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REVIEW

The Cerebellum, THC, and Cannabis Addiction: Findings from Animal and Human Studies

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Abstract
Cannabis is the third most used psychoactive drug worldwide. Despite being legally scheduled as a drug with high harm potential and no therapeutic utility in countries like the USA, evidence shows otherwise and legislative changes and reinterpretations of existing ambiguous laws make this drug increasingly available by legal means. Nevertheless, this substance is able to generate clear addiction syndromes in some individuals who use it, which are accompanied by brain alterations resembling those caused by other addictive drugs. Moreover, there is no available pharmacological treatment for this disorder. This fact motivates a deep study and comprehension of the neural basis of addiction-relevant cannabinoid effects. Interestingly, the cerebellum, a hindbrain structure which involvement in functions not related to motor control and planning is being increasingly recognized in the last decades, seems to be involved in the effects of addictive drugs and addiction-related processes and also presents a high density of cannabinoid receptors. Preclinical research on the involvement of the cerebellum in cannabis' effects has focused in the drug's motor incoordinating actions, potentially underestimating its participation in addiction. Therefore, this review addresses the studies reporting cerebellar involvement in cannabis effects both in experimental animals and human subjects and the possible relevance of these changes for addiction. Additionally, future experimental approaches will be proposed and hopefully this work will stimulate research on the cerebellum in cannabis addiction and help recognizing it as an important part of the neural circuitry affected in cannabis-related disorders.

Keywords Cerebellum · Cannabis · Δ^9-Tetrahydrocannabinol · Addiction · Withdrawal · Craving

Introduction

Cannabis is the third most used recreational drug worldwide, with recent epidemiological surveys and studies showing that up to 232 million people have used it recently [1]. In Europe, out of 80 million people that have used illicit drugs during 2013, 75.1 million (93.87%) used cannabis [2]. This drug is obtained from the plant *Cannabis sativa*, which belongs to the family of Cannabaceae and it is thought to be endemic from Himalaya Mountains [3]. It is normally administered via inhalation of the smoke produced by its combustion. The presentation forms of the drug include marijuana, the dried *C. sativa* flowers which are shredded before smoking them mixed with tobacco or not, and hashish, a preparation consisting in the compact resin of the plant, which is also smoked mixed with tobacco or not [4].

In countries like the USA, this drug is placed on the Schedule I of the Controlled Substances Act. This classification means it is considered to have no medical value and high harm potential [5], as compared to substances like cocaine or methamphetamine. The latter drugs are placed in Schedule II and are, legislation-wise, considered to present more medical uses and less harm potential than Schedule I substances. Nevertheless, available evidence does not seem to support such a classification for cannabis, which is indeed indicative of a relatively low harm potential and several therapeutic applications [6–9]. Accordingly, many governs have made changes on legislations regarding cannabis so that it is becoming legal for medical purposes or even for recreational use in several countries [10–12]. It should be noted, however, that the apparent low-risk profile of cannabis does not imply it is exempt of risks. It is a substance with recognized capacity of creating addiction syndromes [13, 14], for which no medications are available. Its continued use is associated with

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modifications in brain structure and functioning similar to those caused by other addictive drugs [15–17].

Interestingly, the cerebellum, a hindbrain structure that contains more neurons than the rest of the entire brain [18] is starting to be recognized as an important part of the addiction circuitry in light of data coming from addicts and animal studies [19–22]. This cerebellar involvement in addiction-related processes may be partially explained by the connections this area has with other parts of the brain considered as part of the addiction circuitry. This is the case for ventral tegmental area [23, 24], striatal zones [25, 26], prefrontal cortices [27, 28], amygdala [29, 30], and hippocampus [31, 32]. It is also noteworthy that the cerebellum presents a high density of cannabinoid receptors, the proteins through which cannabinoids like Δ9-Tetrahydrocannabinol (THC) exert their effects on neural function [33]. Figure 1 depicts the distribution of the main cannabinoid receptor in the cerebellum. Note widespread receptor expression in the molecular layer. There is also intense expression in the Purkinje cell layer localized in pinceau formations. The granule cell layer shows negligible receptor expression levels.

These reasons make the cerebellum a brain structure that is likely to be responsible for some effects of acute and repeated THC administration. Therefore, it can also be participating on the neural processes related to cannabis addiction. Nevertheless, most of the research on the effects of cannabis and THC on the cerebellum, especially at the preclinical level, has focused on cannabis and cannabinoids' effects related to motor coordination and performance. Probably, this has been influenced by the well-established role of the cerebellum in motor coordination and planning [34–37]. These highly engrained views of the cerebellum as a structure exclusively devoted to motor functions may have contributed generating a biased approach to studying the cerebellar role in the effects

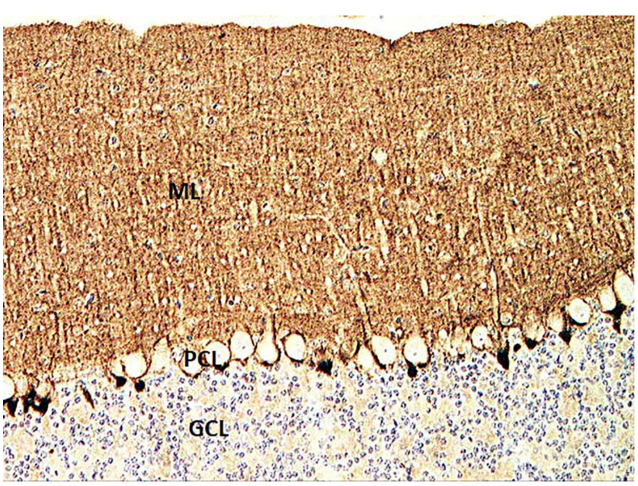

Fig. 1 Cerebellar CB1 receptor expression. Receptors are preferentially distributed in the molecular layer and in the pinceau formations in the Purkinje cell layer. Adapted from histosearch.com. ML, molecular layer; PCL, Purkinje cell layer; GCL, granule cell layer

of cannabis and THC. As a result, its possible involvement in cannabis addiction could have been underestimated.

Therefore, this review provides the first compilation of studies reporting cerebellar involvement in the effects of acute and repeated THC exposure in experimental animals and humans, including those performed in cannabis addicts. Posteriorly, the findings derived from these studies will be discussed, highlighting its possible relevance for addiction. Future experimental approaches aimed at extending the knowledge of the cerebellum as a relevant brain structure for cannabis addiction will be proposed. This would help providing a more accurate picture of cannabis addiction-related circuitry and the generated knowledge could ultimately contribute to developing pharmacological therapies for disorders associated with continuous cannabis use.

Involvement of the Cerebellum in the Effects of Acute and Repeated Cannabis and THC in Experimental Animals

Due to the late discovery of the cannabinoid receptors in the brain, investigations that revealed a possible participation of the cerebellum in the acute effects of cannabis or its main psychoactive compound are anterior to the characterization of the receptors. Results are summarized in Table 1.

To the best of the author's knowledge, the first study pointing to an involvement of the cerebellum in the acute effects of cannabis was the one performed by Ho and colleagues in 1972. They report that a single administration of doses of THC ranging from 0.5 to 10 mg/kg was able to reduce serotonin levels in the cerebellum of monkeys [38]. Other early studies found a reduction of blood flow reaching the cerebellum of THC-exposed rats [39]. Also, acute administration of varying THC doses was found to produce biphasic effects on the levels of cyclic adenosine 3′,5′-monophosphate (cAMP) in the cerebella of THC-treated mice. Doses lower than 1 mg/kg increased the levels and higher concentrations (2–10 mg/kg) reduced them [40]. The activity of the mitochondrial NADH oxidase was also significantly reduced when THC was applied to preparations of rat cerebellar tissue [41]. Interestingly, exposing rats repeatedly to marijuana smoke also provoked neurochemical changes in the cerebellum of rats, increasing acetylcholinesterase and total RNA levels [55].

