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Deconstructing the neurobiology of cannabis use disorder

Jacqueline-Marie N. Ferland[1], **Yasmin L. Hurd**[1,2,†]

[1]Departments of Psychiatry and Neuroscience, Icahn School of Medicine, Mount Sinai Hospital, New York, NY, USA

[2]Addiction Institute of Mount Sinai, Behavioral Health System, Mount Sinai Hospital, New York, NY, USA

Abstract

There have been dramatic changes worldwide in the attitudes and consumption of recreational and medical cannabis. Cannabinoid receptors, which mediate the actions of cannabis, are abundantly expressed in brain regions known to mediate neural processes underlying reward, cognition, emotional regulation and stress responsivity relevant to addiction vulnerability. Despite debates regarding potential pathological consequences of cannabis use, cannabis use disorder is a clinical diagnosis with high prevalence in the population and that often has its genesis in adolescence and in vulnerable populations associated with psychiatric comorbidity, genetic and environmental factors. Integrated information from human and animal studies are beginning to expand insights regarding neurobiological systems associated with cannabis use disorder which often share common neural characteristics as other substance use disorders that could inform prevention and treatment strategies.

Editorial summary

The increasing use of cannabis has brought significant attention to cannabis use disorder (CUD) and its neurobiological underpinnings. Here Ferland and Hurd discuss risk factors related to the development of CUD its neurobiological characteristics.

Marijuana (*Cannabis*) is one of the most popular recreational drugs worldwide, with between 128 and 238 million people reporting use[1]. Over the past 30 years there has been a dramatic shift in attitudes toward the use of cannabis, steered in large part by rapidly changing sociopolitical perceptions and laws regarding this divisive drug. Over 30 states in the USA and 22 countries have legalized some form of marijuana, either for medical use and/or recreational consumption, and these numbers are growing. The dramatic pendulum shift in the broad societal use of cannabis has now prompted vigorous research

† Yasmin.hurd@mssm.edu .

Competing interests

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efforts focused on cannabis to obtain more in-depth biological insights about its potential risk and/or health benefits. Significant knowledge exists regarding the pharmacological actions of prominent cannabinoids in the cannabis plant, but scientific attention specifically focused on neurobiological underpinnings of cannabis addiction has been somewhat limited. Indeed, there remains contention as to whether it is even possible to develop an addiction to cannabis, though based on clinical diagnostic criteria, it is estimated that past-year diagnosis of cannabis use disorder (CUD) amongst cannabis users is approximately 30%[2]. This number is similar to drugs such as heroin (25%)[3] and cocaine (36.5%)[4]. However, the relatively high percentage of CUD diagnosis relates to the greater prevalence of cannabis use in the general population[2] and not to enhanced addiction liability, which is low for cannabis[5]. Additionally, cannabis use does not lead to fatal overdoses as those other drugs can, but as with most substance use disorders (SUDs), CUD carries a significant psychiatric burden[6].

CUD develops as a consequence of chronic neuroadaptations that occur over time to the repeated use of cannabis. The primary psychoactive component of cannabis contributing to its euphorigenic effects is delta-9-tetrahydrocannabinol (Δ^9-THC), which is one of ~140 cannabinoids identified in the cannabis plant, along with over 440 additional compounds including terpenoids that make up the complex effects of the plant[7]. THC concentrations in common recreational plants have increased 700–2,000% over recent decades[8], with current strains containing up to 29% THC[9]. As with all drugs of abuse, as the concentration of the psychoactive component increases, so does the risk for developing a SUD, thus prompting current concerns of increased CUD risk. The consumption of cannabis directly targets the body's natural endogenous endocannabinoid (eCB) system, which comprises the receptors that mediate the direct actions of cannabinoids, as well as the eCB lipid ligands (arachidonoyl ethanolamide, also called anandamide; and 2-arachidonoylglycerol, also called 2-AG) and the associated enzymes responsible for their synthesis and degradation[10]. The stimulation of cannabinoid receptors by THC initiates a cascade of broad biological events due to their abundant expression throughout the brain and body[10,11]. The G_i/G_o-protein-coupled cannabinoid receptor subtype 1 (CB1R) is the predominant form in the brain that mediates the psychoactive effects of cannabis[10,11], and it is expressed in multiple brain areas including in the cerebral cortex, basal ganglia, hippocampus, cerebellum, amygdala, brainstem and hypothalamus[12,13]. CB2 receptors, though very low in abundance in the brain, are implicated in neurobiological actions of THC relevant to addiction[14], but are predominantly in immune cells in the periphery. Activation of cannabinoid receptors impacts multiple physiological functions and behaviors that extend beyond the acute intoxication effects of cannabis and that can promote the development of CUD via alterations of neural systems regulating cognition, memory, reward, mood and stress sensitivity.

In this review, we provide an overview of CUD, focusing on different aspects of its risk, and explore neurobiological adaptations (neural activity, morphology, neurochemical and molecular events) relevant to CUD on the basis of human studies and animal models. Altogether, the accruing evidence reflects neurobiological signatures mirroring key components of addiction pathology.

Deconstructing the vulnerability to cannabis use disorder

Similarly to other SUDs, a diagnosis of CUD is characterized by problematic use that includes escalation with loss of control over use, repeated failures to reduce use or quit, and continued use despite negative consequences[15]. Additionally, the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-5 includes the diagnostic criteria of "craving" and "withdrawal" among the symptoms[15]. Both symptoms are common in CUD, with ~60% of CUD individuals experiencing craving for the drug and 32% undergoing withdrawal[6]. These and other negative features of CUD appear to contribute to high relapse (~67%)[16]. While the high prevalence of CUD is partially attributed to a greater number of people consuming the drug due to its wide availability[2], emerging research has begun to identify factors that may contribute to vulnerability and thus could provide insights about neurobiological processes relevant to CUD sensitivity. The complex and interrelated etiological factors that appear to contribute to risk range from genetics to psychiatric and psychological susceptibility and environmental factors.

