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Recent Evidence on the Relation Between Cannabis Use, Brain Structure, and Function: Highlights and Challenges

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Abstract

Purpose of Review This narrative review provides an update of our knowledge on the relation between heavy cannabis use and cannabis use disorder (CUD) and the brain based on (f)MRI studies conducted in the past 5 years.

Recent Findings Heavy cannabis use and CUD are associated with structural brain changes—particularly volume—as well as altered resting-state functional connectivity (RSFC) in several networks and regions. Task-based fMRI studies reveal altered activity and connectivity in cannabis users compared to controls, but consistency of the results is domain dependent. Heaviness of use, CUD status, age, sex, and tobacco co-use are important potential moderators of the effects of cannabis on the brain.

Summary Heavy cannabis use and CUD are associated with differences in brain structure and function, but causality remains unclear, and long-term effects following abstinence require further investigation. Considering moderators of the effects of cannabis on the brain is crucial to further assess individual differences in the impact of cannabis use.

Keywords Cannabis · Cannabis use disorder · Brain structure · Brain function · Resting-state functional connectivity · MRI

Introduction

Over 200 million people use cannabis every year [1], making it the most widely used drug in the world. Legalization of recreational cannabis use is associated with increased initiation of use, a narrowing gender gap in use (i.e., more female users), and increased daily use, especially among adolescents [1]. More than 30% of daily users are at high risk [2] for the development of a cannabis use disorder (CUD).

Cannabis consists of many compounds, of which psychoactive delta-9-tetrahydrocannabinol (Δ9-THC) and non-psychoactive cannabidiol (CBD) are the most studied. Δ9-THC binds to endocannabinoid 1 (CB1) receptors in the brain [3], causing the experienced "high." The mechanisms of CBD's action on the brain are less understood, but some research suggests it may have medicinal effects, such as reducing inflammation [4]. Some evidence also suggests it may mitigate some of the negative effects of Δ9-THC in certain populations [5, 6], although this is disputed [7]. While high-CBD medicinal products are increasingly available, THC:CBD ratios have risen in commonly used cannabis products, potentially increasing the harmful effects of cannabis use on the brain [1].

In this narrative review, we will provide an updated overview of MRI studies conducted in the past 5 years, focusing on the effects of frequent cannabis use and CUD on the brain. Furthermore, we will present the highlights from recent studies and the remaining challenges in the field.

Recent Evidence on the Effects of Cannabis on Brain Structure and Function

Structural MRI

Historically, frequent cannabis use has most consistently been associated with reduced hippocampal and prefrontal cortex—especially orbitofrontal cortex (OFC)—volume

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[8–11] and increased cerebellar grey matter (GM) volume [12]. One recent meta-analysis found smaller hippocampal and OFC volumes in regular cannabis users [10], while another found reduced thalamus, hippocampus, amygdala, and nucleus accumbens (NAc) volume in CUD [13••] compared to controls. Similarly, dependent cannabis users had reduced bilateral hippocampal volume compared to non-dependent users (who did not differ from controls) even when controlling for use frequency [14]. Several studies found no differences in brain structure between less frequent cannabis users compared to controls [15, 16]. Regarding cortical surface morphology (thickness, surface area, and gyrification), no differences were observed between dependent users, non-dependent users, and controls, and no associations between age of onset and cortical surface morphology [17].

In addition to changes in GM volume, dependent cannabis users exhibited alterations in hippocampal shape—particularly bilateral deflation along the superior-medial body [14]—indicating that hippocampal alterations might be dependent on the subfield assessed [18, 19]. Furthermore, chronic heavy cannabis users exhibit decreased grey matter density in several frontal, temporal, and occipital regions and increased density in basal ganglia, cerebellum, and parietal regions compared to controls [20•].