The already mentioned discovery of the cannabinoid receptors and its presence in the cerebellum [33], later confirmed at the transcript level [56], importantly promoted the study of mechanisms underlying THC effects. Regarding the effects of acute THC administration on cerebellar cannabinoid receptor availability and functionality, a first study found an increase in binding capacity after a 3-mg/kg dose administration to rats [42], but further studies using a higher dose (10 mg/kg) showed no changes in either binding capacity [43] or receptor

Table 1 Studies describing involvement of the cerebellum in the effects of acute THC

Species	Drug	Dose	Main results	Reference number
Monkey	THC	0.5–10 mg/kg	Reduction of cerebellar serotonin content	[38]
Rat	THC	1 mg/kg	Reduction of blood flow reaching the cerebellum	[39]
Mouse	THC	0.1–10 mg/kg	Low doses (0.1–1 mg/kg) cAMP increase; High doses (2–10 mg/kg) cAMP reduction	[40]
Rat (tissue)	THC	10^{-5} M (in vitro)	Reduction of NADH oxidase activity	[41]
Rat	THC	3 mg/kg	Increased CB1 receptor availability	[42]
Rat	THC	10 mg/kg	Unchanged CB1 receptor availability	[43]
Rat	THC	10 mg/kg	Unchanged CB1 receptor functionality	[44]
Rat	THC	5 and 10 mg/kg	Increased levels of pCREB	[45]
Rat	THC	15 mg/kg	Increased levels of pCREB and pERK, increased c-fos expression	[46]
Rat	THC	15 mg/kg	Unchanged levels of cAMP, PKA	[47]
Rat	THC	2.5 and 10 mg/kg	Reduced cerebellar metabolism	[48]
Mouse	THC	0.001 mg/kg	Increased levels of $pERK_{1,2}$	[49, 50]
Mouse	THC	0.001 mg/kg	Reduced levels of $pERK_2$ and ERK phosphatases	[51]
Mouse	THC (intracerebellar)	15 μg	Motor incoordination, adenosine 1 receptor-dependent	[35]
Mouse	THC (intracerebellar)	20 μg	Motor incoordination, nicotinic cholinergic-dependent (α2β4)	[52, 53]
Mouse	THC	4 mg/kg	Improvement of motor deficits in Purkinje cell-defective transgenic animals	[54]

functionality as assessed by agonist-stimulated [35S]GTPγS binding [44]. Nevertheless, additional variables help clarifying and reinforcing the participation of the cerebellum in the acute effects of THC. Acute administration of 5 or 10 mg/kg of THC to rats was able to increase the levels of phosphorylated CREB (pCREB) in the granule cell layer of the cerebellum [45]. A 15-mg/kg dose had the same effect and also enhanced the levels of phosphorylated extracellularly regulated kinase (ERK) and c-fos expression [46] while leaving unaffected cAMP levels and protein kinase A (PKA) activity [47]. Another study described a dose-dependent reduction of rat cerebellar metabolism after acute THC administration [48].

Interestingly, various studies that examined the possible effects of very low doses of THC also reported cerebellar changes. Administering 0.001 mg/kg of THC caused a significant increase in phosphorylated ERK (pERK), observed both after 24 [49] and 72 h [50]. These changes were accompanied by parallel changes in enzymes responsible for initiating or repressing the activity of ERK [51].

The motor disturbances caused by THC [57] have also been associated with the cerebellum. Indeed, the effect shown by systemic THC administration was also obtained when cannabinoids were delivered into the cerebellum, and it involved CB1 receptors [34]. Further studies using intracerebellar THC delivery confirmed more neurotransmission systems to participate. Cannabinoid-induced motor incoordination was shown to be modulated by cerebellar adenosine A1 receptors [35, 58] and alpha4beta2 nicotinic cholinergic receptors [52, 53]. Acute THC administration also improved motor deficits in mutant mice displaying a selective loss of cerebellar Purkinje cells [54].

On the other hand, repeated THC exposure had more profound effects in cerebellar function. The main results are summarized in Table 2.

Regarding receptor availability and functionality, administering 3 mg/kg of THC during 5 days produced an increase in CB1 receptor availability [42], but giving 10 mg/kg for the same time caused a reduction in cannabinoid receptor-binding capacity [43]. Injecting this same dose for 21 days decreased binding capacity of CB1 receptors [59] and their functionality [44, 59, 60]. These changes were paralleled by an increase in CB1 mRNA in one study [60]. Reducing the duration of the administration regimen [36], increasing the dose [47], changing the administration route to intravenous infusion [61], or applying ascending doses of systemic THC [36, 62] produced the same pattern of receptor downregulation and desensitization. Heat shock proteins could mediate receptor availability changes. A protein named activator of heat shock 90 kDa protein ATPase homolog 1 (AHA1) was upregulated in the cerebellum of THC-treated animals, and it was shown to control CB1 receptor internalization/externalization dynamics in vitro [63].

Additional changes reported as a result of repeated THC administration include a decrease of the levels of phosphorylated CREB in the granule cell layer of THC-treated rats when compared to vehicle-treated animals [45]. In addition, a protein responsible for nucleotide exchange named RASGFR1 was also differentially altered [64].

Table 2 Animal studies describing involvement of the cerebellum in the effects of repeated THC

Species	Drug	Dose	Administration schedule	Main results	Reference number
Rat	THC	3 mg/kg	1 adm/day for 5 days	Increased CB1 receptor availability	[42]
Rat	THC	10 mg/kg	1 adm/day for 5 days	Reduced CB1 receptor availability	[43]
Rat	THC	10 mg/kg	1 adm/day for 21 days	Reduced CB1 receptor functionality	[44]
Rat	THC	10 mg/kg	1 adm/day for 21 days	Reduced CB1 receptor availability and functionality	[59]
Rat	THC	10 mg/kg	1 adm/day for 21 days	Reduced CB1 receptor functionality	[60]
Rat	THC	10–60 mg/kg	2 adm/day for 6.5 days (ascending)	Reduced CB1 receptor functionality	[36]
Rat	THC	15 mg/kg	2 adm/day for 6 days	Increased cAMP and PKA levels	[47]
Rat	THC	12.5–100 mg/kg	1 adm/day for 4 days (ascending)	Reduced CB1 receptor availability	[61]
Rat	THC	10–160 mg/kg	2 adm/day for 15 days (ascending)	Reduced CB1 receptor availability	[62]
Rat	THC	5.6 mg/kg	1 adm/day for 40 days	Increased AHA1 levels	[63]
Rat	THC	10 mg/kg	1 adm/day for 28 days	Reduced pCREB levels	[45]
Mouse	THC	10 mg/kg	2 adm/day for 4.5 days	Reduced levels of RASGRF1	[64]
Mouse	THC	10 mg/kg	2 adm/day for 4.5 days	Increased levels of beta-arrestins and G-protein-coupled receptor kinases	[65]
Rat	THC	10 mg/kg	2 adm/day for 4.5 days	Decreased basal NT release probability, facilitation mGluR1-dependent currents, diminished efficacy of cannabinoid-targeting compounds	[66]
Mouse	THC	20 mg/kg	2 adm/day for 5 days	Increased expression of microglial and neuroinflammatory markers	[37]
Mouse	THC + CB1 antagonist	20 mg/kg THC, 10 mg/kg CB1 antagonist	2 adm/day for 5.5 days + post-treatment antagonist single administration	Increased basal, calcium and forskolin-stimulated adenylyl cyclase levels	[67]
Mouse	THC + CB1 antagonist	10 mg/kg THC, 10 mg/kg CB1 antagonist	1 adm/day for 5 days + post-treatment antagonist single administration	Increased forskolin-stimulated adenylyl cyclase levels	[68]
Mouse	THC + CB1 antagonist	20 mg/kg THC, 10 mg/kg CB1 antagonist	2 adm/day for 5.5 days + post-treatment antagonist single administration	Increased basal, calcium and forskolin-stimulated adenylyl cyclase and PKA levels	[69]
Rat	THC	5–40 mg/kg	1 adm/day for 5 days (ascending)	Increased CB1 receptor availability and functionality	[70]
Rat	THC	5 mg/kg	1 adm/day for 40 days (GD5 to PD20)	Impaired astrocyte maturation, AMPA receptor subunit expression and glutamate synthesis and uptake enzymes	[71–73]

Importantly, the decreases in receptor functionality and availability present in the cerebellum in some of the studies were paralleled by a progressive decrease in some effects of THC administration [36, 47], an effect known as tolerance. Tolerance plays a role in the development of addiction that will be discussed later. Studies in which tolerance to THC was developed involve the cerebellum as well. Tolerance to the analgesic effects of THC was associated with an increase in cAMP levels and PKA activation in the cerebellum [47], and a tolerance-inducing regimen was able to enhance the levels of G protein-coupled receptor kinases and beta-arrestins as well [65]. A similar regimen also showed the ability of altering the physiological properties of cerebellar cells and synapses. An increase in the basal release probability of the parallel fiber-Purkinje cell synapse was reported. This observation came together with a facilitation of mGluR1-dependent currents and a decreased efficacy of CB1 agonists in inhibiting synaptic transmission from parallel fibers to Purkinje cells [66]. Interestingly, this tolerance development seems to be mediated by non-neuronal cerebellar cells involved in neuroinflammatory processes, as increases in microglial activation and neuroinflammatory markers were present in the cerebellum of mice treated with a tolerance-inducing regimen [37].