Heredity estimates for a diagnosis of cannabis abus and dependence (DSM-III, DSM-IV) range from 21–78%[17,18]. This wide range may relate to distinct vulnerabilities relevant to different stages of drug use and/or prevalence of the disorder depending on the incidence of other factors (for example, drug availability, as shown in twin studies that cannabis availability explains most of the shared environmental risk of cannabis initiation and abuse[19]). Attempts to identify biological contributions underlying the genetic etiology of CUD have historically used candidate gene association strategies based on specific a priori neurobiological hypotheses, but current efforts have prioritized hypothesis-free genome-wide association study (GWAS) approaches. Early GWAS studies of cannabis abuse and dependence failed to achieve genome-wide significance, but more recent large GWAS investigations have identified risk loci associated with cannabis pathology. Unfortunately, none of the risk loci overlap across studies. Agrawal and colleagues identified a cluster of correlated single-nucleotide polymorphisms (SNPs) within chromosome 10 (spanning multiple genes) associated with cannabis dependence[20]. Demontis and colleagues identified one genome-wide significant intergenic risk locus on chromosome 8 (index variant rs56372821) associated with CUD. rs56372821 is an expression quantitative trait locus (eQTL) for the gene encoding cholinergic receptor nicotinic alpha-2 subunit (*CHRNA2*)[21]. *CHRNA2* is implicated in cigarette smoking-related phenotypes[22], and individuals with CUD are highly comorbid for nicotine use (~70–90% report smoking cigarettes). However, rs56372821 does not meet genome-wide significance for nicotine phenotypes[23], indicating a potential specific relationship to CUD. Another large meta-analysis GWAS—the International Cannabis Consortium study—focusing on lifetime cannabis use[24], not CUD, revealed eight independent SNP associations in multiple chromosome regions. The majority of these were located in or near genes that encode cell adhesion proteins: *CADM2* (cell adhesion molecule 2; rs2875907 top SNP hit), *NCAM1* (neural cell adhesion molecule; rs9919557) and *SDK1* (sidekick cell adhesion molecule; rs10085617). The lack of replication even with GWAS strategies can be due to factors similar to candidate gene approaches, such as heterogeneity of environment (prenatal and/or postnatal), psychiatric comorbidity and behavioral traits, and the cannabis-related phenotype being studied since,

for example, lifetime cannabis use and CUD diagnosis represent different aspects of cannabis use pathology including severity of use. Importantly, CUD is a polygenic disorder with multiple contributing genes. Furthermore, comparison control groups often differ between studies and may or may not include individuals who have ever experimented with the drug. Interestingly, excluding control subjects with no cannabis exposure enhanced the strength of genetic association with cannabis dependence observed by Sherva et al.; nevertheless, the top SNP identified (rs143244591; in *RP11–206M11.7*, an antisense transcript) still did not match other GWAS findings[25].

In addition to genetics, multiple factors contribute to addiction vulnerability, such as the high comorbidity with other psychiatric conditions. An extensive literature documents a strong relationship between cannabis use and the development of psychosis and schizophrenia, particularly with increasing THC content[26] and in individuals with certain genetic risks[27]. There is also a spectrum of other pathologies comorbid with CUD[6]. Aside from other substances of abuse (mainly nicotine and alcohol), the most common psychiatric comorbidities with CUD are mood disorders (primarily bipolar I), post-traumatic stress disorder, personality disorders (in particular borderline and schizotypal) and generalized anxiety disorder (Fig. 1). The strongest associations are in individuals with severe CUD, where there is a six- to ten-fold increase in the chance of such co-occurrence[6]. It is still unclear whether comorbid disorders, which also have strong genetic correlates, predate or are a consequence of cannabis use. Monitoring individuals longitudinally suggest that frequent cannabis use and its abuse are associated with increased risk of a subsequent mental health disorder[28,29]. Conversely, having any mood, anxiety or other substance-use pathology at baseline also predicts future cannabis use and dependence[28]. Behavioral and neurocognitive traits are also an important feature of CUD. As with other drugs of abuse, sensation-seeking and reward sensitivity have been implicated with the initiation of use and severity of the CUD[30]. The recent International International Cannabis Consortium GWAS also revealed a genetic correlation between lifetime cannabis use and traits such as risk-taking behavior[24], highlighting the contribution of genetic variants to phenotypes associated with drug use.

Consistent with the characteristics of a complex psychiatric disorder, environmental factors also modulate predisposition and the course of cannabis use and CUD. For example, increased incidence of traumatic or challenging experiences (including childhood trauma or family or neighborhood adverse events[17,31]) strongly influences CUD risk. Studies incorporating genetic, environmental and behavioral characteristics have also demonstrated complex interactions between genes and environment[32,33], emphasizing multiple intrinsic and extrinsic factors that collectively mediate CUD susceptibility. Irrespective of other factors, age of onset is a strong predictive variable, with significant correlations evident between younger age of cannabis use initiation and CUD liability. Importantly, the risk for CUD onset normally peaks in late adolescence and the early twenties[34], when the brain has not achieved full adult maturity; this is a sensitive developmental window for psychiatric vulnerability. Sex also has important implications for CUD. Men have higher rates of CUD than women, a pattern that is present from childhood, when more boys than girls develop CUD[2,35]. Despite the high prevalence of cannabis-dependent males, the escalation of use and severity of CUD is greater in females, as with many substances of abuse[36].

Deconstructing the neural underpinnings of cannabis use disorder

The neurobiology underlying CUD can be explored at multiple in vivo and postmortem levels of assessments, based on diverse experimental strategies that have been employed investigating cannabis use. While results are not always equivocal, due to various confounds —including issues of the frequency or severity of cannabis use, duration of use and abstinence, comorbid disorders, co-use of other psychoactive drugs, sex and genetics— several consistent patterns have begun to emerge that begins to establish a neurobiological framework for CUD.

Neurochemical signature of CUD

The eCB system, being the prime site for THC's action, has been the focus for positron emission tomography (PET) neuroimaging studies, which consistently demonstrate that CB1Rs[37–39] are dynamically altered depending on the phase of chronic cannabis use (Fig. 2). CB1Rs are generally downregulated in cannabis users, with strongest alteration evident shortly after cannabis use. These changes are predominantly localized to the neocortex and limbic cortices[37,38], which regulate cognition and emotional processing, as well as the ventral striatum[38], which is critically involved in reward and goal-directed behavior[40]. Longer duration of use associates with lower CB1R densities[37]. Postmortem brain analysis substantiates downregulation of CB1R binding in cannabis abusers as well as reduced mRNA expression of the gene (*CNR1*) encoding CB1R[41]. However, reduction of CB1R in cannabis dependent subjects is not permanent, and it normalizes ~2 to 28 days after drug use ceases[39]. The return to apparent normal levels after protracted abstinence might, however, not be paralleled by normalization of receptor function, based on animal studies (see below), suggesting that CB1R may remain functionally altered during abstinence. Nevertheless, reduced CB1R during early stages of the disorder is expected to impact the cascade of downstream neurobiological systems that can maintain persistent changes underling the behaviors characteristic of CUD. Aside from that for CB1R, little in vivo evidence exists for other components of the eCB system, but preliminary data indicate reduced binding of fatty acid amide hydrolase (FAAH), the enzyme that metabolizes anandamide, suggesting altered anandamide levels within corticolimbic brain regions in CUD individuals[42].

