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Review

Sex-specific responses to cannabis exposure: Implications for behavior and beyond

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ABSTRACT

Cannabis is one of the most widely used psychoactive substances worldwide, with a growing interest in its potential therapeutic applications. In recent years, there has been a significant increase in cannabis use, driven by the progressive legalization and acceptance of recreational usage. Despite the expanding legalization and use of cannabis, the effects of this substance on various physiological systems and behaviors are not fully understood. Accumulating evidence suggests that cannabis exposure may elicit sex-specific effects, highlighting the importance of considering sex as a biological variable in cannabis research. Sex can affect many behavioral outcomes, thus these differences should be considered when looking at the continuation of cannabis legalization. Despite the growing recognition of the importance of sex differences in research, the current literature on cannabis use and its effects has not adequately addressed these differences. Understanding sex differences in cannabis use is crucial for developing treatment strategies and informing public health policies. This scoping review aims to address these gaps and highlight instances of sex-specific behavioral responses to cannabis exposure. The purpose of this review is to: 1) give an overview of cannabis, the endocannabinoid system, and sex-differences in scientific literature, 2) provide an overview of the current state of knowledge regarding sex differences in cannabis use, 3) examine how sex differences can influence the behavioral effects of cannabis use. This review will predominantly focus on tetrahydrocannabinol (THC), the principal psychoactive constituent of cannabis. By synthesizing the available literature, this scoping review seeks to identify gaps in our understanding and guide future research efforts in this field.

1. Introduction to cannabis

Cannabis, frequently referred to as marijuana, derives from the *Cannabis sativa* plant. The *Cannabis sativa* plant originated in Central Asia and is one of the oldest plants used for medical purposes (Klumpers and Thacker, 2019). Cannabis has been commonly used for recreational, medicinal, and spiritual purposes for thousands of years (Russo, 2007; Cvijic and Bauer, 2024). The plant has traditionally been utilized in the management and treatment of several different conditions including: inflammation, pain, depression, and nausea (Abdel-Kader et al., 2024).

The main active compounds in cannabis are known as cannabinoids. Among these cannabinoids is Δ9-tetrahydrocannabinol (THC). THC is a psychoactive compound capable of activating the same receptors as naturally occurring neurochemicals that mimic endocannabinoid signaling and affect receptor expression (Meah et al., 2022). In 1964, a pivotal study by Gaoni and Mechoulam reported the first successful isolation and characterization of THC, catalyzing a new era of cannabinoid research (Gaoni and Mechoulam, 1964). THC is responsible for the majority of the drug's psychological effects which are typically sought out for treatment of pain, epilepsy and neurodegenerative diseases (Amin and Ali, 2019). The management of pain stands as one of the earliest medical applications of cannabinoids (Mechoulam, 1986). Other important cannabinoids include cannabidiol (CBD), which is the major non-psychoactive ingredient in cannabis (Amin and Ali, 2019) and unlike THC, comes without the potential for substance use disorder (García-Gutiérrez et al., 2020). CBD constitutes up to 40 % of the *Cannabis sativa* plant's extract (Skaper and Di Marzo, 2012). CBD is not a focus of this review.

Cannabis use has been associated with a wide range of acute and long-term effects on the central nervous system, including altered

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perception, cognition, impulsivity, decision-making, memory and behavior (Crean et al., 2011). The effects of cannabis are mediated through the endocannabinoid system, which is primarily responsible for maintaining homeostasis by balancing a biological systems' internal environmental and energy input and/or output (Lowe et al., 2021). For the purposes of this review, "cannabis" refers to the unrefined plant product that is smoked or otherwise ingested while "THC" refers to the isolated cannabinoid compound.

2. The endocannabinoid system

The endocannabinoid system (ECS) is a complex network comprising receptors, endogenous ligands (endocannabinoids), and enzymes involved in synthesizing and degrading endocannabinoids (Zou and Kumar, 2018). In the brain, the ECS primarily modulates neuronal synaptic communication and influences a broad spectrum of physiological functions, including appetite, anxiety, learning and memory, reproduction, metabolism, growth, and development, through various actions within the nervous system (Skaper and Di Marzo, 2012). The endocannabinoid system has been targeted as a promising therapeutic strategy for a range of neurological and psychiatric disorders, with cannabinoid-based medications being developed for the treatment of epilepsy, brain tumors, Parkinson's disease, Alzheimer's disease, brain trauma, and overall pain (Russo, 2018).