Withdrawal is another addiction-relevant feature that links repeated THC administration with the cerebellum. Withdrawal can be defined as the appearance of symptoms opposed to the ones a drug produces once its repeated use is discontinued. Despite cannabis does not present a very pronounced physical withdrawal syndrome, some symptoms like sleeping trouble, lack of appetite, and anxiety might appear in cannabis addicts who stop using the drug, and animal studies also report cerebellar changes associated with THC withdrawal. Antagonist-precipitated withdrawal in mice receiving repeated THC was associated with an increase in basal and stimulated adenylyl cyclase activity in the cerebellum [67, 68]. Posteriorly, it showed to be accompanied with increased cerebellar cAMP levels and PKA activity as well, and the blockade of cerebellar cAMP upregulation reduced the expression of withdrawal and PKA activation [69].

Additionally, behavioral sensitization to THC has also been associated to changes in the cerebellum. Sensitization, as opposed to tolerance, is the time-dependent increase in the magnitude of drug effects appearing with repeated administration. It is also thought to play a role in the development of addiction [74]. The appearance of this sensitized response in THC-treated rats was associated with an increase in cerebellar CB1 receptor availability and functionality, but not with cAMP-mediated signaling [70].

Finally, exposure to THC during development has also shown to affect neuronal and non-neuronal cells in the cerebellum. Repeated pre/perinatal THC administration disrupted astrocyte maturation, reduced the levels of enzymes responsible for glutamate synthesis and uptake in Bergmann glial cells, and also downregulated the expression of GluR1 and GluR2/3 AMPA receptor subunits in Bergmann glial and Purkinje cells, respectively [71–73]. Figure 2 depicts a schematic representation of the main molecular mechanisms involved in potentially addiction-relevant, THC-induced cerebellar changes.

The Cerebellum, THC, and Cannabis in Humans

The already discussed involvement of the cerebellum in the effects of acute and repeated THC in experimental animals receives crucial support from studies performed in human subjects to further strengthen this notion. In fact, evidence for cerebellar participation of the acute effects of THC and cannabis was reported some decades ago. A first PET study conducted in healthy volunteers demonstrated an increase in cerebellar metabolism after intravenous THC administration, which correlated with the feelings of being high and with THC plasma levels [75]. This finding is consistent with the increase in cerebellar activity fluctuations in a posterior magnetic resonance imaging experiment [76]. A study assessing connectivity changes as a result of THC exposure showed increased connectivity between the cerebellum and cognition-related brain areas like the precuneus or the parietal cortices [77]. Nevertheless, some interindividual differences have been reported regarding the reported cerebellar activation. In one of these studies, although THC administration was associated with increased cerebellar metabolism as in previous studies, it was found that some subjects that presented altered time perception also showed decreased cerebellar metabolism [78]. A similar pattern of results was found when participants were split in two groups regarding the ability of THC to induce a psychotic-like state [79]. Additional evidence comes from investigations assessing the effect of smoking marijuana on brain metabolic activity and attentional functions. Despite smoking marijuana did not affect attentional performance, increased cerebellar metabolism was observed after the participants had smoked the drug [80, 81]. A cognitive function that appeared to be impaired by acute THC and linked to cerebellar changes is working memory. THC administration was associated with a reduction in working memory performance, and this result was accompanied by a disruption of the linear relationship between cerebellar activity and working memory load found in the placebo condition [82]. In addition, in line with the study that linked cerebellar metabolism with altered time perception, smoking marijuana increased the pace of a finger-tapping task that was associated with cerebellar activity changes [83].

Regarding studies that assess the effect of repeated cannabis or THC exposure, a number of investigations have reported cerebellar alterations. These changes were found even when marijuana exposure took place at prenatal stages. A correlation between cerebellar activity and amount of prenatal exposure was reported while subjects performed a working memory task [84]. This correlation was found to be negative when subjects were performing an inhibitory control task [85], and it was also described that connectivity of the medial

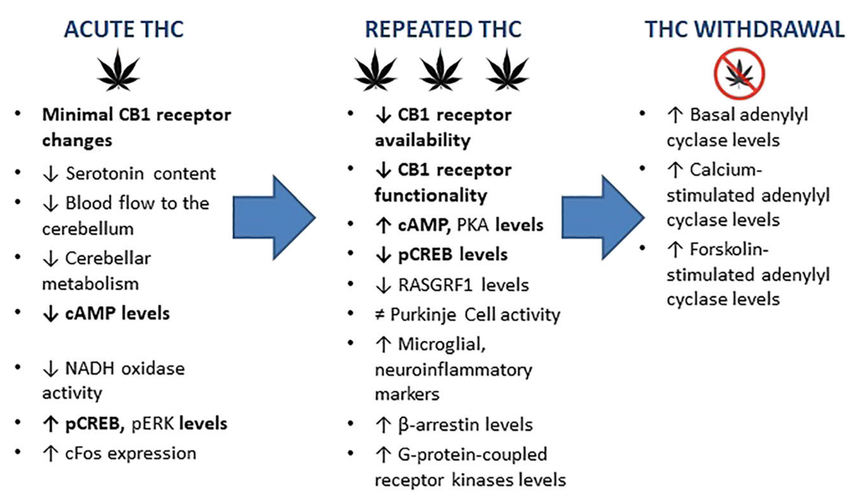

Fig. 2 Main mechanisms involved in potentially addiction-relevant THC-induced cerebellar changes. Mechanisms showing differential changes as a function of THC administration schedule are highlighted in bold

cerebellum with striatal and insular cortical areas was altered by prenatal marijuana exposure [86].

Nevertheless, investigations on frequent cannabis users (including daily heavy users) provide the most substantial amount of evidence linking different types of cerebellar changes with cannabis use patterns potentially indicative of addiction.

One source of evidence comes from studies assessing changes in gray and white matter densities. It was reported that adolescent users under a 4-week abstinence period had enhanced cerebellar gray matter density in the cerebellar vermis [87], and this cerebellar zone was found to have increased gray matter in non-abstinent young adults [88]. Another report found a more extended cerebellar increase in gray matter density, including clusters in the cerebellar hemispheres as well [89]. Cannabis use seems to have the opposite effect on neuronal densities in schizophrenic subjects, as cerebellar gray and white matter were reduced in cannabis-using schizophrenia patients [90, 91], and concomitant cigarettes and cannabis use was shown to reduce cerebellar gray matter volume [92].

Cerebellar metabolism in resting condition seemed to be diminished in chronic cannabis abusers, but after marijuana consumption it increased and correlated with the feeling of being high [93]. Long-term daily cannabis users showed an increase in cerebellar blood volume [94] which persisted after 4 weeks of abstinence [95]. Further investigations demonstrated additional cerebellar changes in baseline conditions in adolescents under cannabis addiction treatment [96], and alterations in cerebellar activity exhibited high discriminative power when differentiating between regular users and non-users [97]. These activity patterns might have been influenced by the altered connectivity found between the cerebellum and the posterior cingulate cortex in cannabis-dependent subjects [98].

Cannabis users showed also impaired performance in a cerebellum-dependent task such as eyeblink conditioning [99], and deficits in this task were observable even in former users [100]. In another task requiring of classical motor cerebellar functions, adolescent cannabis users demonstrated decreased cerebellar activation while performing it [101]. Investigations on reactivity of the cerebellum of cannabis abusers to psychostimulant administration showed these subjects to present both diminished behavioral and cerebellar responses to methylphenidate [102]. These reductions were more pronounced in female abusers [103].

Interestingly, the study of possibly impaired cognitive functions in chronic users also pointed towards cerebellar alterations that may be of relevance for cannabis addiction. Chronic marijuana use did not seem to affect attentional capabilities, but drug abusers showed altered cerebellar activity while performing the task. Remarkably, this activity correlated with the estimated total amount of marijuana use and the age at which the drug was used for the first time [104]. A study on short-term memory demonstrated some deficits in marijuana users that were associated with cerebellar blood flow increases [105], whereas one on inhibitory control also reported impaired performance in chronic users [106]. In this study, chronic users also presented heightened correlations between cerebellum and parietal cortices associated with recent cannabis use. Reward-related decision-making was also studied in chronic abusers. Drug use was negatively associated with performance in a gambling task, and users presented enhanced cerebellar activity as compared to non-using controls [107]. This pattern of general cerebellar hyperactivity during decision-making was replicated in a posterior study [108], but reward losses were accompanied by lower cerebellar activity in chronic cannabis users [109].