Of the neurotransmitter systems linked with addiction, dopamine has received most attention, given its strong role in reward, motivation and goal-directed behavior. Similarly to other substances of abuse, acute THC increases dopamine release in the striatum of healthy subjects[43] (Fig. 2). Following chronic use, there is a reduction of stimulated dopamine levels in CUD[44], as in other SUDs (e.g., psychostimulants, nicotine, alcohol and opioids; Fig. 2). Early age of onset or longer duration of cannabis use correlates with reduced stimulated striatal dopamine release (evoked by psychostimulant administration)[45]. The lower striatal dopamine release apparent in heavy cannabis users relates to inattention and greater negative symptoms[46], and it inversely correlates with negative emotionality and addiction severity[47]. Reduced release also corresponds with decreased dopamine synthesis in cannabis-dependent individuals[48], an effect associated with greater apathy[49]. PET measures of dopamine transporters (necessary for presynaptic dopamine reuptake) also reveal reduced availability in multiple brain areas, including the striatum, in cannabis-dependent people[50]. Altogether,

the presynaptic hypodopaminergic state evident with CUD would be consistent with the classic ‘amotivational syndrome’ and negative affect characteristic of this disorder. However, a feature of many SUDs that often accompanies blunted dopamine release is reduced striatal dopamine D2/D3 receptor availability[51], but this is relatively normal in CUD individuals[44], suggesting potentially unique aspects of dopaminergic transmission with CUD.

The compulsive perpetuation of the addiction cycle is also characterized by alterations of glutamate, which plays a major role in mediating inhibitory control and drug-seeking behaviors[52]. Glutamatergic transmission is highly regulated by eCB signaling[53] (through presynaptic terminal CB1Rs that reduce glutamate release) and thus sensitive to THC[54]. Proton magnetic resonance spectroscopy reveals increased glutamate levels with acute THC use[55], but following chronic use, steady-state glutamate levels are reduced in various brain regions in both adults and teens[56,57] (Fig. 1). Hypoglutamatergic transmission is also evident in other SUDs[58,59], particularly during drug abstinence, and is considered to underlie the impaired decision-making that in turn contributes to continued drug-seeking[52,60].

Morphological characteristics of CUD

Human structural MRI (sMRI) studies consistently document architectural alterations particularly within corticolimbic structures such as the prefrontal cortex (PFC), hippocampus and amygdala with CUD (Fig. 3). The integrity of the orbitofrontal cortex (OFC; localized within the PFC), which contributes to cognitive flexibility, valuation and decision-making[61], is commonly impaired in SUD[62] and strongly relates to problematic cannabis use. Overall, greater disease severity, regularity of use and duration of cannabis use are associated with reduced volume of the medial OFC[63,64]. Reduced OFC volume in young teens predicts initiation of cannabis use in later adolescence, suggestive of a preexisting neurobiological risk factor[65]. A similar sensitivity is evident in the hippocampus, a region central to learning and memory[63,66], in which hippocampal gray matter is inversely associated with the amount of THC consumed, emphasizing the direct contribution of CB1R stimulation. Interestingly, a functional variant of the *CNR1* gene (rs2023239 G allele) linked with higher cortical CB1R is associated with smaller hippocampal volume in chronic cannabis users, but not healthy controls, indicating a potential gene × drug interaction[67]. Likewise, reduced cortical thickness evident in some teens appears to relate to genetics—for example, the negative impact of cannabis use in early adolescence on cortical maturation is only in individuals with a high genetic risk of schizophrenia[68]. Cannabis use and CUD severity also associate, in a graded manner, with deficits of amygdala gray matter volume, with gray matter volume inversely related to CUD severity[69,70]. Given the involvement of the amygdala in emotional regulation, craving and drug-seeking behavior[40], these morphological alterations may relate to the prominent mood and anxiety comorbid characteristics of CUD (Fig. 3). However, the significance of these morphological changes is debated, since twins of cannabis users who themselves do not use cannabis can have lower amygdala volume, suggesting that decreased amygdala volume may be predispositional[71]. Nevertheless, animal models have established a direct causal relationship between THC and changes in cortical structure[72,73] (see below). Overall, preexisting morphological differences in brain regions regulating cognition and emotion may enhance the risk for cannabis use, and they are also impacted by the severity and duration of subsequent cannabis exposure.

The deficits in gray matter volume observed in CUD are mirrored in many SUDs[74–76]. One major difference is the cerebellum, which has increased gray matter volume in CUD subjects[63,69], an effect maintained even a month of abstinence in adolescent cannabis users and which is associated with poor executive functioning[63,69,77]. Although the cerebellum is not typically linked with SUD pathophysiology, a significant body of evidence emphasizes cerebellar involvement in cognition, impulsivity and emotional processing in line with its strong anatomical projections to frontal cortical regions[78]. In contrast to consistent cerebellar findings, the striatum, though critical to reward and habit formation[40], shows no clear pattern of gray matter structural alterations related to CUD[79]. Overall, the CUD neuronal architecture, at least that visible with MRI spatial resolution, primarily indicates sensitivity of structures linked to cognition and emotional processing (Fig. 3 and Table 1).

Functional brain activity of CUD

In addition to morphological changes, various lines of functional MRI evidence reveal specific brain activity signatures with cannabis use relevant to CUD, both during resting conditions and when individuals are engaged in specific tasks (Fig. 4). One of the most common patterns of resting state brain activity identified in chronic cannabis users, as with other SUDs[80], is increased functional connectivity associated with the default mode network (which primarily includes the posterior cingulate cortex, adjacent medial PFC (mPFC) and portions of the parietal cortex, the precuneus and angular gyri) and insula networks[81,82]. The default mode and insula networks are highly interconnected and are primarily activated during self-referential and introspective thought[83]. Importantly, resting-state alterations in frontal and sensory systems persist even following a month of abstinence, but with blunting of the changes[81,84], suggesting the potential of the brain to reverse some of the effects of prior chronic cannabis use.

Functional MRI studies also document differential brain activity during neurocognitive tasks in CUD individuals (Table 1). For example, cost–benefit decision-making conditions in heavy cannabis users associate with reduced activity of the OFC and dorsolateral PFC, but also with increased cerebellar activity (Fig. 4), an effect that tracks tightly with impaired choice outcome[60]. Compromised attentional control is also a feature of SUDs, and multiple brain areas are underactive during cognitive interference conditions (for example, the Stroop task) in cannabis-dependent individuals, including the PFC, striatum, amygdala–parahippocampal gyrus, cerebellum and midbrain[85–87] (Fig. 4). However, the under-recruitment of these circuits during attentional processes often occurs even with no outward deficits in attention[85,86]. Interestingly, the hypoactivity in these neural circuits appear to be mutable, as the pattern reverses after a year of abstinence, with increased activation within many of these areas[85]; this could also suggest a link between enhanced activation during attentional processes with the ability to abstain from drug. For working memory, despite the well-documented negative cognitive impact of acute THC in drug-naïve individuals and infrequent cannabis users, cannabis-experienced users often have normal working memory performance[88,89]. However, neural networks associated with such cognitive function are not normal: chronic and heavy cannabis use is associated with hyperactivation of frontal regions and networks underlying working memory[90]. Similar alterations are also evident in abstinent adolescent cannabis users[91,92]. Collectively, these

modifications suggest an overcompensation of neural networks in individuals with CUD to achieve apparent normal executive function when cognitive demand is required.

