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Mechanisms Underlying Sex Differences in Cannabis Use

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Abstract

Purpose of the Review—Cannabis is the most commonly used illicit substance worldwide. In recent decades, highly concentrated products have flooded the market, and prevalence rates have increased. Gender differences exist in cannabis use, as men have higher prevalence of both cannabis use and cannabis use disorder (CUD), while women progress more rapidly from first use to CUD. This paper reviews findings from preclinical and human studies examining the sex-specific neurobiological underpinnings of cannabis use and CUD, and associations with psychiatric symptoms.

Recent Findings—Sex differences exist in the endocannabinoid system, in cannabis exposure effects on brain structure and function, and in the co-occurrence of cannabis use with symptoms of anxiety, depression and schizophrenia. In female cannabis users, anxiety symptoms correlate with larger amygdala volume and social anxiety disorder symptoms correlate with CUD symptoms. Female cannabis users are reported to be especially vulnerable to earlier onset of schizophrenia, and mixed trends emerge in the correlation of depressive symptoms with cannabis exposure in females and males.

Summary—As prevalence of cannabis use may continue to increase given the shifting policy landscape regarding marijuana laws, understanding the neurobiological mechanisms of cannabis exposure in females and males is key. Examining these mechanisms may help inform future research on sex-specific pharmacological and behavioral interventions for women and men with high-risk cannabis use, comorbid psychiatric disease, and CUD.

Keywords

Cannabis; Cannabis Use Disorder; Sex Differences; Psychiatric Comorbidity

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

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Conflict of Interest

Katina C. Calakos, Shivani Bhatt, Dawn W. Foster, and Kelly P. Cosgrove declare they have no conflict of interest.

Introduction

Cannabis (*sativa, indica*) is the most commonly used illicit substance worldwide [1]. In the United States, the prevalence of past year cannabis use among individuals aged 12 or older increased from 10.9% in 2008–2009 to 13.4% in 2014–2015 [2]. This increase in prevalence may be due in part to increases in illicit use of cannabis in states with medical marijuana laws [3, 4], as well as decreases in perceptions of risks associated with cannabis [5]. Not only has the prevalence of cannabis use increased, but so too have concentrations of Δ^9-tetrahydrocannabinol (THC; the primary psychoactive compound). THC levels in a typical cannabis strain have doubled from 2006 to 2014 [6]. Given the prevalence of cannabis use, the rapidly changing policy landscape, and the proliferation of high-potency products, it is important to investigate the mechanisms underlying cannabis use disorder (CUD), the DSM-V condition characterized by cannabis abuse and dependence.

According to the 2015 National Survey on Drug Use and Health, 2.6% of adolescents (aged 12–17) and 1.4% of adults (aged 18+), met DSM-IV criteria for past year cannabis dependence or abuse, though no gender breakdown was noted [7]. For perspective, 2.5% of adolescents and 6.2% of adults met criteria for past year alcohol use disorder [7]. In a second national study with gender-specific breakdown of CUD, 2.5% of adults met DSM-V criteria for past year CUD, with prevalence in men (3.5%) more than double that in women (1.7%) [8]. In a sample of adults diagnosed with CUD at some point in their lifetime (i.e., with lifetime CUD), men, relative to women, met a greater number of cannabis abuse criteria [9]. However, in comparison to men, women who use cannabis have been shown to more likely exhibit a “telescoping effect”, characterized by faster progression from first use to CUD [9, 10]. Further, women have reported higher ratings of abuse-related subjective effects in response to cannabis use compared to men [11], which may contribute to a more rapid progression to dependence. Additionally, women with lifetime CUD were more likely than men to have psychiatric comorbidities including bipolar I and II, alcohol use disorder, nicotine dependence, and several externalizing disorders, after adjusting for sociodemographic measures and prevalence of psychiatric disorders [9]. Both the rapid progression from first use to CUD and the increased risk for psychiatric comorbidity conferred by CUD in women implicate biological differences underlying the development and maintenance of CUD. This may render women more vulnerable to psychiatric disability.

The purpose of this review, therefore, is to examine potential neurobiological mechanisms of sex differences in cannabis exposure and dependence. Sex differences in the endocannabinoid system and exogenous THC effects on physiology will be reviewed, followed by sex-specific effects of cannabis exposure during the vulnerable period of adolescence. Preclinical and human studies examining sex differences in cannabis exposure effects during adulthood will then be reviewed, followed by sex differences in cannabis use comorbidity with psychiatric symptomatology related to anxiety, depression, and schizophrenia. Overall, the aim of this review is to yield a better understanding of the neurobiological sex differences that may underlie sex-specific vulnerabilities to, and features of, cannabis dependence.

Method

Using PubMed and Google Scholar, we conducted a literature review of peer-reviewed articles published between January 2010 and April 2017. We used the following search terms in various combinations: “cannab*,” “sex,” “gender,” “THC,” “marijuana,” “female,” “sex differences,” “schizophrenia,” “depression,” and “anxiety.” Additional papers are cited to provide context for hypotheses investigated in more recent literature. In accordance with definitions set by the Institute of Medicine, the term “gender” is applied to human studies and the term “sex” is applied to animal studies, as well as joint analyses of preclinical and clinical data, in this review.