Endocannabinoids were named upon the discovery that they activate the same receptors as cannabinoids, the main psychoactive component in cannabis (Mackie, 2008; van der Stelt et al., 2002). The two main and most widely studied endocannabinoids are anandamide (AEA) and 2-arachidonoylglycerol (2-AG) (Alvarez-Jaimes and Palmer, 2011), which are of interest due to their role in influencing the effects of oxytocin (Simmons et al., 2021). 2-AG is the most abundant endocannabinoid in the brain (Joshi and Onaivi, 2019).

The two primary cannabinoid receptors, which were discovered in the early 1990s, are CB1 and CB2 (Matsuda et al., 1990; Munro et al., 1993) (Fig. 1). Similar to AEA and 2-AG, THC possesses the capability to activate both CB1 and CB2 receptors (Pertwee, 2008). CB1 and CB2 receptors can influence blood pressure, heart rate and myocardial contractility (Piotrowska et al., 2018).

The CB1 receptor, a G protein-coupled receptor (GPCR), is believed to exhibit the highest expression among all GPCRs in the brain (Busquets-Garcia et al., 2018). CB1 receptors are highly expressed in the central nervous system with a predominant localization on axons and synaptic terminals, particularly in regions such as the cortex, hippocampus, amygdala, basal ganglia, and cerebellum (Mackie, 2005). The highest CB1 receptor efficiency for G-protein activation is in the hypothalamus followed by an intermediate level in the amygdala, thalamus, sensorimotor cortex, and brainstem and low efficiency in the cerebellum, frontal cortex, hippocampus, and striatum (Sim-Selley, 2003). Endocannabinoids act as retrograde messengers in the brain and are released from postsynaptic neurons which in turn activate presynaptic cannabinoid CB1 receptors (Kano et al., 2009). The CB1 receptor is predominantly found in areas of the brain responsible for regulating movement, coordination, sensory perception, learning and memory, emotions and reward processing, hormonal balance, and body temperature (Cabral et al., 2008). CB1 receptors appear to play a key role in most, if not all, of the centrally mediated effects of cannabinoids (Compton et al., 1993).

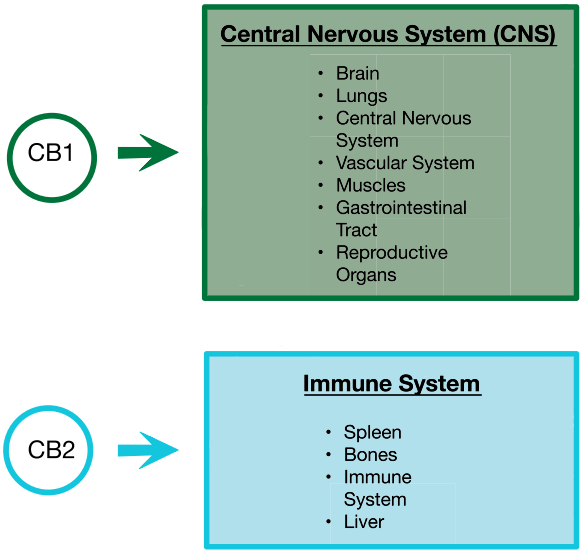

Fig. 1. The distribution and predominant locations of CB1 and CB2 receptors in the human body (Scott et al., 2022).

CB2 receptors, which are also GPCRs, are predominantly located in peripheral tissues, especially in immune cells, and are involved in modulating inflammatory and immune responses (Turcotte et al., 2016). Initially undetected in the brain, CB2 receptors were thought to be expressed solely in peripheral and immune tissues until their functional presence in the brain was discovered a decade later (Onaivi et al., 2006). Besides its involvement in immune cell activities, the CB2 receptor serves a significant role in central nervous system immunity, particularly through microglia, which are resident cells in the brain, spinal cord, and retina (Cabral et al., 2008). CB2 receptors are expressed in specific subpopulations of microglial cells in the human cerebellum, which is significant because perivascular microglial cells are thought to be the primary targets of various virus infections (Núñez et al., 2004). In the literature, CB2 receptors have been less extensively studied compared to CB1 receptors.