Heightened sensitivity to drug cues is a hallmark of addiction that often contributes to craving and relapse, and, consistent with other SUDs, greater activation of the mesocorticolimbic reward pathway (ventral tegmental area, striatum, OFC, anterior cingulate gyrus) to drug cues is observed with CUD[93,94]. Higher response to cannabis cues is associated with greater cannabis-related problems[94,95]. The activity within these reward-related structures in response to cannabis cues has been associated with genetic variants of *CNR1* (rs2023239) and *FAAH* (rs324420), where the heightened response to cues increases as the number of eCB risk alleles increases[96], again suggesting genetic contributions to neural processes relevant to CUD.

Alterations in neurobiological systems associated with emotional processing are also common with cannabis use pathology, influencing the responsivity to anxiety, threat, depression, and maladaptive coping with stress that are associated with relapse risk. Both the PFC and amygdala are particularly reactive to negative stimuli in CUD; stronger medial OFC activity is associated with negative, but not positive, emotional stimuli after nearly a month of abstinence[97]. In contrast, the cognitive appraisal of affective stimuli in heavy cannabis abusers is associated with decreased activity in the mPFC (anterior cingulate and ventromedial PFC)[98]. The greater OFC and amygdala activation in CUD for negative stimuli, concomitant with decreased PFC activation for cognitive evaluation, would suggest an overactive affective neural loop with attenuation of appraisal networks. Combined with heightened sensitivity to drug cues and reward anticipation, these changes would classically reflect an addiction neurobiological signature of relapse vulnerability.

Translational insights from animal studies

While significant neurobiological insights have been garnered about the human brain from in vivo imaging strategies related to CUD, debates continue as to the direct role of cannabis to these apparent perturbations, considering complex issues such as genetic and environmental factors that might account for neurobiological differences predating cannabis use. THC animal models corroborate CB1R alterations observed in humans, establishing a causal impact of THC on CB1R fluctuations across time with proof of receptor desensitization (reflecting attenuated receptor coupling)[99,100]. Such studies also demonstrate that female rats exhibit greater attenuation of CB1R function in most brain regions than males, especially when chronic THC is administered during adolescence rather than in adulthood[100,101], potentially relevant to the greater escalation and severity of CUD in human females than males. As in humans, there is (over time) a recovery to normal levels of CB1R following cessation of THC administration[102]. However, even at time points when apparent receptor binding or the number of CB1R returns to normal, there remain persistent perturbations of intracellular signaling and downstream molecular processes. For example, downstream effectors such as cAMP response element binding (CREB) protein are reduced in the hippocampus[103] following chronic THC administration, an effect that persists weeks after drug exposure. An interesting downstream target of cAMP and CREB are cell adhesion molecules known to play key roles in long-term potentiation (LTP) and synaptic

plasticity[104,105]. Concomitant with disturbances of genes related to synaptic plasticity, rats with chronic THC administration exhibiting impaired learning and memory have reduced hippocampal neuronal cell adhesion molecule, NCAM[106]. Importantly, reduced NCAM is well documented in different THC treatment regimens[107,108]. Moreover, chronic THC exposure in animals with genetic deficiency of polysialylated NCAM exacerbates the genetically induced memory deficits into adulthood[109], supporting a gene × environmental interaction in line with the recent GWAS identifying genetic variants of genes encoding cell adhesion molecules, including *NCAM*, with lifetime cannabis use[110]. Overall, THC-induced alterations of CB1R, CREB and NCAM (Fig. 5) strongly suggest significant modification of synaptic plasticity consistent with the critical role of the eCB system in regulating synaptic transmission.

In addition to providing neurochemical and molecular insights, animal models confirm a direct impact of repeated THC exposure to alter neuronal architecture. For instance, long-term (90 days) exposure to high dose THC strongly reduces neuronal number, as well as the number of synapses and the dendritic length of hippocampal neurons, even months after the last THC dose[72]. Moreover, adolescent THC administration of a dose comparable to low-to-moderate cannabis use reduces the spine number and complexity of branching of PFC pyramidal neurons in adulthood[73]. These morphological changes are accompanied by marked disturbances of genes linked to dendritic development and cytoskeleton organization, as well as reprogramming of the epigenetic transcriptome[73]. Thus, the animal literature largely lends support to the idea of structural alterations being prominent within the cortex and hippocampus following repeated cannabis or THC exposure, emphasizing the cortical sensitivity of chronic use.

Animal models also reveal, at cellular-level resolution, responses relevant to alteration of neural activity detected in individuals with CUD. Notably, chronic THC exposure in most electrophysiological animal studies confirms indices of persistently reduced cortical neuronal activity similar to deficits in neural oscillations reported in humans with CUD[111]. For example, adult rats with adolescent THC exposure exhibit long-term reduction of cortical oscillations in the rostral mPFC specifically mediated by CB1R mechanisms[112]. CB1R-mediated disruption of neural oscillations are linked to reduced transmission of GABAergic interneurons in cortical circuits[113]. Chronic THC exposure also depresses glutamatergic synaptic responsiveness, as evident in the hippocampus where parallel downregulation of NMDA and AMPA glutamate receptor expression could contribute to reduced LTP[103]. Fig. 5 provides an overview of the neurochemical cortical changes generally observed in chronic THC animal models. These alterations are not, however, mirrored in all brain areas, and cell-type- and synapse-specific differences are actively being explored regarding the long-term subregional effects of THC. Such complexity is exemplified by recent evidence demonstrating that long-term THC exposure weakens mPFC inputs to the ventral striatum but strengthens those from the hippocampus and amygdala[114], in line with reduced prefrontal cognitive control but enhanced emotional lability in cannabis users.