Sex Differences in the Endocannabinoid System

Endocannabinoid system biology

The neurobiology of the endocannabinoid system has previously been reviewed [12–15]. Commonly used terms are defined in Table 1. Briefly, the cannabinoid-1 receptor (CB1-R) is the primary mediator of cannabinoid signaling in the central nervous system [16, 17], and is accompanied in lower levels by cannabinoid-2 receptors (CB2-R) [18, 19]. Cannabinoid receptors (CB-Rs) are activated by the endogenous ligands N-arachidonoylethanolamine (AEA) [20] and 2-arachidonoylglycerol (2-AG) [21–23], as well as exogenous ligands including THC and synthetic cannabinoids [24]. CB1-Rs are widely distributed in brain regions including frontal cortex, hippocampus, cerebellum, hypothalamus, basal ganglia, and reward circuit areas such as ventral tegmental area and nucleus accumbens [14]. CB1-Rs are presynaptic terminal bound G-protein coupled receptors (GPCRs) that, when activated, trigger $G_{i/O}$-protein coupling and intracellular events that ultimately reduce intracellular Ca^{2+} and K^{+} concentration and inhibit neurotransmitter release [14]. THC has been shown to induce dopamine release in nucleus accumbens [25, 26], which is thought to underlie the rewarding effects of most drugs of abuse [27]. In addition, cannabinoids are shown to decrease GABA-mediated inhibitory transmission [28], modulate NMDA and AMPA receptor mediated excitatory transmission [29], and exert reinforcing effects via CB1-R activation in reward areas mediated by cholinergic and opioidergic systems [30].

Sex differences in cannabinoid receptor expression

The relationship of sex and the cannabinoid receptor system has long been studied [31–33]. CB1-R mRNA transcript levels have been reported to be higher in anterior pituitary [34] and lower in cerebellum [35], prefrontal cortex, amygdala, and hippocampus [36] in males, compared to females. Greater CB1-R density has been observed in male animals in mesencephalon [37], hypothalamus [38], hippocampus [38, 39], and prefrontal cortex [40], compared to females, with mixed results in amygdala [38, 40], though other evidence suggests greater widespread CB1-R density in females, compared to males [41]. In humans, *in vivo* positron emission tomography (PET) imaging demonstrated that CB1-R availability is lower in healthy men compared to healthy women in most regions [42, 43], though some evidence indicates higher CB1-R availability in men, compared to women, in the cortico-striatal-thalamic-cortical circuit [44]. Conflicting evidence may, in part, be attributed to differences in experimental design, specifically in CB1-R-specific radioligand as well as

outcome measure. Interestingly, CB1-R availability has been shown to increase with age in women, but not men, in basal ganglia, limbic regions, lateral temporal cortex, and hippocampus [44]. Hormones appear to play a role in these differences since ovariectomized female rats exhibit higher CB1-R expression in frontal cortex [40] and hippocampus [38] compared to intact females, though mixed trends emerge in the amygdala [38, 40]. Sex differences here, and throughout the remainder of this review, with a focus on neurobiological changes in striatum, hippocampus, amygdala, and frontal cortex, are reported in Table 2.

Sex differences in cannabinoid physiological effects and metabolism

Prior to examining sex differences in cannabis exposure-related behavioral, structural, and functional phenomena, it is important to understand how cannabinoids sex-specifically impact physiology. In humans, cannabis exposure increases heart rate in both women and men [45, 46], but to a lesser extent in women [46–48]. Women have reported greater sedative effects [46] and dizziness [49] compared to men in response to cannabis, though amount of cannabis per body weight was not adjusted. Women also responded to cannabis extract with significantly greater fatigue, drowsiness, and psychomotor suppression compared to women treated with placebo [50].

These sex-dependent physiological effects may, in part, be attributed to sex differences in cannabinoid metabolism. In one study, THC metabolism in female rats yielded the primary metabolite 11-OH-THC only, compared to multiple metabolites in males [51]. Brain levels of metabolite 11-OH-THC were higher in THC-exposed female rats compared to male rats [52, 53], yet plasma THC levels have been shown to be both higher [54] and lower [55] in THC-exposed women, compared to men. This is important, as the typical THC content in cannabis continues to increase over time [6], and may contribute to sex-specific trajectories to dependence. Together, these differences suggest women may experience more depressive-like symptoms from cannabis exposure, including sedation and psychomotor suppression, which may help inform the following findings on sex differences in cannabis use related behaviors.

Adolescent Cannabinoid Exposure Impacts Adulthood: Preclinical Studies

Cannabis use is typically initiated in adolescence [9], a period marked by robust behavioral and brain development. Cannabinoid use in adolescence has profound effects on cannabis use and related changes in biology and behavior in adulthood [56, 57], in a sex-dependent manner [58–60]. The majority of the literature examining these effects at the neurobiological level is in animal models, with some investigation in humans.