Finally, the evaluation of neural reactivity to cannabis-associated cues in addict subjects also provide a potentially relevant source of cerebellar involvement in cannabis addiction, as the presentation of drug-related cues is thought to play an important role in the maintenance of the disorder. The first study assessing addicts' brain responses to cannabis cues reported widespread cerebellar activation when they were presented with those cues [16]. These activation patterns were correlated with subjective craving ratings in posterior studies [110, 111]. Cannabis-dependent individuals also showed enhanced functional connectivity with the nucleus accumbens when they upon cannabis cue presentation [112]. Additionally, cerebellar activity during cannabis cue exposure correlated with the presence of risk alleles of genes encoding proteins of the endocannabinoid system, associated with increased risk of cannabis dependence [113]. Additionally, a study in which heavy users performed an approach-bias task using cannabis cues as distractors demonstrated enhanced cerebellar activity in users while performing it [114].

Possible Involvement of the Cerebellum in Multiple Stages of the Development of Cannabis Addiction

Overall, the previously discussed studies provide substantial evidence to consider the cerebellum as an important part of the brain circuits involved the acute and chronic effects of THC and cannabis. Nevertheless, some methodological factors may have had an influence in the discussed results. In neuroimaging studies, variables such as the number of subjects, their age, IQ scores, socioeconomic status, gender, amount of drug used, total time using the drug, age at which the drug was used for the first time, and duration of abstinence are not comparable in some studies. Differences in the neuroimaging techniques used for tracking brain activity, including PET and fMRI scans and differences within the studies using the same technique (different tracers for PET scans, different intensities of magnetic fields in fMRI studies) might have also had an effect in the described findings. In animal studies, the use of different doses of THC and different chemical substances with known effects on physiology and behavior (such as dimethyl sulfoxide or ethanol) as solvents for THC might also limit the comparability of these results.

Nevertheless, there seems to be a high degree of consistency between studies, as similar behavioral and neurobiological alterations induced by THC are found in studies in different species [36, 47], and variations in administered drug dose [43, 47], or in the administration schedule [43, 59] also demonstrate similar results.

In human studies, consistency is also observed. Variables such as an enhanced cerebellar activity after use [75, 93], effects on gray matter densities [87, 89], activation when cannabis cues are presented [16, 110, 111], or when regular users' cognitive functions are assessed [105, 107, 108] point towards the same direction despite some methodological variability.

Interestingly, some of the discussed findings involving the cerebellum in the effects of THC and cannabis are linked with different features of relevance for addiction.

First, there is converging evidence between animal and human studies for an involvement in the direct psychoactive actions of THC. Animal studies demonstrate that the main observable behavioral phenotype induced by systemic drug administration in rodents is also achieved by intracerebellar drug administration. Moreover, this effect is also dependent on specific neuromodulating systems within this brain area [35, 52]. These findings might not allow concluding directly that the cerebellum is involved in the psychoactive effects that human users seek when they take the drug but support the cerebellum being a substrate for the acute effects of THC. Nonetheless, studies in human subjects confirm this involvement, as cerebellar activity was positively correlated with the sense of feeling high induced by drug administration both in non-using subjects and regular users [75, 93]. Notably, these direct pleasant psychoactive effects are what drug users seek during the first episodes of drug use. Consequently, they exert a role in repeating the experience of drug taking that characterizes initial steps of the development of addiction [115–118]. Therefore, in light of the previously mentioned studies, it is likely that the cerebellum contributes to the development of cannabis addiction at very early stages of the process.

The development of tolerance to the psychoactive effects of THC has also been linked to changes in the cerebellum like CB1 receptor desensitization and downregulation [36, 47]. Being in a tolerant state implies that, for achieving an effect of similar magnitude to the one obtained while the subject was in a non-tolerant state, the amount of drug needed will be higher than in the non-tolerant state. This tolerance then contributes to an increasing amount of drug used, which is thought to enable the triggering of neuroadaptations that will contribute to the development of the addicted state characterized by compulsive drug-seeking and -taking [118–121]. Hence, the cerebellar alterations caused by tolerance-inducing regimens of THC administration might as well contribute to the establishment of a pattern of increased drug use necessary for the transition to an addict state.

Withdrawal symptoms caused by THC have also been associated to cerebellar changes, especially in preclinical studies. Importantly, these studies include a demonstration of a reduction of THC withdrawal caused by preventing the activation of signaling pathways within the cerebellum, thereby providing direct evidence for the cerebellar role in THC withdrawal [69]. Despite cannabis does not present a very marked withdrawal syndrome, cannabis withdrawal can be accompanied by non-psychological symptoms such as lack of appetite or nausea, and psychological features such as restlessness, dysphoria, and anxiety are common. It is thought that psychological withdrawal symptoms like those often observed in abstinent cannabis users might play a more important role in the maintenance of addiction than physical withdrawal symptoms [118, 120]. Notably, the cerebellum has been involved in the withdrawal symptoms caused by other drugs such as opioids [122, 123] and ethanol [124, 125]. Therefore, cerebellar participation in cannabis withdrawal might as well be contributing to the maintenance of continued drug use that leads to addiction in cannabis users as in users of other drug types.

Another process of relevance for addiction with reported cerebellar participation in studies on THC and cannabis is sensitization [70]. Sensitization is a phenomenon that can be described as a progressive increase in the magnitude of drug-induced symptoms with repeated drug exposure. This phenomenon has also been associated with the maintenance of addiction. It has been proposed that the appearance of sensitized responses to drug administration and drug-related cues could be reflecting an increasing incentive salience attributed to drug and drug-associated stimuli [74]. This incentive salience attribution to drug-related stimuli allows them acting as powerful behavior drivers, eliciting approach towards them and narrowing the interest of the subject to drug-associated stimuli when they are present in the environment. Accordingly, this mechanism has been proposed to underlie drug craving and relapse [126]. Given that the cerebellum also plays a role in sensitization to other drugs of abuse [127, 128], it could also be possible that the cerebellar involvement in THC-induced sensitization plays a role in the development of cannabis addiction.

In addition, neuroimaging studies on cannabis-dependent subjects have demonstrated that presentation of cannabis-associated cues reliably activates the cerebellum of these subjects [16, 110, 111, 114]. The appearance of drug-related cues in the addicts' environment is a reliable inductor of drug craving. Craving, in turn, can lead to drug use in non-abstinent addicts and can precipitate relapse in abstinent addicts [22], highlighting the importance of drug-related cues for the maintenance of addiction [129, 130]. Interestingly, in some of the studies describing cerebellar responsivity to cannabis cues, cerebellar activation correlated with craving scores [110, 111]. This cerebellar responsivity to drug-related cues is observed in addicts to other types of drugs [19, 131, 132], so it is conceivable that the cerebellum is also part of the neural circuits contributing to relapse to cannabis use when a cue is encountered in the environment.

Despite these studies show a potential involvement of the cerebellum in multiple cannabis addiction phases, there would be some experiments that would help strengthening the notion of the cerebellum as an important part of the brain circuits underlying cannabis-related disorders. In studies with human addicts combining exposure to cannabis-related cues with temporary modifications of cerebellar activity via transcranial magnetic stimulation while monitoring craving levels would help providing a more causal sort of evidence. It could also be of interest to perform magnetic resonance spectroscopy studies on the cerebellum of cannabis addicts to shed light on the neurochemical basis of altered cerebellar function in addicts.