The use of animal models to inform neurobiological underpinnings associated with phenotypes relevant to CUD-comorbid disorders, such as addiction to other substances,

have firmly established that adolescent THC exposure increases the sensitivity in adulthood to opioid reward[115–118]. There remains, however, a surprising paucity of animal studies evaluating the interaction of THC with other drugs, despite the high comorbidity of CUD with alcohol and nicotine addiction[119]. Of the few existing studies found that short-term THC exposure increased the likelihood of rats to acquire nicotine self-administration[120]. Unfortunately, study of chronic THC animal models focused on psychiatric-related phenotypes such as anxiety-like behavior is also limited, despite the tight link between the eCB and stress systems[121]. In the published behavioral data, the effects of THC exposure are variable, but might reflect important aspects of dose, neurodevelopmental sensitivity and sex that are also evident in humans. For instance, high THC doses increase anxiety-like behaviors, whereas low doses lead to a decrease[122]. Additionally, females appear more sensitive to the anxiogenic properties of THC than males, even during THC-abstinent periods[122]. Moreover, chronic cannabinoid administration during adolescence, but not adulthood, increases anxiety behavior weeks after exposure[123].

Although THC animal models substantiate a number of alterations detected in humans, there remains a significant gap of in-depth knowledge critical to advance fundamental mechanistic underpinnings of CUD. A major challenge for translational efforts is that the prevalent short-term and often excessive THC doses used in many animal models do not reflect the human condition, thus lacking face validity for CUD. Moreover, the gold standard self-administration animal models normally used in the addiction field are challenging for cannabis because rodents experience THC as aversive and thus do not readily acquire or maintain stable self-administration behavior[124]. To circumvent such challenges, most animal research has mainly used passive parenteral THC administration routes. New animal inhalation self-administration models for THC[125] and cannabis cigarette[126] will help bridge the translational gap to advance molecular and cellular knowledge relevant to CUD.

Treatment: reconstructing neurobiological systems impacted by cannabis

Despite the millions of people diagnosed with CUD there are presently no approved FDA pharmacotherapies. Psychosocial interventions, which are normally the first line of treatment, have the potential to modify gray matter volume as well as to increase the functional and structural connectivity between frontal and limbic cortices[127,128] as well as cerebellar cognitive-related circuits[129]. However, no studies to date have examined whether cognitive–behavioral strategies can improve the neural alterations and behavioral outcomes in individuals with CUD.

The majority of pharmacological interventions being explored for CUD are substitution therapies with cannabinoid agonists as well as agents targeting neurotransmitter systems known to be aberrant in addiction. Table 2 provides a summary of these agents. In addition, recent attention has focused on cannabidiol (CBD), a non-intoxicating cannabinoid which has anxiolytic properties[130–132] and appears to reverse behaviors and neural systems relevant to the effects of cannabis. For instance, cognitive and anxiety-like behaviors induced by chronic THC administration during adolescence in rodent models are prevented by the co-administration of CBD[133]. Additionally in humans, CBD blocks THC-induced anxiety[134] and reduces wanting and liking of cannabis-related stimuli in

cannabis users[130]. On a neurobiological level, animal studies demonstrate that CBD normalizes glutamatergic systems[135], known to be dysregulated in SUDs including CUD. Moreover, CBD activates corticolimbic structures and circuits that are reduced during attentional processing in individuals with CUD[136]. Concomitant to reducing anxiety, CBD also reduces stress-induced activation of the hippocampus and other cortical areas[132] and restores hippocampal volume in current cannabis users, particularly those with greater lifetime cannabis exposure[137]. However, acute administration of CBD does not impact the reinforcing or physiological effects of smoked cannabis in cannabis users[138]. Thus, CBD's potential therapeutic value might relate more to alleviating craving and stress-related responses that contribute to relapse in CUD[6] rather than blocking the acute rewarding effects of THC. Overall, the current medications are still in relatively early phases of exploration as potential CUD pharmacotherapeutics, but the list is expected to grow as greater insights are gleaned about the underlying pathophysiology of CUD.

Summary and future directions

CUD is a multifactorial complex disorder in which there is interaction among genetic and environmental factors that, in combination with psychiatric comorbidity and the continued use of cannabis, contribute to neurobiological alterations that underlie the addiction phenotype (Fig. 6). There is still much to learn about the neurobiology of CUD, but contrary to the growing nonchalance regarding cannabis use by many in society, the neurobiological evidence demonstrates multilevel divergent patterns in neurochemistry, morphology and neural activity in brain regions that are highly implicated in other SUDs. The shared neurobiological signature may underlie common addiction behavioral phenotypes, such as compromised decision-making and attentional processing, marked drug craving and sensitivity to drug cues, as well as anxiety and negative affect particularly associated with drug withdrawal.

Definitive conclusions about specific neurobiological features of CUD still remain elusive due to complex heterogeneous factors, such as genetics, environment and sex, evaluated across studies. While the 'chicken or egg' pre-existing or direct cannabis cause of such factors can continue to be debated, it is clear that individuals with and without pre-existing neurobiological risk are being exposed more than ever to high THC doses. This is of particular concern for the vulnerable neurodevelopmental periods—prenatal, childhood and adolescence. Longitudinal projects, such as the Adolescent Brain Cognitive Development (ABCD) Study and new trans-NIH baby Brain Cognitive Development (bBCD) project to monitor normative and drug-exposed neurodevelopmental trajectories starting from adolescent and prenatal stages, respectively, are important steps to identify specific early risk factors and expand knowledge about the long-term impact of cannabis (and other drug) exposure. Data from the Dutch Generation R Study, a population-based prospective cohort study from fetal life until young adulthood, is already being leveraged to understand the influence of the prenatal environment on brain maturation and childhood behavior[139]. Moreover, accrued data has established that the adolescent brain is not impervious to cannabis effects, with early onset of use often associated with greater changes in brain structure and activity.

What is nevertheless also apparent is the potential for some neurobiological alterations to be reversed during extended abstinence. This emphasizes the adaptive and continued dynamic nature of the brain when drug-free. However, animal models overwhelmingly demonstrate protracted molecular alterations subsequent to THC use, suggesting that underlying molecular and cellular processes may remain sensitive to subsequent drug use later in life even if general neurobiological features appear relatively normal. The neurobiological mechanisms that maintain these protracted effects are likely epigenetic processes[140], which means that they are malleable. As such, the drug-abstinence window may be a critical period for targeting these molecular processes to improve long-term outcomes.

Despite significant insights gleaned about the in vivo neurobiological patterns of CUD, there still remains a surprising large gap of knowledge from animal studies. In-depth preclinical molecular interrogations based on the human brain findings are limited. For instance, the cerebellum is not well studied in animals, though individuals with CUD have clear differences in this region. Moreover, despite the growing animal literature on THC, dosing regimen and treatment strategies more reflective of the human condition are lacking in the field. Enhanced integration of human and preclinical animal research would significantly expand neurobiological knowledge important to guiding prevention and treatment strategies.

Finally, the ability to expedite scientific understandings of CUD is unfortunately hindered today in a sociopolitical quagmire in the US, where the public perceives little risk of cannabis use, while governmental regulations still consider it a Schedule I drug, which impedes critical research necessary to provide guidance about cannabis risk–benefit and potential treatments. Reducing such impediments will greatly advance scientific and clinical discoveries toward treatment development and to promote evidence-based policies.