3. Studying sex differences in science

The recognition of behavioral and physiological differences between sexes has been growing in importance across a myriad of disciplines, including biological and psychological research, with an increasing emphasis placed on the significance of incorporating sex as a biological variable (Becker et al., 2005; Bale and Epperson, 2017). Many neuroscientists either study only one sex, or neglect to record or report the sex of their experimental animals, due to the assumption that basic principles of neuroscience apply similarly to both sexes (McCarthy et al., 2012). These assumptions have been proven wrong in many ways through abundant research that has demonstrated the significant impact of sex on various aspects of brain function and behavior, encompassing emotion, memory, sensory processing, pain perception, navigation, neurotransmitter levels, stress hormone effects on the brain, and disease states (Cahill, 2006). Several studies from the past indicate a reluctance to use female animals in research. The bias against using females may stem from concerns regarding their inherent variability due to cyclical reproductive hormones, potentially deeming them unsuitable as baseline models (Zucker and Beery, 2010; Zucker et al., 2022). For instance, the identification of sex disparities in daily activity, elucidated through the examination of estrous-related variations among female rats in a 1923 study and published in 1925, may have contributed to the reluctance to routinely include females in animal research (Wang, 1925).

Despite the NIH mandating the inclusion of women in human clinical trials in 1993, for many years there were no parallel initiatives to promote research on female animals, leading to a historical neglect of female mammals in biomedical research (Beery and Zucker, 2011). NIH's sex as a biological variable (SABV) policy, implemented in early 2016, marks a significant scientific progression toward improving knowledge about overall health for men and women alike. It mandates researchers to incorporate both sexes in vertebrate animal and human studies, recognizing that male and female disparities extend beyond reproductive and hormonal concerns (Clayton, 2018).

In 1959, the notion that gonadal signals might induce sexual

differentiation in the brain was put to the test by Phoenix and colleagues. In their study, they discovered that exposing female guinea pigs to testosterone during the fetal period resulted in permanent masculinization and defeminization of their sexual behavior (PHOENIX et al., 1959). It is now understood that sexual distinctions are present throughout the brain, encompassing numerous 'cognitive' areas such as the hippocampus, amygdala, and neocortex (Cahill, 2006). Variations in neural and behavioral phenotypes between sexes partially stem from the different gonadal hormones released by male and female gonads throughout life (Arnold and Chen, 2009). Gonadal hormones exert their effects either in adulthood, with distinct impacts of ovarian and testicular hormones, or during early developmental stages, particularly influenced by testicular hormones (McCarthy et al., 2012). Experimental evidence shows that tissues, including the brain, exhibit sexual dimorphism in both XX and XY individuals even under identical hormonal conditions, indicating that sex chromosome complement can independently influence brain and cell function (Arnold and Burgoyne, 2004).

Sex differences in cognitive abilities have been extensively studied. While both sexes perform similarly on general intelligence tests, specific cognitive domains show variations. For instance, males tend to outperform females in spatial abilities, particularly in mental rotation tasks (Voyer et al., 1995; Yuan et al., 2019). Conversely, females are generally considered to excel in verbal abilities, such as speed of articulation, accuracy of speech production, and fluency, as well as in some non-verbal abilities, like episodic memory tasks involving word recall and word recognition (Weiss et al., 2003). Biological factors such as hormones and brain structure influence these differences, yet their consistency and magnitude across studies vary and are also susceptible to the influence of sociocultural factors like gender stereotypes and socialization experiences (Miller and Halpern, 2014). A 1981 meta-analysis found that sex differences accounted for only 5 % of the variability in spatial task performance (Hyde, 1981), while a later meta-analysis found that the magnitude of sex difference depended on the test used (Voyer et al., 1995).

Many neuropsychiatric disorders exhibit sex differences in occurrence, age of onset, symptom presentation, and treatment response. Sex differences in the prevalence and presentation of neuropsychiatric disorders have been well-documented, with women being more likely to develop depression, anxiety disorders, and eating disorders, while men are more prone to substance misuse, attention-deficit/hyperactivity disorder (ADHD), and schizophrenia (Bao and Swaab, 2010). In addition, autism spectrum disorder (ASD) is diagnosed more frequently in males, with a male-to-female ratio of approximately 4:1 (Werling and Geschwind, 2013; Geier et al., 2012). However, females with ASD often present with different symptoms compared to males, leading to potential underdiagnosis (Lai et al., 2015). In contrast, depression is more prevalent in females, with women roughly twice as likely to develop depression compared to men throughout their lifetime (Kuehner, 2017). These differences may be attributed to a combination of biological factors, including hormonal fluctuations and genetic susceptibilities. Women experience varying exposure to reproductive hormones and peptides during the menstrual cycle, pregnancy, and lactation which could impact behavior (Altemus et al., 2014).