Few studies have explored the association between volume alterations and cognitive performance. Lower left hippocampal volume has been shown to mediate the association between higher cannabis exposure and lower working memory performance [21]. Also, lower left anterior cingulate cortex (ACC) volume in cannabis users was associated with lower accuracy on an emotion discrimination task [22]. Grey matter volume changes in the cortical-thalamic-cerebellar-cortical circuit in heavy male cannabis users compared to controls are associated with impaired sensorimotor performance [23•]. Reduced cortical thickness in the right entorhinal and left OFC in male cannabis users compared to controls was associated with poorer performance on a verbal learning task [24].

Longitudinal studies assessing causal effects of cannabis use on brain structure are rare. One study in adolescents found an association between higher lifetime cannabis use and bilateral thinness of the prefrontal cortex at a 5-year follow-up, but cortical thickness at baseline was not associated with lifetime cannabis use at follow-up [25]. As there was no association between cortical thickness at baseline and lifetime cannabis use at follow-up, the findings suggest that the observed changes in cortical thickness could be attributable to cannabis use during the interim period. Additionally, higher cannabis use was associated with faster age-related cortical thinning in the prefrontal cortex. Meier et al. (2019) found that cannabis use trajectories in a sample of male adolescents were not associated with altered GM volume and cortical thickness in adulthood [26•]. However, Burggren et al. (2018) showed that individuals who used heavily during adolescence (> 19 uses/month for at least 1 year) had thinner hippocampi later in life (age 57–75), even when use reduced in adulthood (< 3 uses/month after age 35). Furthermore, a 3-year longitudinal study found that cannabis use was related to altered cerebellar thickness, with cannabis users showing a larger increase in thickness in several cerebellar lobules compared to controls. This increase was associated with age of onset of cannabis use and cannabis use and related problems (CUDIT score, [27]) at both baseline and follow-up [28•].

The prevalence of co-use of tobacco and cannabis has been reported to be particularly high [29], highlighting the need to disentangle the effects on the brain resulting from singular or co-use. Daniju et al. (2022) compared grey matter volume between cannabis users who also smoke tobacco cigarettes, non-cannabis-using tobacco cigarette smokers, and non-cannabis/tobacco-using controls. Co-users of cannabis and tobacco as well as those only using tobacco showed lower GM volume in the inferior frontal gyrus (IFG) and higher putamen volume compared to non-using controls. Lower right frontal pole volume was specifically associated with lifetime cannabis use in cannabis-tobacco co-users [30] (Table 1).

Resting-State fMRI

A recent systematic review of resting-state functional connectivity (RSFC) in adolescents and adults found that cannabis users exhibit higher frontal-frontal, fronto-striatal, and fronto-temporal RSFC than controls [31•] across 40% of included studies, but these effects were inconsistently associated with cannabis use measures. Focusing on emotion processing regions, a more recent study found that individuals with CUD showed lower amygdala-cortical and cingulate-temporal RSFC and higher cingulate-occipital RSFC compared to controls, with most of these alterations associated with higher CUD symptom count and cannabis use disorder identification test (CUDIT) scores (except left ACC—lateral occipital [32]). Heavy cannabis users, compared to controls, showed increased connectivity between anterior cerebellar regions and the posterior cingulate cortex (PCC), as well as reduced connectivity between the other cerebellar regions (Crus I and II; lobule VIIb, VIIIa, VIIIb, IX, and X) and cortical regions (frontal gyri, insula, caudate, putamen, and middle temporal gyri). These alterations were not associated with measures of cannabis use (lifetime use and age of onset, [33]) and are largely inconsistent with the findings of another study except for similar cerebellar-insula RSFC [34]. Focusing on the OFC, PCC, and hippocampus in older (age 60–88) weekly cannabis users, higher RSFC was observed between the left cerebellum and left hippocampus compared

Table 1 Summary of recent evidence (2018–2023) for the effects of cannabis on the brain