Adolescent cannabinoid exposure has sex specific effects on CB1-Rs in adulthood

Preclinical cannabinoid exposure in adolescence largely induces a sex-independent, widespread reduction in CB1-R density [41, 61–63], although enhancement in hippocampus in female animals [64–66], and striatum in both sexes [64], has been observed. Chronic THC exposure during adolescence led to a reduction in CB1-R density in the amygdala [61], caudate, putamen, nucleus accumbens, and substantia nigra [41] of adult male rats. In THC-

exposed female rats, reductions were also observed in these regions, as well as ventral tegmental area [41, 61] prefrontal cortex, globus pallidus, and hypothalamus [41]. CB1-R reduction was observed in hippocampus in females and males, though in more hippocampal sub-regions in females [63]. Additionally, THC exposure reduces striatal CB1-R density in female rats, independent of ovarian hormone status [67]. Adolescent THC exposure has been shown to lead to sex-dependent reduction in agonist-induced activation of CB1-Rs in adulthood, specific to hippocampus, in males, and to amygdala and nucleus accumbens, in females [61]. Deficits in cannabinoid signaling in these brain regions, therefore, could impact emotion and reward regulation.

Adolescent cannabinoid exposure has sex specific effects on other receptor systems in adulthood

Cannabinoid exposure in adolescence impacts the glutamate, GABA and dopaminergic systems in adulthood. In the glutamate system, adult female rats, with cannabinoid exposure in adolescence, showed reduced NMDA receptor density [41, 68] and reduced glutamate release in hippocampus [68], compared to control females. Adult male rats with cannabinoid exposure in adolescence, in contrast, have shown enhanced NMDA subunit GluN2B expression and AMPA subunit expression compared to control males [69]. In the GABAergic system, both sexes have shown elevated GABA release in adulthood, after cannabinoid exposure in adolescence, but female rats specifically show enhanced hippocampal GABA-A receptor expression compared to control females [68]. In the dopaminergic system, adolescent THC exposure enhanced dopamine D1 receptor density in nucleus accumbens of adult male [70] and female animals [41], increased dopamine D2 receptor density in the prefrontal cortex of males [41], and reduced dopamine D2 receptor density in hippocampus of both sexes [70]. In humans, adult cannabis users with onset in adolescence have shown no difference in striatal dopamine D2/D3 receptor availability compared to healthy controls [71, 72], but do show blunted dopamine transmission compared to healthy controls [73]. Sex differences, however, have not been examined in these imaging studies.

Adolescent cannabinoid exposure has sex specific effects on cannabinoid reinforcing efficacy in adulthood

Preclinical self-administration paradigms can be used to examine the reinforcing efficacy of drugs of abuse by modeling acquisition and maintenance of drug use [74], including cannabinoid use [75, 76]. Male rats that self-administer cannabinoids in adolescence have exhibited faster and more robust self-administration in adulthood compared to controls [77]. They have also shown a blunted cannabinoid-induced dopamine release in the ventral tegmental area and nucleus accumbens, compared to controls, suggesting a long-lasting deficit in the dopaminergic circuitry [77]. One limitation, however, is that no similar study has been conducted in females to allow for exploration of sex differences. In all, further investigation into female-specific, adolescent cannabinoid exposure effects on THC self-administration and reinforcing efficacy in adulthood is needed.

Adolescent Cannabis Exposure Effects on Adolescence and Adulthood: Human Studies

Similar to preclinical studies, several human studies reveal adolescent cannabis use effects on the brain [78, 79]. Few, however, include female cannabis users and, in those that do, analyses with gender as a main effect is either unreported or unattainable due to statistical limitations [80–82]. Thus, in contrast to the previous exclusive focus on adolescent cannabis use effects on the adult brain, this section's focus is on studies with analyses of gender differences in adolescent cannabis use effects on brain structure and function during adolescence as well as adulthood.

Gender differences in human adolescent cannabis exposure on brain structure and function in adolescence

In one study, female cannabis using adolescents had significantly larger right amygdalae compared to female non-users, an effect not observed in males [83]. During late adolescence and young adulthood, both female and male cannabis users had smaller grey matter volumes than non-users in decision making and executive function areas of the brain, i.e., the medial orbitofrontal and inferior parietal cortices [84]. In adolescents with substance use disorder and co-morbid conduct problems, many of whom were cannabis dependent, females had less cortical thickness in parts of the anterior cingulate cortex and medial orbitofrontal cortex compared to female controls [85], with no similar effect observed in males [86]. In a separate set of studies, comparably characterized subjects had significantly less grey matter volume than gender-matched controls in left and right dorsolateral prefrontal cortex, in males [87] and females [88], respectively. Bilateral cerebellum was also smaller in male users compared to male controls, and in female users, less grey matter volume was observed in several additional frontal and parietal regions. Together, this evidence indicates gender-specific differences in adolescent cannabinoid exposure on executive function and decision-making areas of the brain, which may inform gender-specific cognitive effects of cannabis as well as optimal treatment strategies for cannabis dependence.