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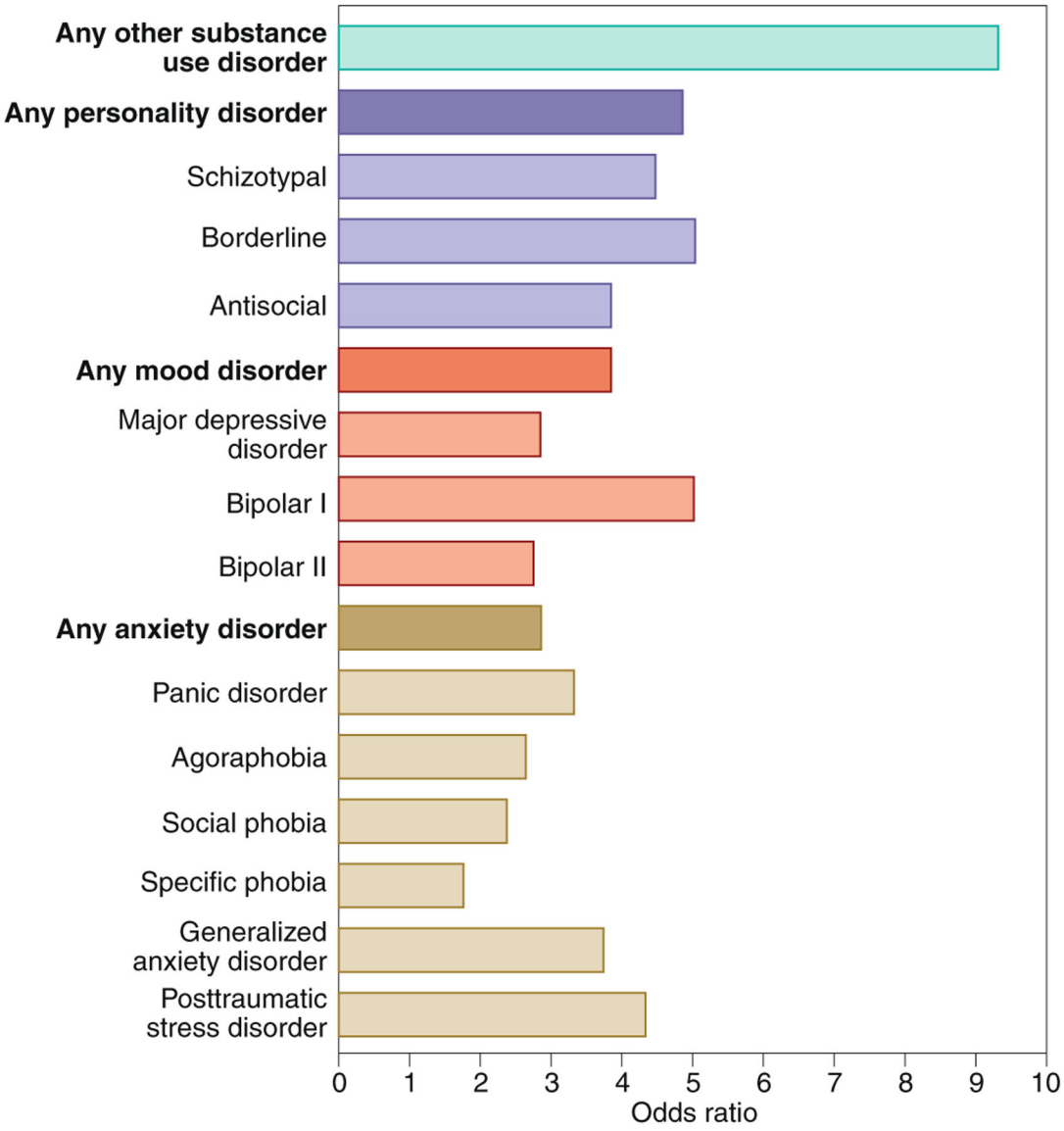

Fig. 1 |.

Odds ratios of psychiatric conditions associated with CUD. Data based on the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study[6]. Figures: Debbie Maizels/Springer Nature.

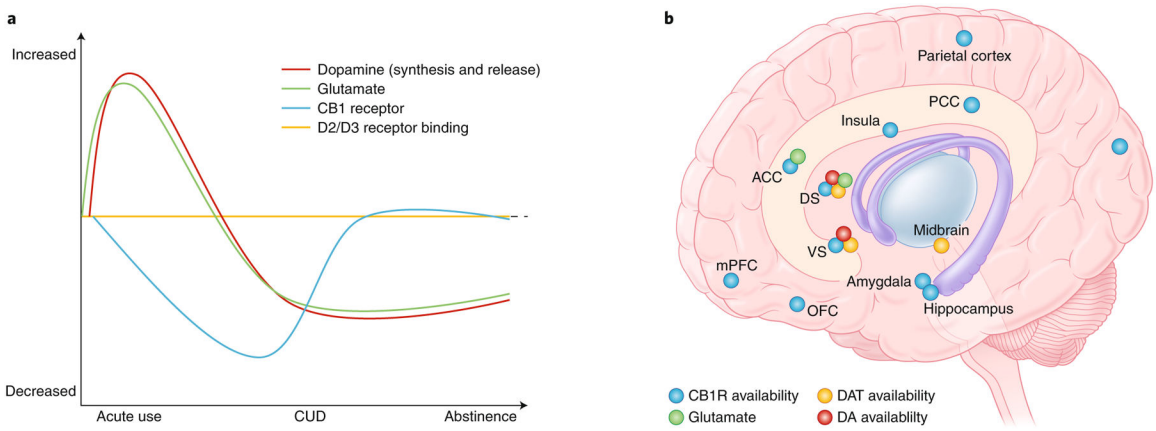

Fig. 2 |.

Overview of the dynamic patterns of the in vivo neurochemical-related alterations (based on PET, functional MRI, and H-MRS studies) associated with CUD. **a**, Line graphs indicate specific alterations during acute use as compared to neurobiological state in individuals with CUD, including during periods of abstinence. **b**, Dots indicate brain regions in which neurochemical marks reflective of CB1R, dopamine transporter (DAT) and dopamine (DA) synthesis have been detected in individuals with CUD. ACC, anterior cingulate cortex; DS, dorsal striatum; PCC, posterior cingulate cortex; VS, ventral striatum. Figures: Debbie Maizels/Springer Nature.