Preclinical studies could also help reinforcing the role of the cerebellum in processes of relevance for cannabis addiction. Akin to one study demonstrating that THC withdrawal could be reduced by counteracting a biochemical modification occurring in the cerebellum [69], attempting to counteract THC-induced tolerance or sensitization by specific cerebellar manipulations would be of use for strengthening the relevance of the cerebellum in cannabis addiction-relevant processes. It is also worth to mention that, in comparison with other addictive drugs, the level of development of preclinical models of THC addiction and relapse is low. Probably, this is influenced by the fact that THC is not readily self-administered in rodents [133]. Nonetheless, there exist a number of studies reflecting technological developments that might help overcome this underdevelopment. Some recent works show that THC can be effectively delivered to rodents via inhalation, the preferred human administration route [134–136]. Importantly, administering THC through the pulmonary route was able to shift the conditioned aversion generated by intraperitoneal THC administration towards conditioned preference [134], a result that points to enhanced rewarding properties of THC when delivered through this route. This is similar to what is observed with other addictive drugs that are readily self-administered [21]. An interesting possibility for establishing a reliable model of THC self-administration would be to combine this delivery method with operant responding as it has already been done for opioids [137], nicotine [138], and alcohol [139]. If stable, high THC self-administration rates could be obtained with this method, it would be possible to study processes like the acquisition of responding for THC- or cue-induced relapse and their underlying brain mechanisms. Disruptions of cerebellar function by means of pharmacological deactivations or lesions, or more modern approaches like optogenetics or DREADDs, could definitely contribute to verify a crucial role for the cerebellum in cannabis addiction as well.

In conclusion, cannabis addiction is a condition that seriously impairs lives of the one afflicted from it, and it might be lacking effective treatments because of an incomplete understanding of its neurobiological substrates. Data on the cerebellum and THC and cannabis effects in experimental animals and humans indicate its involvement in several addiction-relevant functions, well beyond being a substrate for its motor incoordinating effects. Characterizing in depth the involvement of the cerebellum in different cannabis addiction-relevant processes will definitely help to provide a more accurate picture of the neural circuitry underlying this disorder, which, in turn, could be the ground for developing improved treatment strategies for cannabis addiction.

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Compliance with Ethical Standards

Conflict of Interest The author declares no conflict of interest.

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References

1. United Nations Office on Drugs and Crime. World drug report 2015. Vienna: United Nations publications; 2016.
2. European Monitoring Centre for Drugs and Drug Addiction. European Drug Report 2015. Luxembourg: Publications Office of the European Union; 2016.
3. Clarke RC, Merlin MD. Cannabis: evolution and ethnobotany. Berkeley: University of California Press; 2013.
4. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med. 2014a;370(23):2219–27.
5. Mead A. The legal status of cannabis (marijuana) and cannabidiol (CBD) under U.S. law. Epilepsy Behav. 2017;70(Pt B):288–91.
6. Nutt DJ, King LA, Phillips LD. Independent Scientific Committee on Drugs. Drug harms in the UK: a multicriteria decision analysis. Lancet. 2010;376(9752):1558–65.
7. Alexander SP. Therapeutic potential of cannabis-related drugs. Prog Neuro-Psychopharmacol Biol Psychiatry. 2016;64:157–66.
8. Novack GD. Cannabinoids for treatment of glaucoma. Curr Opin Ophthalmol. 2016;27(2):146–50.
9. Fanelli G, De Carolis G, Leonardi C, Longobardi A, Sarli E, Allegri M, et al. Cannabis and intractable chronic pain: an explorative retrospective analysis of Italian cohort of 614 patients. J Pain Res. 2017;10:1217–24.
10. Kim HS, Monte AA. Colorado cannabis legalization and its effect on emergency care. Ann Emerg Med. 2016;68(1):71–5.
11. Kilmer B. Recreational cannabis - minimizing the health risks from legalization. N Engl J Med. 2017;376(8):705–7.
12. Belackova V, Wilkins C. Consumer agency in cannabis supply – exploring auto-regulatory documents of the cannabis social clubs in Spain. Int J Drug Policy. 2018;54:26–34.

13. Piomelli D, Haney M, Budney AJ, Piazza PV. Legal or illegal, cannabis is still addictive. Cannabis Cannabinoid Res. 2016;1(1): 47–53.
14. Amann M, Haug S, Wenger A, Baumgartner C, Ebert DD, Berger T, et al. The effects of social presence on adherence-focused guidance in problematic cannabis users: protocol for the CANreduce 2.0 randomized controlled trial. JMIR Res Protoc. 2018;7(1):e30.
15. Grant S, London ED, Newlin DB, Villemagne VL, Liu X, Contoreggi C, et al. Activation of memory circuits during cue-elicited cocaine craving. Proc Natl Acad Sci U S A. 1996;93(21): 12040–5.
16. Filbey FM, Schacht JP, Myers US, Chavez RS, Hutchison KE. Marijuana craving in the brain. Proc Natl Acad Sci U S A. 2009;106(31):13016–21.
17. Zehra A, Burns J, Liu CK, Manza P, Wiers CE, Volkow ND, et al. Cannabis addiction and the brain: a review. J NeuroImmune Pharmacol. 2018 (In press;13:438–52.
18. Herculano-Houzel S. The human brain in numbers: a linearly scaled-up primate brain. Front Hum Neurosci. 2009;3:31.
19. Anderson CM, Maas LC, Bd F, Bendor JT, Spencer TJ, Livni E, et al. Cerebellar vermis involvement in cocaine-related behaviors. Neuropsychopharmacology. 2006;31(6):1318–26.
20. Moulton EA, Elman I, Becerra LR, Goldstein RZ, Borsook D. The cerebellum and addiction: insights gained from neuroimaging research. Addict Biol. 2014;19(3):317–31.
21. Carbo-Gas M, Moreno-Rius J, Guarque-Chabrera J, Vazquez-Sanroman D, Gil-Miravet I, Carulli D, et al. Cerebellar perineuronal nets in cocaine-induced pavlovian memory: site matters. Neuropharmacology. 2017;125:166–80.
22. Moreno-Rius J, Miquel M. The cerebellum in drug craving. Drug Alcohol Depend. 2017;173:151–8.
23. Ikai Y, Takada M, Shinonag Y, Mizuno N. Dopaminergic and non-dopaminergic neurons in the ventral tegmental area of the rat project, respectively, to the cerebellar cortex and deep cerebellar nuclei. Neuroscience. 1992;51(3):719–28.
24. Etkin A, Prater KE, Schatzberg AF, Menon V, Greicius MD. Disrupted amygdalar subregion functional connectivity and evidence of a compensatory network in generalized anxiety disorder. Arch Gen Psychiatry. 2009;66(12):1361–72.
25. Cauda F, Cavanna AE, D'agata F, Sacco K, Duca S, Geminiani GC. Functional connectivity and coactivation of the nucleus accumbens: a combined functional connectivity and structure-based meta-analysis. J Cogn Neurosci. 2011;23(10):2864–77.
26. Bostan AC, Dum RP, Strick PL. The basal ganglia communicate with the cerebellum. Proc Natl Acad Sci U S A. 2010;107(18): 8452–6.
27. Watson TC, Becker N, Apps R, Jones MW. Back to front: cerebellar connections and interactions with the prefrontal cortex. Front Syst Neurosci. 2014;8:4.
28. Tomasi D, Volkow ND. Functional connectivity hubs in the human brain. NeuroImage. 2011;57(3):908–17.
29. Farley SJ, Radley JJ, Freeman JH. Amygdala modulation of cerebellar learning. J Neurosci. 2016;36(7):2190–201.
30. Sang L, Qin W, Liu Y, Han W, Zhang Y, Jiang T, et al. Resting-state functional connectivity of the vermal and hemispheric subregions of the cerebellum with both the cerebral cortical networks and subcortical structures. NeuroImage. 2012;61(4):1213–25.
31. Yu W, Krook-Magnuson E. Cognitive collaborations: bidirectional functional connectivity between the cerebellum and the hippocampus. Front Syst Neurosci. 2015;9:177.
32. Iglói K, Doeller CF, Paradis AL, Benchenane K, Berthoz A, Burgess N, et al. Interaction between hippocampus and cerebellum crus I in sequence-based but not place-based navigation. Cereb Cortex. 2015;25(11):4146–54.
33. Herkenham M, Lynn AB, Little MD, Johnson MR, Melvin LS, de Costa BR, et al. Cannabinoid receptor localization in brain. Proc Natl Acad Sci U S A. 1990;87(5):1932–6.
34. DeSanty KP, Dar MS. Cannabinoid-induced motor incoordination through the cerebellar CB(1) receptor in mice. Pharmacol Biochem Behav. 2001a;69(1–2):251–9.
35. Dar MS, Mustafa SJ. Acute ethanol/cannabinoid-induced ataxia and its antagonism by oral/systemic/intracerebellar A1 adenosine receptor antisense in mice. Brain Res. 2002;957(1):53–60.
36. McKinney DL, Cassidy MP, Collier LM, Martin BR, Wiley JL, Selley DE, et al. Dose-related differences in the regional pattern of cannabinoid receptor adaptation and in vivo tolerance development to delta9-tetrahydrocannabinol. J Pharmacol Exp Ther. 2008;324(2):664–73.
37. Cutando L, Busquets-Garcia A, Puighermanal E, Gomis-González M, Delgado-García JM, Gruart A, et al. Microglial activation underlies cerebellar deficits produced by repeated cannabis exposure. J Clin Invest. 2013;123(7):2816–31.
38. Ho BT, Taylor D, Fritchie GE, Englert LF, McIsaac WM. Neuropharmacological study of 9- and 8-L-tetrahydrocannabinols in monkeys and mice. Brain Res. 1972;38(1):163–70.
39. Goldman H, Dagirmanjian R, Drew WG, Murphy S. delta9-tetrahydrocannabinol alters flow of blood to subcortical areas of the conscious rat brain. Life Sci. 1975;17(3):477–82.
40. Dolby TW, Kleinsmith LJ. Effects of delta 9-tetrahydrocannabinol on the levels of cyclic adenosine 3′,5′-monophosphate in mouse brain. Biochem Pharmacol. 1974;23(13):1817–25.
41. Bartova A, Birmingham MK. Effect of delta9-tetrahydrocannabinol on mitochondrial NADH-oxidase activity. J Biol Chem. 1976;251(16):5002–6.
42. Romero J, García L, Fernández-Ruiz JJ, Cebeira M, Ramos JA. Changes in rat brain cannabinoid binding sites after acute or chronic exposure to their endogenous agonist, anandamide, or to delta 9-tetrahydrocannabinol. Pharmacol Biochem Behav. 1995;51(4):731–7.
43. Romero J, Garcia-Palomero E, Castro JG, Garcia-Gil L, Ramos JA, Fernandez-Ruiz JJ. Effects of chronic exposure to delta9-tetrahydrocannabinol on cannabinoid receptor binding and mRNA levels in several rat brain regions. Brain Res Mol Brain Res. 1997;46(1–2):100–8.
44. Sim LJ, Hampson RE, Deadwyler SA, Childers SR. Effects of chronic treatment with delta9-tetrahydrocannabinol on cannabinoid-stimulated [35S]GTPgammaS autoradiography in rat brain. J Neurosci. 1996;16(24):8057–66.
45. Casu MA, Pisu C, Sanna A, Tambaro S, Spada GP, Mongeau R, et al. Effect of delta9-tetrahydrocannabinol on phosphorylated CREB in rat cerebellum: an immunohistochemical study. Brain Res. 2005;1048(1–2):41–7.
46. Rubino T, Forlani G, Viganò D, Zippel R, Parolaro D. Modulation of extracellular signal-regulated kinases cascade by chronic delta9-tetrahydrocannabinol treatment. Mol Cell Neurosci. 2004;25(3):355–62.
47. Rubino T, Vigano' D, Massi P, Spinello M, Zagato E, Giagnoni G, et al. Chronic delta-9-tetrahydrocannabinol treatment increases cAMP levels and cAMP-dependent protein kinase activity in some rat brain regions. Neuropharmacology. 2000;39(7):1331–6.
48. Whitlow CT, Freedland CS, Porrino LJ. Metabolic mapping of the time-dependent effects of delta 9-tetrahydrocannabinol administration in the rat. Psychopharmacology. 2002;161(2):129–36.
49. Senn R, Keren O, Hefetz A, Sarne Y. Long-term cognitive deficits induced by a single, extremely low dose of tetrahydrocannabinol (THC): behavioral, pharmacological and biochemical studies in mice. Pharmacol Biochem Behav. 2008;88(3):230–7.
50. Amal H, Fridman-Rozevich L, Senn R, Strelnikov A, Gafni M, Keren O, et al. Long-term consequences of a single treatment of