Gender differences in human adolescent cannabinoid exposure on brain structure and function in adulthood

In one study, a mixed-gender adult population with adolescent-onset (<17 yrs) cannabis use exhibited less grey matter and more white matter, as a percentage of whole brain volume, compared to young adult-onset users [89]. In a second study, adolescent-onset users (<16 yrs) showed greater brain activity, measured by blood-oxygen-level dependent (BOLD) functional magnetic resonance imaging (fMRI), in dorsal striatum in response to cannabis cues, compared to young adult-onset users [90]. Although not gender-linked, this may be driven by the significantly more women comprising the adolescent-onset group, though further analysis is necessary [90]. Independent of gender, smaller orbitofrontal cortex volume at age 12 was associated with early cannabis use, highlighting the role of decision-making in drug taking behaviors [91]. These findings suggest that regardless of gender, cannabis use leads to a reduction in brain volume in adulthood, which may render early

cannabis users vulnerable to disease in adulthood, as well as deficits in cognition and behavior, though further investigation is needed to evaluate these implications.

Sex Differences in the Rewarding Properties of Cannabinoids

Preclinical cannabinoid self-administration

Preclinical cannabinoid self-administration in adulthood is characterized by an inverted U-shape dose-effect curve that has been demonstrated with CB1-R agonists and THC, although some studies report insufficient reinforcement by THC [92–94]. Cannabinoid self-administration has led to enhanced extracellular dopamine levels in the nucleus accumbens [95–97], and is modulated by CB1-R [93, 97–99], opioidergic [99–103], and adenosine 2A receptor [104, 105] antagonism, and by anabolic steroid hormone treatment [106]. Although sex differences in drug self-administration in general have been reported [107], sex differences tend not to emerge in the cannabinoid literature due to largely male samples. Only one group has explored cannabinoid self-administration in females, and significantly faster acquisition, as well as more robust maintenance, was observed in female rats compared to male rats [108]. Sex-dependent differences do emerge irrespective of self-administration, such as enhanced sensitivity to THC-induced taste avoidance [109] and THC discrimination [110] in female rats, but further investigation must be done to systematically examine preclinical sex differences in cannabinoid reinforcement.

Human cannabinoid self-administration

A small but growing gender-inclusive literature exists on human studies of cannabinoid self-administration [111]. One study of a male cannabis using sample found that participants exhibited preference for and choice of active cannabis over placebo [112]. Other work among male cannabis users has demonstrated increased subjective intoxication, heart rate, and “liking” of drug as a function of THC potency in self-administered cannabis [113, 114]. One study including a female cannabis using sample found that participants similarly exhibited increased intoxication and elevated pulse rate after cannabis use [115]. Further, acute cannabis self-administration by females with moderate cannabis use enhanced confusion, vigor, elation, and friendliness, but prolonged self-administration reduced these feelings [115]. Increased cannabis use during the premenstrual phase of the ovulatory cycle has been reported, and was correlated with significantly greater depressive features [116]. However, no consistently significant relationship between menstrual cycle phase and modulation of cannabis self-administration has been observed [116, 117]. Gender-inclusive studies report similar findings, and additionally demonstrate modulation of self-administration by treatment with oral THC [118, 119], oral cannabidiol [120], and an opioid receptor antagonist [121]. These studies, however, either lack adequate power to test for gender differences, or do not report analyses of gender differences.

Cannabis-induced subjective effects

Cannabis and THC alone typically increase subjective “high” ratings in both women and men, but studies conflict as to whether gender-dependent differences exist. One study demonstrated a greater increase in cannabis-induced “high” in female cannabis users compared to males [122], yet another study in non-users exposed to cannabis reported

greater increases in “high” ratings in males compared to females [123]. Conflicting evidence may be due to smoking status differences in the populations of each study, as well as differences in THC capsule dosing indicated in each experimental design. Cannabis-induced increases in “good” and “take again” ratings were shown to be enhanced in women compared to men [11], but also shown to be gender-independent [48]. In a female-only study, cannabis exposure increased ratings of confusion among regular and intermittent cannabis users, although this effect was stronger among intermittent users [45]. Other female-only work has demonstrated increased psychiatrist-rated scores of poor affective response and emotional withdrawal in drug-naïve females [50].