In the domain of emotional processing, women have been found to exhibit greater sensitivity to negative emotional stimuli while men showed a greater activation for positive emotion (Stevens and Hamann, 2012). A study using functional magnetic resonance imaging (fMRI) revealed sex differences in brain activation patterns during emotional processing, with women showing greater activation in emotion-related regions such as the amygdala and prefrontal cortex (Whittle et al., 2011).

Sex differences are also evident in substance misuse patterns and their consequences. Men typically exhibit higher rates of substance use disorders than women; for example, men were over five times as likely to receive a diagnosis of alcohol-use disorder and two to three times more likely to have a drug-use disorder compared to women (Brady and Randall, 1999; Fonseca et al., 2021). Furthermore, Davis et al. (2024) showed that alcohol use may increase cannabis craving among men, but lower desire for cannabis among women. However, women may be more vulnerable to the adverse health consequences of substance misuse, such as liver damage from alcohol use (Erol and Karpyak, 2015). Women meet the criteria for drug dependence more rapidly, seek treatment earlier, and are more prone to experiencing cravings, suggesting a potentially faster progression from casual substance misuse to dependence compared to men (Lynch et al., 2002; Lynch, 2006). Examining the rate of escalation in drug use, women generally show a faster increase in consumption of alcohol, marijuana, opioids, and cocaine compared to men (Becker and Hu, 2008).

Recognizing the significance of sex differences in research, it is crucial to incorporate sex as a biological variable to understand the intricate relationship between biology and behavior. Studies should encompass both sexes and provide comprehensive, translatable findings, especially in areas like drug use and misuse where sex differences in dependence, consumption, and expression exist.

4. Sex differences in cannabis use and effects

Recent studies in humans have highlighted sex differences in cannabis use patterns, pharmacokinetics, and subjective effects. Data suggests that while men have higher rates of cannabis use compared to women, the gender gap in cannabis use has been narrowing over the past few decades (Carliner et al., 2017; Kroon et al., 2023). Boehnke et al. (2019) found that women typically opt for lower potency cannabis products and prefer edibles, topicals, and tinctures, whereas men are more inclined to select higher potency products and prefer smoking or vaping. Women may also be more sensitive to the subjective effects of cannabis, reporting more nausea, loss of appetite, and anxiety compared to men (Cuttler et al., 2016) (Fig. 2). Pharmacokinetic studies also suggest the existence of sex differences in the absorption, distribution, and metabolism of cannabinoids. For instance, since cannabinoids are lipophilic and women have a higher percentage of body fat compared to men, women may metabolize cannabinoids differently and may exhibit weaker effects since THC is retained by fat cells (Fattore and Fratta, 2010). A study by Lake et al. (2023) found that women reported higher ratings of positive cannabis-specific effects compared to men after smoking cannabis, further supporting the notion of sex differences in cannabis sensitivity. While these studies are suggestive, they do not address the mechanism underlying the differences in metabolic processing of THC. Thus, further work in non-human subjects is required to conclusively answer these remaining questions.

Cannabis exposure has also been shown to affect reproductive function in both females and males, with sex-specific effects reported in

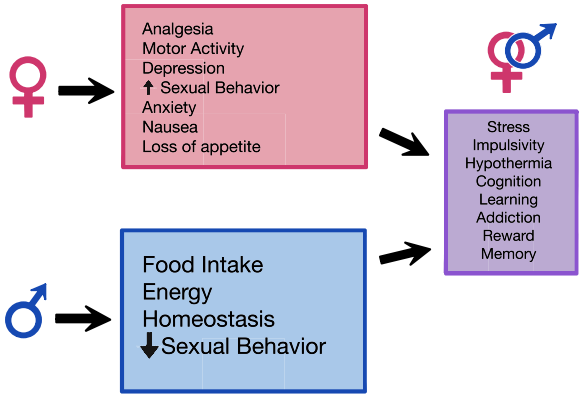

Fig. 2. Sex-dependent differences in the effects of cannabis exposure. Blue: effects that are more apparent in males. Pink: effects that are more apparent in females. Purple: effects have not been found to be sex dependent (Fattore and Fratta, 2010; Cuttler et al., 2016).

various studies. Estradiol, a primary female sex hormone, has been shown to influence cannabinoid receptor density and signaling in various brain regions. For example, in the hypothalamus of female rats, the density of CB1 receptor fluctuates during the estrous cycle, peaking during diestrus and reaching a minimum in estrus (de Fonseca et al., 1994). The cannabinoid receptor binding site density was lower in female rats than male rats in the hypothalamus but higher in females in the amygdala, a difference that appears to be estradiol-dependent (Riebe et al., 2010). A review by Brents (2016) suggested that women may experience increased sensitivity to the drug during the luteal phase when estradiol levels are high, suggesting that hormonal fluctuations across the menstrual cycle can influence the effects of cannabis on the female body and brain. THC has been shown to suppress the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus in female mice, leading to reduced secretion of luteinizing hormone (LH) from the pituitary gland and suppressing gonadal function (Gammon et al., 2005; Maccarrone and Wenger, 2005).