mice with an ultra-low dose of Δ9-tetrahydrocannabinol (THC). Behav Brain Res. 2010;206(2):245–53.
51. Fishbein M, Gov S, Assaf F, Gafni M, Keren O, Sarne Y. Long-term behavioral and biochemical effects of an ultra-low dose of Δ9-tetrahydrocannabinol (THC): neuroprotection and ERK signaling. Exp Brain Res. 2012;221(4):437–48.
52. Smith AD, Dar MS. Mouse cerebellar nicotinic-cholinergic receptor modulation of Δ9-THC ataxia: role of the α4β2 subtype. Brain Res. 2006;1115(1):16–25.
53. Smith AD, Dar MS. Involvement of the alpha4beta2 nicotinic receptor subtype in nicotine-induced attenuation of delta9-THC cerebellar ataxia: role of cerebellar nitric oxide. Pharmacol Biochem Behav. 2007;86(1):103–12.
54. Lorivel T, Hilber P. Motor effects of delta 9 THC in cerebellar Lurcher mutant mice. Behav Brain Res. 2007;181(2):248–53.
55. Luthra YK, Rosenkrantz H, Braude MC. Cerebral and cerebellar neurochemical changes and behavioral manifestations in rats chronically exposed to marijuana smoke. Toxicol Appl Pharmacol. 1976;35(3):455–65.
56. Matsuda LA, Bonner TI, Lolait SJ. Localization of cannabinoid receptor mRNA in rat brain. J Comp Neurol. 1993;327(4):535–50.
57. Patel S, Hillard CJ. Cannabinoid CB(1) receptor agonists produce cerebellar dysfunction in mice. J Pharmacol Exp Ther. 2001;297(2):629–37.
58. DeSanty KP, Dar MS. Involvement of the cerebellar adenosine A(1) receptor in cannabinoid-induced motor incoordination in the acute and tolerant state in mice. Brain Res. 2001;905(1–2): 178–87.
59. Breivogel CS, Childers SR, Deadwyler SA, Hampson RE, Vogt LJ, Sim-Selley LJ. Chronic Δ9-tetrahydrocannabinol treatment produces a time-dependent loss of cannabinoid receptors and cannabinoid receptor-activated G proteins in rat brain. J Neurochem. 1999;73(6):2447–59.
60. Zhuang S, Kittler J, Grigorenko EV, Kirby MT, Sim LJ, Hampson RE, et al. Effects of long-term exposure to delta9-THC on expression of cannabinoid receptor (CB1) mRNA in different rat brain regions. Brain Res Mol Brain Res. 1998;62(2):141–9.
61. Breivogel CS, Scates SM, Beletskaya IO, Lowery OB, Aceto MD, Martin BR. The effects of Δ9-tetrahydrocannabinol physical dependence on brain cannabinoid receptors. Eur J Pharmacol. 2003;459(2–3):139–50.
62. Selley DE, Cassidy MP, Martin BR, Sim-Selley LJ. Long-term administration of Δ9-tetrahydrocannabinol desensitizes CB1-, adenosine A1-, and GABAB-mediated inhibition of adenylyl cyclase in mouse cerebellum. Mol Pharmacol. 2004;66(5):1275–84.
63. Filipeanu CM, Guidry JJ, Leonard ST, Winsauer PJ. Δ9-THC increases endogenous AHA1 expression in rat cerebellum and may modulate CB1 receptor function during chronic use. J Neurochem. 2011;118(6):1101–12.
64. Colombo G, Rusconi F, Rubino T, Cattaneo A, Martegani E, Parolaro D, et al. Transcriptomic and proteomic analyses of mouse cerebellum reveals alterations in RasGRF1 expression following in vivo chronic treatment with delta 9-tetrahydrocannabinol. J Mol Neurosci. 2009;37(2):111–22.
65. Rubino T, Viganò D, Premoli F, Castiglioni C, Bianchessi S, Zippel R, et al. Changes in the expression of G protein-coupled receptor kinases and beta-arrestins in mouse brain during cannabinoid tolerance: a role for RAS-ERK cascade. Mol Neurobiol. 2006;33(3):199–213.
66. Tonini R, Ciardo S, Cerovic M, Rubino T, Parolaro D, Mazzanti M, et al. ERK-dependent modulation of cerebellar synaptic plasticity after chronic Δ9-tetrahydrocannabinol exposure. J Neurosci. 2006;26(21):5810–8.
67. Hutcheson DM, Tzavara ET, Smadja C, Valjent E, Roques BP, Hanoune J, et al. Behavioural and biochemical evidence for signs of abstinence in mice chronically treated with Δ-9-tetrahydrocannabinol. Br J Pharmacol. 1998;125(7):1567–77.
68. Wise LE, Varvel SA, Selley DE, Wiebelhaus JM, Long KA, Middleton LS, et al. Δ(9)-Tetrahydrocannabinol-dependent mice undergoing withdrawal display impaired spatial memory. Psychopharmacology. 2011;217(4):485–94.
69. Tzavara ET, Valjent E, Firmo C, Mas M, Beslot F, Defer N, et al. Cannabinoid withdrawal is dependent upon PKA activation in the cerebellum. Eur J Neurosci. 2000;12(3):1038–46.
70. Rubino T, Viganò D, Massi P, Parolaro D. Cellular mechanisms of Δ^9-tetrahydrocannabinol behavioural sensitization. Eur J Neurosci. 2003;17(2):325–30.
71. Suárez I, Bodega G, Fernández-Ruiz JJ, Ramos JA, Rubio M, Fernández B. Reduced glial fibrillary acidic protein and glutamine synthetase expression in astrocytes and Bergmann glial cells in the rat cerebellum caused by Δ(9)-tetrahydrocannabinol administration during development. Dev Neurosci. 2002;24(4):300–12.
72. Suárez I, Bodega G, Rubio M, Fernández-Ruiz JJ, Ramos JA, Fernández B. Prenatal cannabinoid exposure down- regulates glutamate transporter expressions (GLAST and EAAC1) in the rat cerebellum. Dev Neurosci. 2004a;26(1):45–53.
73. Suárez I, Bodega G, Fernández-Ruiz J, Ramos JA, Rubio M, Fernández B. Down-regulation of the AMPA glutamate receptor subunits GluR1 and GluR2/3 in the rat cerebellum following pre- and perinatal Δ^9-tetrahydrocannabinol exposure. Cerebellum. 2004b;3(2):66–74.
74. Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Brain Res Rev. 1993;18(3):247–91.
75. Volkow ND, Gillespie H, Mullani N, Tancredi L, Grant C, Ivanovic M, et al. Cerebellar metabolic activation by delta-9-tetrahydro-cannabinol in human brain: a study with positron emission tomography and 18F-2-fluoro-2-deoxyglucose. Psychiatry Res. 1991;40(1):69–78.
76. van Hell HH, Bossong MG, Jager G, Kristo G, van Osch MJ, Zelaya F, et al. Evidence for involvement of the insula in the psychotropic effects of THC in humans: a double-blind, randomized pharmacological MRI study. Int J Neuropsychopharmacol. 2011;14(10):1377–88.
77. Klumpers LE, Cole DM, Khalili-Mahani N, Soeter RP, Te Beek ET, Rombouts SA, et al. Manipulating brain connectivity with δ^9-tetrahydrocannabinol: a pharmacological resting state FMRI study. NeuroImage. 2012;63(3):1701–11.
78. Mathew RJ, Wilson WH, Turkington TG, Coleman RE. Cerebellar activity and disturbed time sense after THC. Brain Res. 1998;797(2):183–9.
79. Atakan Z, Bhattacharyya S, Allen P, Martín-Santos R, Crippa JA, Borgwardt SJ, et al. Cannabis affects people differently: inter-subject variation in the psychotogenic effects of Δ9-tetrahydrocannabinol: a functional magnetic resonance imaging study with healthy volunteers. Psychol Med. 2013;43(6):1255–67.
80. O'Leary DS, Block RI, Koeppel JA, Flaum M, Schultz SK, Andreasen NC, et al. Effects of smoking marijuana on brain perfusion and cognition. Neuropsychopharmacology. 2002;26(6):802–16.
81. O'Leary DS, Block RI, Koeppel JA, Schultz SK, Magnotta VA, Ponto LB, et al. Effects of smoking marijuana on focal attention and brain blood flow. Hum Psychopharmacol. 2007;22(3):135–48.
82. Bossong MG, Jansma JM, van Hell HH, Jager G, Oudman E, Saliasi E, et al. Effects of δ9-tetrahydrocannabinol on human working memory function. Biol Psychiatry. 2012;71(8):693–9.
83. O'Leary DS, Block RI, Turner BM, Koeppel J, Magnotta VA, Ponto LB, et al. Marijuana alters the human cerebellar clock. Neuroreport. 2003;14(8):1145–51.
84. Smith AM, Fried PA, Hogan MJ, Cameron I. Effects of prenatal marijuana on visuospatial working memory: an fMRI study in young adults. Neurotoxicol Teratol. 2006;28(2):286–95.