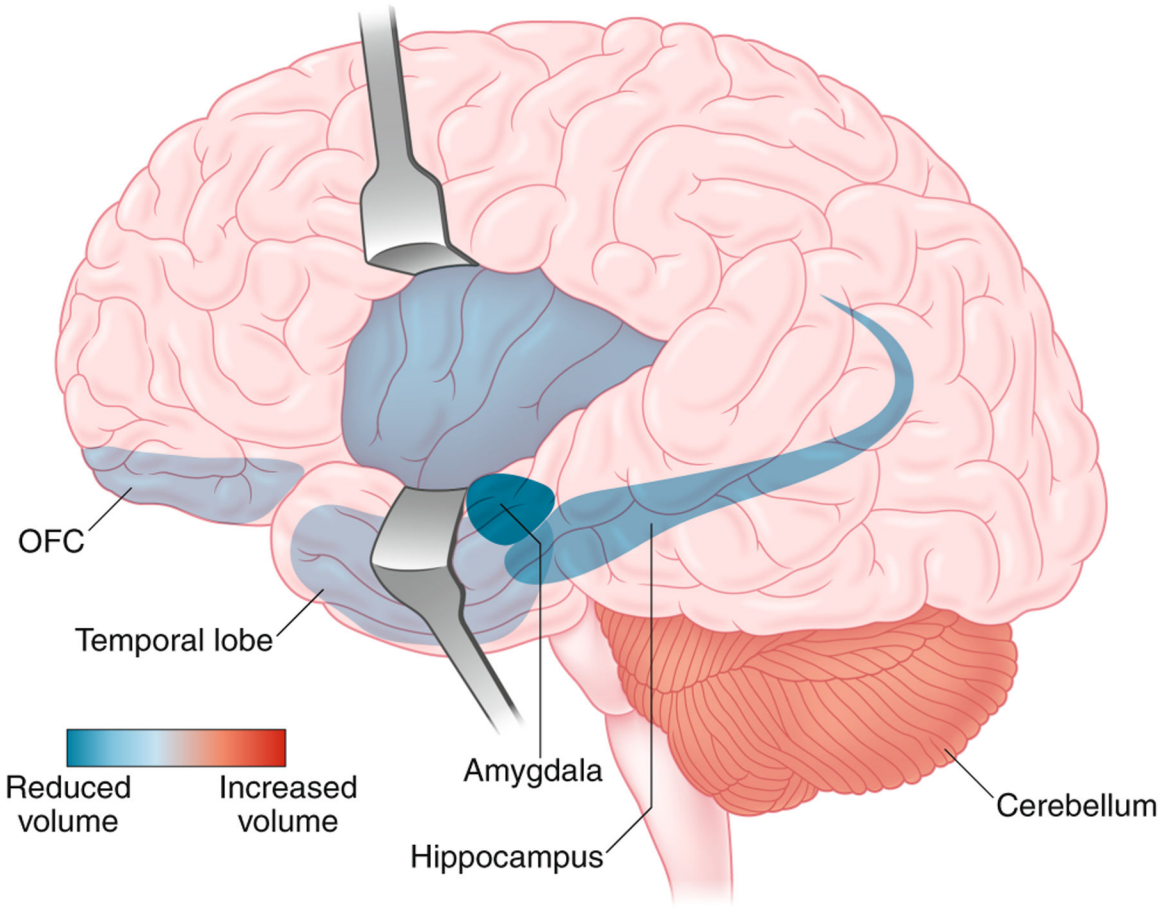

Fig. 3 |.

Alterations of gray matter volume (based on MRI studies) detected in individuals with CUD. Colors denote decreased (red) and increased (blue) gray matter volume. Figures: Debbie Maizels/Springer Nature.

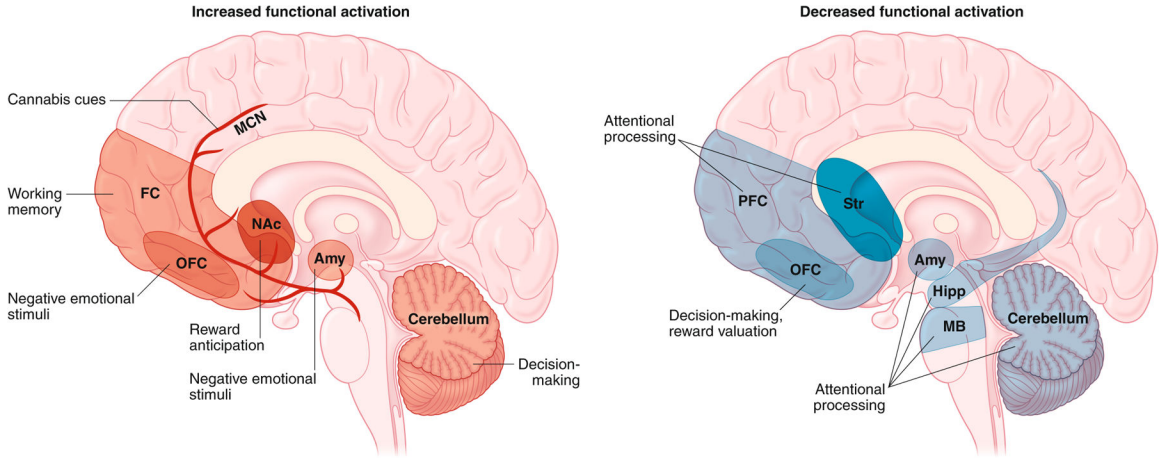

Fig. 4 |.

Differences in functional activity (based on functional MRI and electroencephalogram studies) detected in the brain of abstinent individuals with CUD during exposure to specific tasks and stimuli. Increased activation in specific regions is indicated in the left panel in red, and reduced activation is depicted in the right panel in blue. The specific task- or stimulus-driven alteration in activity is indicated in each region and circuit. Amy, amygdala; hipp, hippocampus; MCN, mesocorticolimbic network; FC, frontal cortex; NAc, nucleus accumbens; Str, striatum; MB, midbrain. Figures: Debbie Maizels/Springer Nature.