In male mice, chronic THC exposure was found to impact the weights of the testes and seminal vesicles, alter plasma androgen and gonadotropin levels, and affect sexual behavior, specifically copulatory activity (Dalterio, 1980). These effects may be mediated by the direct actions of THC on the hypothalamic-pituitary-gonadal (HPG) axis, which regulates reproductive function. Cannabis exposure has also been associated with adverse effects on sperm parameters and fertility. Alagbonsi et al. (2016) found that THC administration decreased sperm count and motility, while increasing abnormal sperm morphology in rats. Similarly, Gundersen et al. (2015) reported that regular cannabis use was associated with lower sperm concentration and motility in humans. These effects may be mediated by the presence of cannabinoid CB1 receptors in the male reproductive system, including the testes, the prostate, the vas deferens, and Leydig cells (Rossato et al., 2008). Activation of these receptors by THC may interfere with spermatogenesis and sperm function, leading to reduced fertility in males.

5. Cannabis and sex differences in behavior

Cannabis use has been associated with a range of behavioral effects and accumulating evidence suggests that these effects may differ between males and females. In humans, sex differences in the behavioral effects of cannabis have been reported in various domains, including cognitive function, emotional processing, and addiction vulnerability. For example, greater lifetime cannabis use was associated with poorer decision-making performance among male cannabis users but not among females, while it was negatively associated with episodic memory performance in both male and female users (Crane et al., 2013a). In contrast, other studies indicate that there are no interaction effects of sex and cannabis use on episodic memory (Tait et al., 2011). In humans, women showed nonstatistically-significant slower reaction times to task switching despite receiving a smaller dose of marijuana suggesting that cognitive flexibility could be impaired (Anderson et al., 2010). Additionally, women are more likely to report an increase in sexual desire following cannabis consumption, while men experience a large range of adverse effects including decreases in sexual motivation and erectile dysfunction (Gorzalka et al., 2010). Among young adults, women who use cannabis regularly may be more susceptible to developing anxiety and depression compared to their male counterparts (Patton et al., 2002). Furthermore, both male and female adolescents who habitually used marijuana demonstrated poorer performance on tests measuring attention, learning, and spatial working memory (Jacobus and Tapert, 2014), yet male adolescent users seem to exhibit a more pronounced cognitive slowing and decline in cognitive function when compared to females (Lisdahl and Price, 2012). These differences may be related to the complex interactions between the endocannabinoid system, gonadal hormones, and stress-related neurocircuitry.

Sex differences in cannabis addiction and treatment outcomes have also been reported. While men show overall greater levels of cannabis use disorder (CUD) (Zhu and Wu, 2017), women have been shown to have other susceptibilities to cannabis misuse. Women typically progress from initial cannabis use to dependence more rapidly than men, a phenomenon known as "telescoping" (Hernandez-Avila et al., 2004). Additionally, women exhibit a higher potential for misuse and may experience more severe withdrawal symptoms, higher levels of chronic pain and an increased number of cannabis-related medical problems (Sherman et al., 2017). Other recent studies have shown that women may be more susceptible to the negative consequences of cannabis use, such as anxiety, depression and dependence liability (Calakos et al., 2017; Kerridge et al., 2018). Moreover, women who use cannabis regularly may experience more severe withdrawal symptoms during abstinence compared to men, including an increase in irritability, restlessness, anger, violent outbursts, and nausea (Herrmann et al., 2015). These findings suggest that women may benefit from sex-specific treatment approaches for cannabis-related disorders, considering their distinctive vulnerabilities and challenges during withdrawal and recovery to optimize outcomes.