85. Smith AM, Fried PA, Hogan MJ, Cameron I. Effects of prenatal marijuana on response inhibition: an fMRI study of young adults. Neurotoxicol Teratol. 2004;26(4):533–42.
86. Grewen K, Salzwedel AP, Gao W. Functional connectivity disruption in neonates with prenatal marijuana exposure. Front Hum Neurosci. 2015;9:601.
87. Medina KL, Nagel BJ, Tapert SF. Abnormal cerebellar morphometry in abstinent adolescent marijuana users. Psychiatry Res. 2010;182(2):152–9.
88. Cousijn J, Wiers RW, Ridderinkhof KR, van den Brink W, Veltman DJ, Goudriaan AE. Grey matter alterations associated with cannabis use: results of a VBM study in heavy cannabis users and healthy controls. NeuroImage. 2012a;59(4):3845–51.
89. Battistella G, Fornari E, Annoni JM, Chtioui H, Dao K, Fabritius M, et al. Long-term effects of cannabis on brain structure. Neuropsychopharmacology. 2014;39(9):2041–8.
90. James A, Hough M, James S, Winmill L, Burge L, Nijhawan S, et al. Greater white and grey matter changes associated with early cannabis use in adolescent-onset schizophrenia (AOS). Schizophr Res. 2011;128(1–3):91–7.
91. Solowij N, Yücel M, Respondek C, Whittle S, Lindsay E, Pantelis C, et al. Cerebellar white-matter changes in cannabis users with and without schizophrenia. Psychol Med. 2011;41(11):2349–59.
92. Wetherill RR, Jagannathan K, Hager N, Childress AR, Rao H, Franklin TR. Cannabis, cigarettes, and their co-occurring use: disentangling differences in gray matter volume. Int J Neuropsychopharmacol. 2015a;18(10):pyv061.
93. Volkow ND, Gillespie H, Mullani N, Tancredi L, Grant C, Valentine A, et al. Brain glucose metabolism in chronic marijuana users at baseline and during marijuana intoxication. Psychiatry Res. 1996;67(1):29–38.
94. Sneider JT, Pope HG Jr, Silveri MM, Simpson NS, Gruber SA, Yurgelun-Todd DA. Altered regional blood volume in chronic cannabis smokers. Exp Clin Psychopharmacol. 2006;14(4):422–8.
95. Sneider JT, Pope HG Jr, Silveri MM, Simpson NS, Gruber SA, Yurgelun-Todd DA. Differences in regional blood volume during a 28-day period of abstinence in chronic cannabis smokers. Eur Neuropsychopharmacol. 2008;18(8):612–9.
96. Orr C, Morioka R, Behan B, Datwani S, Doucet M, Ivanovic J, et al. Altered resting-state connectivity in adolescent cannabis users. Am J Drug Alcohol Abuse. 2013;39(6):372–81.
97. Cheng H, Skosnik PD, Pruce BJ, Brumbaugh MS, Vollmer JM, Fridberg DJ, et al. Resting state functional magnetic resonance imaging reveals distinct brain activity in heavy cannabis users - a multi-voxel pattern analysis. J Psychopharmacol. 2014;28(11):1030–40.
98. Wetherill RR, Fang Z, Jagannathan K, Childress AR, Rao H, Franklin TR. Cannabis, cigarettes, and their co-occurring use: disentangling differences in default mode network functional connectivity. Drug Alcohol Depend. 2015b;153:116–23.
99. Skosnik PD, Edwards CR, O'Donnell BF, Steffen A, Steinmetz JE, Hetrick WP. Cannabis use disrupts eyeblink conditioning: evidence for cannabinoid modulation of cerebellar-dependent learning. Neuropsychopharmacology. 2008;33(6):1432–40.
100. Steinmetz AB, Edwards CR, Vollmer JM, Erickson MA, O'Donnell BF, Hetrick WP, et al. Examining the effects of former cannabis use on cerebellum-dependent eyeblink conditioning in humans. Psychopharmacology. 2012;221(1):133–41.
101. Lopez-Larson MP, Rogowska J, Bogorodzki P, Bueler CE, McGlade EC, Yurgelun-Todd DA. Cortico-cerebellar abnormalities in adolescents with heavy marijuana use. Psychiatry Res. 2012;202(3):224–32.
102. Volkow ND, Wang GJ, Telang F, Fowler JS, Alexoff D, Logan J, et al. Decreased dopamine brain reactivity in marijuana abusers is associated with negative emotionality and addiction severity. Proc Natl Acad Sci U S A. 2014b;111(30):E3149–56.
103. Wiers CE, Shokri-Kojori E, Wong CT, Abi-Dargham A, Demiral ŞB, Tomasi D, et al. Cannabis abusers show hypofrontality and blunted brain responses to a stimulant challenge in females but not in males. Neuropsychopharmacology. 2016;41(10):2596–605.
104. Chang L, Yakupov R, Cloak C, Ernst T. Marijuana use is associated with a reorganized visual-attention network and cerebellar hypoactivation. Brain. 2006;129(Pt 5):1096–112.
105. Block RI, O'Leary DS, Hichwa RD, Augustinack JC, Boles Ponto LL, Ghoneim MM, et al. Effects of frequent marijuana use on memory-related regional cerebral blood flow. Pharmacol Biochem Behav. 2002;72(1–2):237–50.
106. Behan B, Connolly CG, Datwani S, Doucet M, Ivanovic J, Morioka R, et al. Response inhibition and elevated parietal-cerebellar correlations in chronic adolescent cannabis users. Neuropharmacology. 2014;84:131–7.
107. Bolla KI, Eldreth DA, Matochik JA, Cadet JL. Neural substrates of faulty decision-making in abstinent marijuana users. NeuroImage. 2005;26(2):480–92.
108. Vaidya JG, Block RI, O'Leary DS, Ponto LB, Ghoneim MM, Bechara A. Effects of chronic marijuana use on brain activity during monetary decision-making. Neuropsychopharmacology. 2012;37(3):618–29.
109. Wesley MJ, Hanlon CA, Porrino LJ. Poor decision-making by chronic marijuana users is associated with decreased functional responsiveness to negative consequences. Psychiatry Res. 2011;191(1):51–9.
110. Charboneau EJ, Dietrich MS, Park S, Cao A, Watkins TJ, Blackford JU, et al. Cannabis cue-induced brain activation correlates with drug craving in limbic and visual salience regions: preliminary results. Psychiatry Res. 2013;214(2):122–31.
111. Filbey FM, Dunlop J, Ketcherside A, Baine J, Rhinehardt T, Kuhn B, et al. fMRI study of neural sensitization to hedonic stimuli in long-term, daily cannabis users. Hum Brain Mapp. 2016;37(10):3431–43.
112. Filbey FM, Dunlop J. Differential reward network functional connectivity in cannabis dependent and non-dependent users. Drug Alcohol Depend. 2014;140:101–11.
113. Filbey FM, Schacht JP, Myers US, Chavez RS, Hutchison KE. Individual and additive effects of the CNR1 and FAAH genes on brain response to marijuana cues. Neuropsychopharmacology. 2010;35(4):967–75.
114. Cousijn J, Goudriaan AE, Ridderinkhof KR, van den Brink W, Veltman DJ, Wiers RW. Approach-bias predicts development of cannabis problem severity in heavy cannabis users: results from a prospective FMRI study. PLoS One. 2012b;7(9):e42394.
115. Wise RA, Bozarth MA. Brain mechanisms of drug reward and euphoria. Psychiatr Med. 1985;3(4):445–60.
116. Wise RA, Bozarth MA. A psychomotor stimulant theory of addiction. Psychol Rev. 1987;94(4):469–92.
117. Wise RA, Rompre PP. Brain dopamine and reward. Annu Rev Psychol. 1989;40:191–225.
118. Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2010;35(1):217–38.
119. Ehrman R, Ternes J, O'Brien CP, McLellan AT. Conditioned tolerance in human opiate addicts. Psychopharmacology. 1992;108(1–2):218–24.
120. Koob GF, Le Moal M. Drug abuse: hedonic homeostatic dysregulation. Science. 1997;278(5335):52–8.
121. Ahmed SH. Escalation of drug use. In: Olmstead MC, editor. Animal models of drug addiction, neuromethods, vol. 53. New York: Humana; 2011. p. 267–92.
122. Volicer L, Puri SK, Choma P. Cyclic GMP and GABA levels in rat striatum and cerebellum during morphine withdrawal: effect of apomorphine. Neuropharmacology. 1977;16(11):791–4.