Cannabis cue reactivity and cue-induced craving

Gender differences emerge less in the magnitude of cue reactivity, but more in the underlying neural mechanism. For example, prior work has shown that greater cannabis use in both women and men is associated with greater cannabis cue reactivity [124]. Women, compared to men, exhibited larger cue-induced enhancement of event related potential signals, specifically in P300 amplitude, shown to be enhanced in many studies of drug-related cue reactivity, and in early posterior negativity amplitude, shown to be sensitive to motivation-related stimuli [124]. In cannabis users exposed to subliminally presented cannabis cues, men had preferential BOLD signal response in left striatum and left lateral orbitofrontal cortex, yet women preferentially responded in striatum, left hippocampus and amygdala [125]. Some groups have examined cue-reactivity associations with risk genes *CNR1* and *FAAH*, but gender differences were either not found [126] or not further analyzed [127]. Cannabis cue-induced craving has been reported in both men and women [128]. Further, in a mostly female sample of cannabis users, cue-induced craving was correlated with occipital cortex, parahippocampal gyrus, thalamus, hippocampus, superior temporal pole, and middle occipital gyrus activation [129]; however, within-group gender differences were not reported. In women, cannabis cue-induced neural activation of bilateral anterior insula and left lateral orbitofrontal cortex positively and negatively correlated with baseline craving, respectively [125]. In men, striatal activation was associated with craving [125]. Thus, although overlap exists in brain regions associated with cannabis cue presentation between women and men, the correlation of regional activation with cannabis craving is gender-dependent, which may inform optimal treatment strategies aimed at reducing craving and preventing relapse in cannabis-dependent individuals.

Gender Differences in Brain Structure and Function in Cannabis Users in Adulthood

Gender differences in brain structure

Several groups have investigated structural brain changes related to cannabis use [130, 131], yet as with the adolescent literature, few studies include women or analyze gender differences, as discussed and reviewed by Ketcherside and colleagues [132]. In mixed-gender populations, cannabis users have exhibited more grey matter volume in cerebellum [133], left putamen, and right precentral gyrus [134], and less thalamic [134] grey matter volume compared to healthy controls. Further, smaller volumes in right amygdala and

bilateral hippocampus were associated with greater cannabis dependence severity and amount of cannabis used per week, respectively [133]. Volume of ventricular cerebrospinal fluid was reported to be lower in cannabis users, compared to controls, without varying by gender [135]. In one recent study, dependent cannabis users, compared to non-dependent users, had significantly smaller volumes in medial and lateral orbitofrontal cortex, the latter effect being more pronounced in women than men [136]. Overall, more structural neuroimaging of gender differences in current cannabis users is needed to elucidate consistent patterns of change in brain structure, specific to female and male cannabis users.

Gender differences in brain function

Similarly, several functional neuroimaging studies inclusive of women cannabis users lack statistical power or do not report gender differences [71, 73, 137, 138]. Of those that examine gender differences, mixed results emerge. In an electroencephalogram study, female cannabis users showed altered visual processing as indicated by reduced visual steady state evoked potential spectral power at low frequency stimulation compared to female controls, an effect not observed in males [139]. In adulthood, males who began using cannabis during adolescence had significantly higher cerebral blood flow compared to those who initiated use as young adults, though females showed no significant difference [89]. Female cannabis users did, however, exhibit region-specific lower levels of glucose metabolism in left superior frontal gyrus, right occipital cortex, and right anterior cingulate cortex compared to female controls, an effect not observed in men [140]. Further, female cannabis users, but not male cannabis users, had blunted methylphenidate-induced enhancement of glucose metabolism in cerebellum, medial frontal gyrus, pons, hippocampus, thalamus, and midbrain compared to female controls [140]. In a mixed group of adolescents and young adults, female cannabis users, in dorsal striatum, had lower scaled levels of glutamate and glutamine compared to female controls, an effect not observed in males, as well as higher *myo*-inositol levels, a glial marker observed in high concentrations in early dementia, compared to female controls and all males [141].

Sex Differences in Cannabis Use Comorbidity with Psychiatric Symptoms

Comorbidity with anxiety symptoms

Female cannabis users have self-reported significantly higher levels of anxiety problems during withdrawal compared to male cannabis users [142]. Females seeking treatment for cannabis dependence, particularly in late adolescence and middle adulthood, have also shown higher rates of anxiety compared to males [143]. Social anxiety disorder symptoms were correlated with cannabis use disorder symptoms in women but not men [144]. This relationship appears to be nuanced, however, by reported motives for cannabis use. Specifically, social anxiety in males has been associated with cannabis use motives related to conformity (e.g., to fit in with a group I like) and coping (e.g., to forget my worries) [145]. By contrast, in females, social anxiety has been associated with social-based motives (e.g., to enjoy a party) to use cannabis [145]. It is unclear what mechanism may contribute to these differences, although the amygdala has been implicated [83]. Specifically, as detailed earlier, female cannabis users had larger right amygdala volumes compared to female non-users, an effect not observed in males [83]. Further, in female cannabis users, larger right amygdala

volume was associated with worse anxiety and depression symptomatology, yet the opposite trend was observed in female controls and males [83]. While gender differences have emerged with respect to anxiety symptoms and motives, additional work is needed to elucidate gender differences in mechanisms related to cannabis motives and anxiety.