Numerous studies have investigated sex-specific behavioral responses to cannabis exposure in animal models. Female rats have been found to exhibit greater sensitivity to the rewarding and motivational effects of cannabinoids compared to males, as demonstrated by higher and more rapid rates of self-administration (Fattore et al., 2007). These differences may be mediated by the modulatory effects of estradiol on the endocannabinoid system, as ovariectomized female rats show reduced cannabinoid self-administration compared to intact females (Fattore et al., 2010). This evidence points to a higher sensitivity to the rewarding properties of cannabis in females. Additional studies have demonstrated that other behavioral effects of cannabis differ between sexes. Female rats were reported to be more sensitive to both the overall dose and anxiogenic properties of cannabinoids of THC compared to males (Wiley et al., 2017; Harte-Hargrove and Dow-Edwards, 2012). These findings suggest that females may be more vulnerable to the anxiety-inducing properties of cannabis, which could have important implications for the development of anxiety disorders in women who use cannabis. In males, Biscaia et al. (2003) found that chronic treatment with synthetic cannabinoid receptor agonist CP 55,940 induced sex-dependent changes in behavior in adulthood, with male rats exhibiting a decrease in exploratory activity in the open field and in the plus-maze tests. However, a 2019 study exposed adolescent male and female rats to cannabis smoke then tested them on several behavioral tasks during adulthood (Bruijnzeel et al., 2019). These behavioral tasks, including open field test and elevated plus maze, are often used as proxies for measuring anxiety. In these tests, the researchers found that female rats consistently showed less anxiety-like behavior than males, and cannabis exposure had only very subtle effects on the behavior of either sex. The researchers suggested that many of the effects of THC that are reported in animal studies may be due to the fact that many animal studies administer much higher doses of THC than are typically used by the average human. If so, this raises the question of what behavioral differences would be seen using a more “naturalistic” dosing regime.

THC exposure has also been investigated across various developmental stages, including the prenatal, perinatal, and adolescent periods in both human and animal studies. The ECS is crucial in brain development and early development, affecting processes like implantation into the uterus, neural differentiation and synaptic plasticity, and initiation of milk suckling (Fride et al., 2009). Exposure to non-endogenous cannabinoids during critical periods of development can have long-lasting effects on the ECS, brain function and behavior, with sex-specific outcomes. Understanding sex-specific patterns of cannabis use and biological responses is especially critical in prenatal exposure research because women are consuming the substance during gestation and may experience unique physiological and hormonal interactions that may influence fetal development differently in male and female offspring. In fact, both epidemiological and animal studies show that

prenatal THC exposure is associated with sex-dependent outcomes including those pertaining to birth weight and growth (Gillies, et al., 2020; Benevenuto, et al., 2017) and pathophysiological phenotypes like anxiety and social cognition (DeVuono et al., 2024).

Prenatal exposure to cannabis has been associated with many different altered neurodevelopmental outcomes. In humans and non-humans, prenatal exposure occurs indirectly via maternal exposure. Specifically, THC passes from maternal blood through the placenta into the fetal blood circulation. Although this period of exposure is challenging to study, its importance is underscored by recent findings that approximately 17 % of pregnant women report using cannabis during pregnancy (Zaugg et al., 2024). Animal studies have demonstrated that prenatal THC exposure can lead to sex-specific alterations in dopaminergic and glutamatergic neurotransmission, with male offspring, but not females, showing substantial molecular and synaptic alterations in dopaminergic neurons, which are implicated in the regulation of motivation, reward, and cognitive function (Frau et al., 2019). A study by de de de Salas-Quiroga et al. (2020) identified sex-specific deficits in spatial memory in male mice prenatally exposed to THC in an Object Location task. Prenatal exposure to THC has also been shown to reduce social interaction and reduce endocannabinoid long-term depression in males (Bara et al., 2018). In humans, prenatal exposure has been associated with altered neurodevelopmental outcomes observed at age 10 in both boys and girls, including heightened hyperactivity, impulsivity, inattention symptoms and increased delinquency (Goldschmidt et al., 2000). The Goldschmidt et al. study suggests that there may be differences in how prenatal exposure affects boys and girls, but additional research is required to understand these variances fully.