123. Leza JC, Lizasoain I, Cuéllar B, Moro MA, Lorenzo P. Correlation between brain nitric oxide synthase activity and opiate withdrawal. Naunyn Schmiedeberg's Arch Pharmacol. 1996;353(3):349–54.
124. Phillips SC, Cragg BG. Alcohol withdrawal causes a loss of cerebellar Purkinje cells in mice. J Stud Alcohol. 1984;45(6):475–80.
125. Beckmann AM, Matsumoto I, Wilce PA. AP-1 and Egr DNA-binding activities are increased in rat brain during ethanol withdrawal. J Neurochem. 1997;69(1):306–14.
126. Robinson TE, Berridge KC. Review. The incentive sensitization theory of addiction: some current issues. Philos Trans R Soc Lond Ser B Biol Sci. 2008;363(1507):3137–46.
127. Bhargava HN, Kumar S. Sensitization to the locomotor stimulant activity of cocaine is associated with increases in nitric oxide synthase activity in brain regions and spinal cord of mice. Pharmacology. 1997;55(6):292–8.
128. Hamamura M, Ozawa H, Kimuro Y, Okouchi J, Higasa K, Iwaki A, et al. Differential decreases in c-fos and aldolase C mRNA expression in the rat cerebellum after repeated administration of methamphetamine. Brain Res Mol Brain Res. 1999;64(1):119–31.
129. Robbins TW, Ersche KD, Everitt BJ. Drug addiction and the memory systems of the brain. Ann N Y Acad Sci. 2008;1141:1–21.
130. Venniro M, Caprioli D, Shaham Y. Animal models of drug relapse and craving: from drug priming-induced reinstatement to incubation of craving after voluntary abstinence. Prog Brain Res. 2016;224:25–52.
131. Schneider F, Habel U, Wagner M, Franke P, Salloum JB, Shah NJ, et al. Subcortical correlates of craving in recently abstinent alcoholic patients. Am J Psychiatry. 2001;158(7):1075–83.
132. Smolka MN, Bühler M, Klein S, Zimmermann U, Mann K, Heinz A, et al. Severity of nicotine dependence modulates cue-induced brain activity in regions involved in motor preparation and imagery. Psychopharmacology. 2006;184(3–4):577–88.
133. Wakeford AGP, Wetzell BB, Pomfrey RL, Clasen MM, Taylor WW, Hempel BJ, et al. The effects of cannabidiol (CBD) on Δ^9-tetrahydrocannabinol (THC) self-administration in male and female Long-Evans rats. Exp Clin Psychopharmacol. 2017;25(4):242–8.
134. Manwell LA, Charchoglyan A, Brewer D, Matthews BA, Heipel H, Mallet PE. A vapourized Δ(9)-tetrahydrocannabinol (Δ(9)-THC) delivery system part I: development and validation of a pulmonary cannabinoid route of exposure for experimental pharmacology studies in rodents. J Pharmacol Toxicol Methods. 2014;70(1):120–7.
135. Manwell LA, Ford B, Matthews BA, Heipel H, Mallet PE. A vapourized Δ(9)-tetrahydrocannabinol (Δ(9)-THC) delivery system part II: comparison of behavioural effects of pulmonary versus parenteral cannabinoid exposure in rodents. J Pharmacol Toxicol Methods. 2014 Jul-Aug;70(1):112–9.
136. Nguyen JD, Aarde SM, Vandewater SA, Grant Y, Stouffer DG, Parsons LH, et al. Inhaled delivery of Δ(9)-tetrahydrocannabinol (THC) to rats by e-cigarette vapor technology. Neuropharmacology. 2016 Oct;109:112–20.
137. Vendruscolo JCM, Tunstall BJ, Carmack SA, Schmeichel BE, Lowery-Gionta EG, Cole M, et al. Compulsive-like sufentanil vapor self-administration in rats. Neuropsychopharmacology. 2018;43(4):801–9.
138. Kallupi M, George O. Nicotine vapor method to induce nicotine dependence in rodents. Curr Protoc Neurosci. 2017;80:8.41.1–8.41.10.
139. de Guglielmo G, Kallupi M, Cole MD, George O. Voluntary induction and maintenance of alcohol dependence in rats using alcohol vapor self-administration. Psychopharmacology. 2017 Jul;234(13):2009–18.