Preclinical investigation has begun to address this gap by exploring potential mechanistic explanations for sex-dependent associations between cannabinoid exposure and anxiety. Some groups reported no effects of adolescent cannabinoid exposure in rodents on anxiety in adolescence [146] or adulthood [61, 69], and others reported a male-specific reduction in anxiety or anxious behavior with cannabinoid exposure [147–149]. Adequate comparison of conflicting results is limited, however, as these studies vary in their administered cannabinoid (i.e., CP 55,940 vs. THC) which may impact potency of effect at the receptor level. Female rats have similarly shown mixed anxiety effects to cannabinoid exposure [150], and cannabinoid-induced enhancement of social anxiety, specifically, has been noted in females [151] and males [147]. CB1-R activity may mediate these effects, as global knockout of this receptor expression increased anxiety in male mice compared to controls, an effect not observed in female mice [152]. Further, specific CB1-R knockout on cortical glutamatergic and forebrain GABAergic neurons was associated with reduction in social interaction in male mice, with no females tested in this experiment [153].

Comorbidity with depressive symptoms

Evidence for gender-specific associations of depression and cannabis use is mixed. Cross-sectional work has indicated a stronger association between cannabis use and depression in females, compared to males [154], but longitudinal work indicates a strong association over time in both females [155] and males [156]. Adolescent cannabis use has been shown to be predictive of depression in male and female adolescent students [157]. Adolescent cannabis use, however, did not significantly predict young adult depression [158]. Studies on factors associated with depression have shown that in comparison to males, female cannabis-using adolescents are at greater risk for suicide [143], as well as self-harm as a function of cannabis use [159]. In a longitudinal study, heavy cannabis use in males, but not females, was significantly associated with increased odds of later suicidal ideation [160]. In contrast, past suicidality in females, but not males, was associated with initiation of cannabis use [160]. Another study showed that cannabis craving was correlated with self-reported depression, and when depression was held as a covariate, greater craving scores emerged for males compared to females [161]. Further, cannabis-dependent males in a separate study exhibited greater feelings of “down” in response to cannabis cues compared to females [162], and as previously mentioned, cannabis-naïve females showed increased, cannabis-induced, psychiatrist-rated poor affective response and emotional withdrawal [50]. While the literature is mixed, it seems apparent that gender differences exist, and additional work is needed to understand mechanisms contributing to these patterns.

Aside from the aforementioned evidence for increased anxiety and depression symptomatology with right amygdala volume in female cannabis users [83], we are not aware of further mechanistic understanding of gender differences in cannabis use associated with depression. Investigations in mixed-gender populations have indicated that smaller

white matter volume is associated with greater depression symptomatology in adolescent cannabis users [163]. Cannabis users had more cerebellar grey matter volume compared to non-users, but this was not associated with depressive symptoms [133]. Preclinical studies have indicated that adolescent THC exposure elevates depressive-like behavior in adulthood in female rats [61, 164] but not male rats [61]. Cannabinoid exposure in males, in contrast, has been shown to decrease depressive-like behavior [149, 165]. Conflicting evidence does exist, however, as elevated depressive symptoms in both sexes [41], or no effects in males [69], have been reported. Altogether, cannabis use correlates with several measures of depression in humans, cannabinoid exposure has mixed effects on depressive symptoms in preclinical animal models, and varied sex-specific associations between cannabis use and depression emerge across studies, necessitating further inclusion of females in studies of depression in cannabis use.

Comorbidity with schizophrenia and psychotic symptoms

Cannabis use has been implicated in the onset of schizophrenia and psychotic symptoms [166]. Men have been shown to have an earlier onset of schizophrenia than women [167, 168], and age of onset of in cannabis users is shown to be earlier than non-users [168, 169]. Though cannabis use was shown to be more prevalent among men with schizophrenia relative to women [170], female cannabis users are reported to be at higher risk of early onset of psychosis compared to male users [171]. Possible genetic factors involved in gender-specific differences in age of psychosis onset have been reported [167, 172]. Neuroimaging studies suggest that individuals with schizophrenia who use cannabis have an altered subcortical region shape [173] and have less grey matter in anterior cingulate [174], posterior cingulate cortex [175], and more widespread regions in the brain [176, 177] compared to non-using controls with schizophrenia, though gender difference analysis is not reported or not observed as in one case [174]. In rodents, psychotic-like behavior is modeled by diminished prepulse inhibition, related to deficits in sensorimotor gating and attention in people with schizophrenia, and enhanced acoustic startle reflex [178]. THC exposure significantly reduced prepulse inhibition in female rats [178] and enhanced acoustic startle activity in both males and females [179]. These findings highlight potential mechanisms that may contribute to sex differences in the impact of cannabis on schizophrenia and psychosis.

Conclusion

Cannabis is the most commonly used illicit substance, and as it becomes increasingly accessible, it is critical to understand how the neurobiological underpinnings of cannabis addiction differ between women and men. Sex differences exist in the endogenous cannabinoid receptor system, cannabis metabolism, and the subjective effects of cannabis. There are not yet studies, however, reporting consistent differences in brain structure or function between female and male cannabis users. More commonly, gender differences emerge in how female or male cannabis users compare with their same-gender non-user counterparts. This is evident structurally, with less grey matter volume and cortical thickness observed, and functionally, with blunted methylphenidate-induced enhancement of glucose metabolism in hippocampus and frontal cortex, in female cannabis users compared to female non-users.