Domain	Evidence for group differences	Evidence for associations with use and problem severity	Additional potential moderators	Suggested reading
Structural MRI	↑GM density basal ganglia, cerebellum, and parietal regions in *heavy users* compared to *controls* ↓Hippocampal and OFC volumes in *heavy users* compared to *controls* ↓Amygdala, hippocampus, NAc, OFC, and thalamus volume in *CUD* compared to *controls* ↓GM density in frontal, temporal, and occipital cortices in *heavy users* compared to *controls* ≈Cortical surface morphology (thickness, surface areas, and gyrification) between *CUD*, *heavy users*, and *controls*	↑Age-related cortical thinning associated with heavier cannabis use ↑Cerebellar thickness associated with higher lifetime use ↓Cortical thickness associated with higher lifetime use ↓Hippocampal volume later in life (57–75) associated with heavy use during adolescence	Age, age of onset, co-use of tobacco	[8–30]
Resting-state fMRI	↑Frontal-frontal, fronto-striatal, and fronto-temporal RSFC in *heavy users* compared to *controls* (note: only observed in 40% of studies) ↑Cingulate-occipital RSFC in *CUD* compared to *controls* ↑Connectivity between anterior cerebellar regions and PCC in *heavy users* compared to *controls* ↑Left cerebellar-hippocampal RSFC in older (60–88) *heavy users* compared to *controls* ↓Amygdala-cortical and cingulate-temporal RSFC in *CUD* compared to *controls* ↓RSFC between frontal gyri, insula, caudate, putamen, and middle temporal gyri in *heavy users* compared to *controls*	↑Cingulate-occipital RSFC associated with higher CUD symptom count and CUDIT scores ↓Amygdala-cortical and cingulate-temporal RSFC associated with higher CUD symptom count and CUDIT scores	Age, craving	[31•, 32–35]

Table 1 (continued)

Domain	Evidence for group differences	Evidence for associations with use and problem severity	Additional potential moderators	Suggested reading
Task-based fMRI				
Working memory	↑Connectivity in left STG–thalamus in *heavy users* compared to *controls* ↑WM-related activity bilateral temporal regions and right SFG in *heavy users* compared to *controls* ↑WM-related activity in SFG in *male heavy users* compared to *female heavy users* ↑WM-related effective connectivity changes lDLPFC–left caudate, rDLPFC–right caudate, and rVLPFC–left caudate in *CUD* compared to *controls* ↓WM-related activity in insula, thalamus, SPL, and SMG in *heavy users* compared to *controls* ↓Connectivity in STG–ACC and OFC, MFG–right parahippocampal gyrus, and VTA–frontal, temporal, and limbic regions in *heavy users* compared to *controls* ↓WM-related effective connectivity changes rDLPFC–left caudate in *CUD* compared to *controls*	↑rDLPFC activation during maintenance and retrieval associated with heavier use	Age of (CUD) onset, context, sex	[9•, 36–40]
Decision-making and inhibition	↑Inhibition-related activity in left MFG, left SFG, and left ACC in *heavy users* compared to *controls* ≈Risk-taking-related activity in *heavy users* compared to *controls* ↓Inhibitory effects of dACC on NAc in *heavy users* compared to *controls*	Not assessed	Co-use of tobacco	[41, 42]
Reward, error, and time processing	↑Frontal pole, SMG, and angular gyrus activity in *heavy users* compared to *controls* during feedback ↑Feedback-related activity in the SFG in adolescent *heavy users* compared to adult *heavy users* ↓Cerebellar, MTG, STG, fusiform gyrus, and lateral occipital activity when envisioning future events in *heavy users* compared to *controls* ↓Social reward processing in *male heavy users* compared to *heterosexual male controls*	↑Blunted responsiveness to affective future events associated with higher CUDIT scores ↓Responsiveness to errors associated with heavier use ↓Tendency to seek novel stimuli associated with more severe use in adolescent heavy users	Not assessed	[43•, 44–49]

Table 1 (continued)