Moving beyond prenatal exposure, researchers have also investigated the impacts of cannabis during the perinatal and postnatal period. Perinatal cannabis exposure, which encompasses both prenatal and postnatal periods, has also been associated with sex-specific behavioral outcomes in offspring. The postnatal period is defined as the period after birth until weaning from parental care. Moreno et al. (2003) observed that perinatal THC exposure, via daily single oral doses to the pregnant female rats from the 5th day of gestation until the 24th day of lactation, disrupted the developmental pattern of motor behaviors and altered the behavioral response to acute injections, resulting in a significant increase in spontaneous immobility and a decrease in locomotion in the open field, with these effects being more pronounced in male rats compared to females. Furthermore, Trezza et al. (2008), observed altered vocalization and play behavior in male rats exposed indirectly, via dams' oral exposure from the 15th day of gestation until the 9th postnatal day to THC during the perinatal period. Alternatively, a recent study in rats from Pham et al. (2025) found that postnatal THC exposure via a 5 mg/kg intraperitoneal (IP) injection once daily from P0 to P6 resulted in an increased number of play behaviors in a social play test and decreased the recognition index in a social recognition test for both sexes.

As development progresses, the adolescent period presents another critical window where cannabis exposure can have significant impacts. During adolescence, sex differences in the effects of cannabis exposure have also been reported. Bara et al. (2021) found that THC exposure induced depressive-like behaviors, social avoidance and memory deficits in female adolescent rats, but not in males. Ferland et al. (2023) demonstrate that adolescent THC exposure in male rats significantly impacts long-term behavior, with dosage and stress playing a critical role in the presentation of THC-related behavioral phenotypes, and high doses causing prolonged effects through astrocyte dysregulation, leading to increased stress sensitivity. Human studies have also revealed sex differences in the effects of adolescent cannabis use, with findings indicating that for young male adult cannabis users more lifetime cannabis use was associated with poorer decision-making performance, but not females (Crane et al., 2013b). These findings suggest that the developmental stage at which cannabis exposure occurs may interact with sex to influence behavioral outcomes. Collectively, these studies across different developmental stages emphasize the complex and often sex-specific effects of cannabis exposure on neurodevelopment and behavior.

Future studies should also consider the role of gonadal hormones in modulating the effects of cannabis. For example, female rats in late proestrus showed heightened sensitivity to the antinociceptive effects of THC compared to males, a response modulated by estradiol, potentially indicating an enhancement of cannabinoids' effects in females (Wakley and Craft, 2011). Furthermore, in female rats, the presence of ovarian hormones was found to modulate the long-term effects of chronic THC exposure on operant learning and performance tasks, along with changes in THC sensitivity during adulthood, indicating a potential protective function of these hormones against the adverse effects of cannabis on memory and learning (Winsauer et al., 2011). In humans, levels of estrogen during the early follicular (EF) and late follicular (LF) phases did not strongly influence responses to THC with the only effect of the cycle phase being slightly earlier ratings of "Wanting More" drug and anxiety after oral THC administration during the EF phase (Pabon and de Wit, 2023). These findings highlight the importance of considering the hormonal status of female participants in cannabis research.

The mechanisms underlying these sex differences in behavioral responses to cannabis are not fully understood but may involve complex interactions between the endocannabinoid system, gonadal hormones, and other neurotransmitter systems. For example, animal studies have shown that females generally exhibit higher levels of the endocannabinoid anandamide in the brain compared to males, with fluctuations observed during the ovarian cycle in both the anterior pituitary gland and the hypothalamus, potentially contributing to their increased sensitivity to the rewarding effects of cannabinoids (González et al., 2000). Sex differences in the expression and function of cannabinoid receptors (CB1 and CB2) have been reported in various brain regions and are implicated in anxiety, memory, and addiction outcomes (Rubino et al., 2012). Furthermore, cannabinoid receptors may be modulated by gonadal hormones, with estradiol enhancing or decreasing CB1 receptor density and signaling in certain brain regions (Riebe et al., 2010). These findings underscore the importance of considering sex-specific factors when studying the effects of cannabis and developing personalized treatment strategies for cannabis-related disorders.

6. Discussion

The present review highlights the importance of considering sex differences in cannabis research, as the effects of this widely used substance on behavior and health outcomes may vary between males and females. This overview examines how sex differences exist in various aspects of cannabis use, including patterns of use, subjective effects, and behavioral consequences.

The reluctance to study sex differences due to fears of perceived sexism often neglects research showing women's strengths, providing essential empirical evidence to challenge gender stereotypes (Halpern, 2014). Despite the growing recognition of the importance of sex differences in research, we know very little about sex differences in drug use in humans or in animal models (Becker and Hu, 2008). Many studies have neglected to include both sexes or failed to analyze data by sex (Fattore and Fratta, 2010).