Gender differences emerge in behavioral and neurobiological profiles of cannabis users with comorbid symptomatology related to anxiety, depression, and schizophrenia. Social anxiety disorder symptoms correlated with CUD symptoms in women, but not men, and anxiety symptoms correlated with larger amygdala volume in female cannabis users. Female cannabis users are shown to be especially vulnerable to earlier onset of schizophrenia, compared to male cannabis users, but it is unclear what neurobiological sex differences contribute to this phenomenon and more studies are necessary. Lastly, in depression, mixed trends emerge in support of enhanced depressive symptoms with cannabis use in both females and males. Amygdala is again implicated in females, but further investigation is required.

Taken together, the studies reviewed here that examine gender differences in neurobiological mechanisms of cannabis use yield mixed results and thus, more evidence is needed to fully understand how cannabis use differentially impacts females and males. Differences in experimental design of preclinical studies may contribute to conflicting findings, such as differences in cannabinoid used to antagonize the CB1-R system or in paradigms used to evaluate reinforcing efficacy of cannabis. Similarly, differences in neuroimaging parameters, cannabis dosing, and type of cannabis administration in clinical studies may produce competing results obtained to answer the same research question. Further, many studies still do not include female subjects and in those that do, gender is not often discussed as a variable of interest. This makes it difficult to identify promising avenues for investigating gender differences in future research.

In future studies, it is important to actively include female and male subjects, and to systematically examine sex differences, with adequate power, in both preclinical and clinical samples. The majority of clinical studies on gender differences in cannabis use either administer cannabis to assess subjective effects without measures of neural activity or examine neural activity in cannabis users without active cannabis administration. To fully understand gender differences in cannabis use, it is critical that new studies bridge the gap between these two paradigms and incorporate active cannabis administration into neuroimaging studies. Acute effects of cannabis use, both behaviorally and neurobiologically, could then be identified and analyzed for differences between women and men. Examination of sex differences and related neurobiological mechanisms is critical to inform future research on gender-specific pharmacological and behavioral interventions for women and men with high-risk cannabis use, comorbid psychiatric disease, and CUD.

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Table 1

Key Terms and Definitions Used in Text

Term	Definition
Cannabis	The inhaled or ingested substance commonly known as marijuana; derived from plant in *Cannabis* genus (species *sativa* is common in recreational use and in research studies)
Cannabinoid	Exogenous CB1-R agonist; examples include THC and synthetic agonists WIN 55,212-2, CP 55,940, and HU-210
CB1-R	Cannabinoid receptor type 1; present throughout human and rodent brains
Endocannabinoid	Endogenous CB1-R agonist; examples include *N*-arachidonoylethanolamine (AEA) and 2-arachodonylglycerol (2-AG)
Gender	Descriptive term used in analysis of differences between women and men in clinical studies
Ovariectomy	Surgical removal of ovaries in rodents; used to examine the role of female sex hormones in cannabinoid biology
Sex	Descriptive term used in analysis of differences between females and males in preclinical studies
THC	Δ^9-tetrahydrocannabinol; the primary psychoactive ingredient in cannabis

Table 2

Sex Differences Across Striatal, Limbic, Cortical Regions

Reference	Outcome Measure	Subjects; Condition	Striatum	Hippocampus	Amygdala	Frontal Cortex
	CB1-R Properties	***No cannabinoid or cannabis exposure***				
41	CB1-R density	rats	f > m (Cd, Pu, GP, NAcc)	f > m	f > m	f > m
38	CB1-R density	rats			f > m	m > f
39	CB1-R density	rats		m > f		
40	CB1-R density	rats			m > f	m > f
40	CB1-R density	rats; OVX and INT females only			OVX > INT	OVX > INT
38	CB1-R density and affinity	rats; OVX and INT females only		OVX > INT	OVX < INT (density only)	
43	CB1-R availability, [^{11}C]OMAR PET	humans	f > m (mean composite)	f > m (mean composite)	f > m (mean composite)	f > m (mean composite)
42	CB1-R availability, [^{11}C]OMAR PET	humans	f > m (Cd, Pu, GP)	f > m (global measure)	f > m	f > m (global measure)
44	CB1-R availability, [^{18}F]MK-9470 PET	humans	f only incr. with age	f only incr. with age	f only incr. with age	f only incr. with age
44	CB1-R availability, [^{18}F]MK-9470 PET	human	m > f (Pu)			m > f (OFC, SG, R INS)
	CB1-R Properties	***Adolescent cannabinoid exposure***				
66	CB1-R density in adults	rats		f only > ctrl; m only < ctrl		
64	CB1-R density in adults	rats	f = m: > ctrl	f only > ctrl; m only <ctrl		
41	CB1-R density in adults	rats	f only < ctrl (GP); f = m: < ctrl (Cd, Pu, NAcc)		f only < ctrl	f only < ctrl (PFC)
61	CB1-R density in adults	rats	f only < ctrl (NAcc)		f = m: < ctrl	
65	CB1-R density in adults	rats; OVX and INT females only	OVX < INT	INT only > ctrl		
67	CB1-R protein expression	rats; OVX and INT females only	OVX = INT: < ctrl			
149	CB1-R mRNA expression	rats			f only > ctrl (CeA)	
61	CB1-R activity, CP-stimulated GTPγS binding	rats	f only < ctrl (NAcc)	m only < ctrl	f only < ctrl	