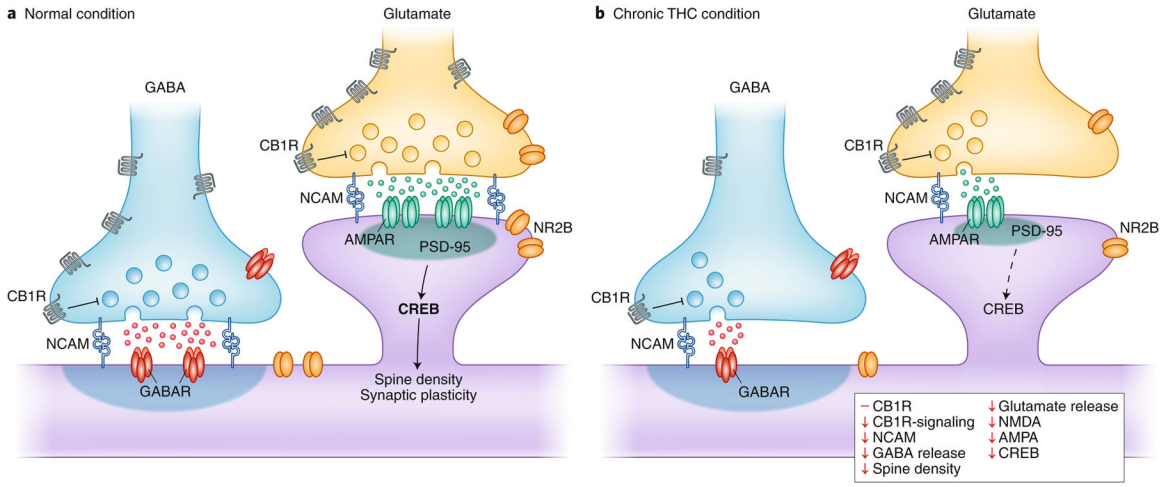

Fig. 5 |.

Synaptic perturbations based on animal models associated with chronic THC exposure (right) as compared to control condition (left) in glutamate and GABA synapses in the cortex. THC is known to have a greater effect on the interneuronal GABA microcircuit, most likely due to the greater (~20-fold) number of CB1R on cortical GABAergic interneuron axon terminals compared to glutamatergic terminals[141]. AMDAR, AMDA receptor; GABAR, GABA receptor; NCAM, neural cell adhesion molecule; NMDAR, NMDA receptor. Figures: Debbie Maizels/Springer Nature.

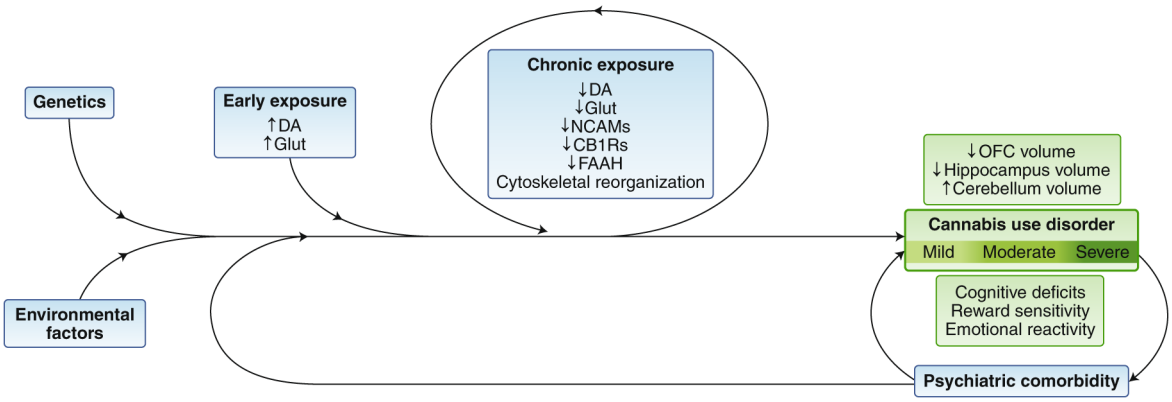

Fig. 6 |.

Factors contributing to CUD. Schematic summary of multiple factors that contribute to the neurobiological patterns documented in relation to cannabis use and eventual CUD, where the more pronounced neurobiological alterations are associated with greater severity of the disorder and behavioral consequences. FAAH, fatty acid amide hydrolase; Glut, glutamate; Vol, volume. Figures: Debbie Maizels/Springer Nature.

Table 1 |

Alterations detected in specific brain regions of in vivo measures of gray matter volume and functional activity, associated with certain tasks and stimuli, in abstinent individuals with CUD.

Region / circuit	Morphology	Neural activity	Association with function- or task-based activation
Frontal cortex/ prefrontal cortex	Decrease in volume (OFC)[63,64,142]	Decrease[60,86,98,143] or increase[90–92,97] in activity based on task and absinence[85]	Decreased in decision-making[60]; decreased activity with uncertain reward[143]; decreased during cognitive appraisal of emotional stimuli[98]; decreased activity on attention task[85,86], but increased activity after 1 year of abstinence is associated with better treatment outcome[85]; increased activity on working memory tasks[90–92] and responsivity to negative emotional stimuli[97]
Ventral striatum	*[79]	Decrease[85,#] or increase in activity[144], based on task and abstinence	Decreased activity on an attentional task[85]; increased activity during reward anticipation[144]
Dorsal striatum	*[79]	Decrease in activity[85,#]	Decreased activity during attentional processing[85]
Hippocampus/ temporal lobe	Decrease in volume[63,66]	Decrease in activity (hipp)[85,#]	Attentional processing[85]
Amygdala	Decrease in volume[69,70,145]	Decrease[85,#] or increase[97] in activity based on task	Decreased functionality associated with attentional performance[85], increased activation in response to negative emotional stimuli[97]
Cerebellum	Increase in volume[63,69]	Decrease[86,#] or increase[60,#] in activity based on task	Increased activation during decision-making[60], decreased activity associated with attentional processing[86]
Mesocorticolimbic pathway		Increase in activity[93,94,146,147]	Cannabis cue reactivity[93,94,146,147]

The majority of individuals with CUD were studied during periods of short abstinence from ~12 h to 4–5 days.

#, longer periods of abstinence, from ~1 to 36 months;

*, inconsistent observations.

Table 2 |

Putative pharmacotherapeutics that have been investigated for CUD.

Pharmacotherapy (market name(s))	Formulation	Mechanism of action	Mitigates intoxication	Mitigates withdrawal symptoms	Mitigates relapse	Citation
Dronabinol (Marinol, Syndros)	Extracted Δ^9-THC in capsule	CB1 agonist	Yes, at high doses	Yes	No	[148]
Nabilone (Cesamet)	Synthetic Δ^9-THC mimetic in capsule	CB1 agonist	-	Yes	Yes	[148]
Nabiximols (Sativex)	Δ^9-THC + CBD in nasal spray	CB1 agonist	-	Yes	No	[148]
CBD	Cannabis extract in capsule		No	Yes, but limited	-	[138,149]
PF-04457845	Capsule	FAAH inhibitor	-	Yes	Yes	[150]
Gabapentin (Neurontin)	Capsule	GABA analog, voltage-gated Ca^{2+} antagonist	-	Yes	Yes	[148]
N-acetylcysteine	Capsule	Glutamate agonist	-	-	Yes, in adolescents	[148]
Topiramate (Topamax)	Capsule	GABA agonist, glutamate antagonist			Decreased amount smoked, but not overall relapse, and poorly tolerated	[148]
Guanfacine (Tenex)	Capsule	Alpha-2a adrenergic agonist	-	Yes	-	[148]