Sex differences in the behavioral effects of cannabis may be mediated by the complex interactions within the endocannabinoid system. The endocannabinoid system itself exhibits sex differences in the expression and function of cannabinoid receptors as well as endocannabinoid levels (Gorzalka and Dang, 2012). For example, animal studies have shown that prenatal stress resulted in a decrease in CB1 receptors in males and an increase in females within the hippocampus, suggesting that stress can modulate the responsiveness of the endocannabinoid system in sex-specific manners (Dow-Edwards et al., 2016). Cycling female rats were also found to have lower CB1 receptor density in the prefrontal cortex and amygdala compared to males (Paola Castelli et al., 2014).

These differences may contribute to the differential effects of cannabis on behavior and health outcomes between males and females.

Another important consideration for future research is the investigation of sex differences in the long-term consequences of cannabis use. Chronic cannabis use has been associated with a range of adverse outcomes, including cognitive impairment, altered brain development, reduced life satisfaction, and dependence (Volkow et al., 2014). However, few studies have examined whether these outcomes differ between males and females. Longitudinal studies that follow participants over extended periods are needed to determine the sex-specific trajectories of cannabis use and its long-term effects on behavior and health.

Future animal studies should also explore various routes of administration and volume of consumption. A notable limitation of current animal research is the predominant use of oral or intraperitoneal injections for cannabis administration (Dow-Edwards and Silva, 2017). Inhalation, however, results in more rapid increases in brain concentrations and short duration of THC action compared to other methods, such as oral or injection (Wiley et al., 2021). Therefore, researchers should consider employing smoke or vaping apparatuses for drug delivery to enhance the clinical relevance of animal study findings. There are also key differences in the volume of consumption between humans and rodents. Future studies will need to specifically determine the exact quantity of THC that is comparable between species.

The investigation of sex differences in cannabis use should also be extended to the realm of medical cannabis. With the increasing legalization of cannabis for medical purposes, it is crucial to understand whether the therapeutic effects and adverse side effects of cannabinoid-based medications differ between males and females. Sex-specific dosing guidelines and treatment protocols may be necessary to optimize the safety and efficacy of medical cannabis for all patients. Sex-specific approaches should be integrated into clinical practice, with treatment providers considering the distinct needs and experiences of both women and men when designing interventions for cannabis-related disorders. Additionally, public health campaigns could be tailored to target sex-specific risk factors and motivations for cannabis use.

Despite the growing evidence of sex differences in cannabis use and its effects, many studies have neglected to include both sexes or failed to analyze data by sex. This lack of consideration for sex as a biological variable may have contributed to the inconsistencies and knowledge gaps in the current literature. Few studies have looked at the behavioral effects of cannabis use. Some limitations for the current field include the fact that many studies use small sample sizes, making it difficult to detect sex differences. Furthermore, a lack of standardization in cannabis use measures and the reliance on self-report data may limit the generalizability of findings. Future research should prioritize the inclusion of both sexes and the analysis of sex differences to gain a more comprehensive understanding of the effects of cannabis on behavior and health outcomes.

7. Conclusion

This review emphasizes the significance of sex differences in cannabis research and the need for a more inclusive approach that considers sex as a biological variable. The literature demonstrates that males and females differ in their patterns of cannabis use, subjective effects and behavioral consequences. These differences may have important implications for the development of personalized prevention and treatment strategies for cannabis-related disorders.

To address these knowledge gaps, future studies should prioritize the inclusion of both sexes and the analysis of sex differences in cannabis research. Investigators should design studies with adequate statistical power to detect sex differences and report their findings by sex, even when no significant differences are observed. Furthermore, researchers should consider the role of gonadal hormones and their interactions with the endocannabinoid system when investigating the effects of cannabis on behavior and health outcomes.

By incorporating sex as a biological variable in cannabis research, we can gain a more comprehensive understanding of the effects of this substance on the brain and behavior, ultimately leading to the development of more effective and personalized prevention and treatment strategies for cannabis-related disorders. This approach will not only improve the translational value of preclinical studies but also promote the development of sex-specific public health policies and clinical guidelines for the safe and effective use of cannabis and its derivatives.

CRediT authorship contribution statement

Sophia Rogers: Writing – original draft. **Sabrina L. Mederos:** Writing – review & editing. **Adele M.H.Seelke:** Writing – review & editing. **Karen L. Bales:** Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. This review was conducted as part of academic research at the University of California, Davis. No external funding was received for the preparation of this manuscript. All authors contributed to the development, writing, and revision of the manuscript and have approved the final version for submission.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.brainresbull.2025.111530.

Data availability

No data was used for the research described in the article.

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