Reference	Outcome Measure	Subjects; Condition	Striatum	Hippocampus	Amygdala	Frontal Cortex
146	CB1-R activity, CP-stimulated GTPγS binding	rats		m only > ctrl (CA1, CA2)		
	Glutamate/GABA	***Adolescent cannabinoid exposure, cannabis use***				
68	$GABA_A$-R density	rats		f only > ctrl		
41	NMDA-R density in adults	rats; maternal deprivation (MD)	f only MD < ctrl (Cd, Pu)	f only no MD < ctrl		
69	AMPA-R subunit expression	rats; males only		m only > ctrl		
68	glutamate release in adults	rats		f only < ctrl		
141	glutamate and myo-inositol, MRS	humans	f only < ctrl glutamate; f only > ctrl myo-inositol (DS)			
	Dopamine System	***Adolescent cannabinoid exposure***				
41	D1-R and D2-R density in adults	rats	f only > ctrl in D1-R (NAcc)			m only > ctrl in D2-R (PFC)
70	D1-R and D2-R density in adults	rats	m only > ctrl in D1-R (NAcc)	f = m: < ctrl in D2-R		
77	DA release, WIN-induced	rats; male only	m only < ctrl (NAcc)			
	Structural Differences	***Cannabis use***				
136	volume, MRI	humans				f only dep. < non-dep. (lOFC)
85	cortical thickness, MRI	humans; female only, poly-SUD (CUD 91%) and conduct disorder				f only < ctrl (L ACC, mOFC)
88	GMV, MRI	humans; female only, poly-SUD (CUD 91%) and conduct disorder				f only < ctrl (ACC, R dlPFC, L vlPFC, mPFC, mOFC)
87	GMV, MRI	humans; male only, poly-SUD (CUD 84%) and conduct disorder				m only < ctrl (L dlPFC)
133	GMV, MRI	humans		f = m GMV; (−) correlation with weekly use	f = m GMV; (−) correlation with dependence	
134	GMV, MRI	humans	f = m: > ctrl (L Pu)			f = m: > ctrl (R PCG)
	Functional Differences	***Cannabis use***				

Reference	Outcome Measure	Subjects; Condition	Striatum	Hippocampus	Amygdala	Frontal Cortex
140	Baseline glucose metabolism, [^{18}F]FDG PET	humans				f only < ctrl (R ACC, L SFG)
140	MPD-induced glucose metabolism, [^{18}F]FDG PET	humans		f only < ctrl		f only < ctrl (MFG)
125	subliminal cue-induced activation, fMRI; pre-cue craving	humans	m only (+) correlation			f only (+) correlation (INS) f only (−) correlation (L lOFC)
	Anxiety and Depression					
153	social interaction with female stimulus	rats; males only, Cnr1 KO	m only Cnr1 KO < WT (global)	m only Cnr1 KO < WT (global)	m only Cnr1 KO < WT (global)	m only Cnr1 KO < WT (cortical glutamate); m only Cnr1 KO > WT (fore-brain GABAergic)
83	volume, MRI	human; adolescent cannabis users			f only > ctrl (R AMY)	
83	anxiety/depression symptoms; volume, MRI	humans; adolescent cannabis users			f only (+) correlation	

Subjects. f: female, m: male, f = m: no sex difference/interaction, ctrl: same-sex/same-surgical status control without cannabinoid/cannabis, f only/m only: female or male cannabinoid-exposed compared to same-sex control, OVX: ovariectomized, INT: surgically intact, MD: maternal deprivation, dep.: dependent, non-dep.: non-dependent, CP: CP 55,940, WIN: WIN 55,212-2, MPD: methylphenidate, CnR1: CB1-R receptor gene, KO: knockout, WT: wild-type **Outcome Measures.** EPM: elevated plus maze, FST: forced swim test, DA: dopamine, GMV: gray matter volume, SUD: substance use disorder **Regions.** Cd: caudate, Pu: putamen, GP: globus pallidus or pallidum, NAcc: nucleus accumbens, DS: dorsal striatum, PFC: prefrontal cortex, ACC: anterior cingulate cortex, OFC: orbitofrontal cortex, PCG: precentral gyrus, SFG: superior frontal gyrus, MFG: medial frontal gyrus, HIPP: hippocampus, AMY: amygdala, SG: subgenual area, INS: insula **Sub-regions.** dl: dorsolateral, vl: ventrolateral, vm: ventromedial, m: medial, l: lateral, R: right, L: left