-induced craving for cigarettes in non-deprived smokers and did not find any differences between men and women (29). There were, however, fluctuations in the craving-related fMRI activations across the menstrual cycle in women. I should highlight that in our study we tested only non-deprived smokers, while studies that have reported sex differences, typically assessed craving following a period of abstinence [e.g., Ref. (30, 31)]. Indeed, some studies suggest that men are more sensitive

to cue-induced craving, while women react stronger to stress-induced craving [e.g., Ref. (32)]. These and similar studies may be helpful in developing gender-sensitive treatment programs.

I presented just two examples of neuropsychiatric problems where unraveling sex differences may benefit women and deepen our understanding of the disorders. For instance, several promising clinical trials have already been performed with low doses of estradiol to treat women and men with schizophrenia (19, 33). In terms of drug addiction, most rehabilitation programs are still based on a male model, but it is recognized that women may require additional support (e.g., family planning, childcare services) and approaches that emphasize stress reduction (34).

Before closing I would like to mention gender, femininity/masculinity and related variables, which have been almost entirely absent from the neuroscience research, with a few exceptions. For example, in one early study, Cahill et al. (35) demonstrated that although no differences were detected between sexes in emotional memory, when gender was taken into consideration, individuals with more masculine traits showed superior recall of central emotional information, whereas individuals with more feminine traits exhibited better recall of peripheral details. More recent neuroanatomical studies reveal comparable results. Thus, a study in healthy adults showed that identification with more feminine traits correlated with greater straight gyrus volume (part of the ventral frontal cortex) and with better performance on a social cognition task [interpersonal perception task; (36)]. A different study, in children, reported that higher masculinity predicted greater volumes of white matter in the frontal lobe, while higher femininity predicted greater volumes of gray matter in the temporal lobe (37). These studies point to the possibility that even though sex and gender are closely related, in some situations, gender differences may be more important than sex differences and thus both should be studied in human participants. However, we need better gender measures, as many tests and questionnaires, such as the popular Bem Sex Role Inventory (38) were developed in 1970s.

To conclude, neurocognitive, neurobiological, and clinical studies that do not include female participants (animal or human) present only half of the story, the male part. In some cases, this may not be a problem, but in many it can deter us from scientific progress in understanding etiology, and in developing successful treatments for neurological and neuropsychiatric disorders in men and women. Studies that do not include females are only half-truth, and as Cahill (39) so eloquently stated using a Yiddish proverb – "A half-truth is a whole lie."

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