Domain	Evidence for group differences	Evidence for associations with use and problem severity	Additional potential moderators	Suggested reading
Emotion and face processing	↑Responsiveness to negative emotional stimuli compared to positive emotional stimuli in *heavy users* compared to *controls* ↑mOFC activity and functional connectivity between left dorsal striatum and left amygdala (even after prolonged abstinence) in *heavy users* compared to *controls* ↑Correlation between cognitive brain processes and emotional brain processes in *CUD* but not in *heavy users* or *controls* ↓Segregation of emotional and cognitive processing in *CUD* but not in *heavy users* and *controls*	↓Responsiveness to faces (regardless of emotion) in left superior-medial PFC and ACC associated with higher CUDIT scores in adolescent users	Valence	[50–52]
Cue-reactivity	↑cue-reactivity to *cannabis stimuli* compared to *neutral stimuli* in frontal, parietal, and subcortical regions known to be involved in reward processing in *heavy users* ↑Cue-reactivity in reward-related regions in response to *cannabis odors* compared to *floral odors* in *heavy users* ↑Cue-reactivity in reward-related regions in *heavy users* compared to *controls* in response to visual and odor cannabis cues compared to neutral cues, but not when compared to flower cues ↑Cannabis cue-reactivity dorsal striatum in *CUD* compared to *heavy users* ↑Cannabis cue-reactivity amygdala in *heavy users* compared to *controls* ≈Cannabis cue-reactivity in *co-users of cannabis and cigarettes* compared to *cigarette using controls*	Not assessed	Co-use of tobacco, craving	[29, 53••, 54–57]

Variables that were found to have a potential moderating effect were added to the table; although at this stage, results are inconclusive ↓Findings indicate reduction or impairment; ↑findings indicate increase or improvement; ≈findings indicate no alteration or difference *ACC* anterior cingulate cortex, *CUD* cannabis use disorder, *CUDIT* cannabis use disorder identification test, *DLPFC* dorsolateral prefrontal cortex, *MFG* medial frontal gyrus, *MTG* middle temporal gyrus, *NAc* nucleus accumbens, *OFC* orbitofrontal cortex, *PCC* posterior cingulate cortex, *PFC* prefrontal cortex, *RSFC* resting-state functional connectivity, *SFG* superior frontal gyrus, *SMG* supramarginal gyrus, *SPL* superior parietal lobe, *STG* superior temporal gyrus, *VLPFC* ventrolateral prefrontal cortex, *VTA* ventral tegmental area, *WM* working memory

to controls [35]. Comparing older to younger non-using individuals, the younger group exhibited higher RSFC between the left cerebellum and left hippocampus, suggesting potentially protective effects of cannabis use in older age, but further research is needed.

Task-Based fMRI

Working Memory

Findings from studies assessing working memory (WM) performance and associated brain activity have been inconsistent [9•]. Altered default mode network activity (precuneus and PCC) was observed in heavy-dependent cannabis users compared to controls during a letter N-back task, but this effect was not related to task performance or cannabis use and related problems [36]. Exploratory analyses revealed increased WM-related activity in the superior frontal gyrus (SFG) in male compared to female cannabis users.

In an adapted letter N-back task, the presence of cannabis words (flankers) was associated with decreased WM-load–related activity in the insula, thalamus, superior parietal lobe (SPL), and supramarginal gyrus (SMG) in cannabis users compared to controls. The cannabis and control groups did not differ in task performance, which was not affected by the cannabis and neutral word flankers [37].

Using a similar letter N-back task, cannabis users exhibited increased activation in bilateral temporal regions and the right SFG compared to controls [38•]. Functional connectivity analyses showed altered connectivity between various seed regions, including lower connectivity from the left superior temporal gyrus (STG) to the ACC and OFC, as well as lower connectivity between the medial frontal gyrus (MFG) and right parahippocampal gyrus. Additionally, cannabis users exhibited higher connectivity between the left STG and the thalamus and decreased functional connectivity of the ventral tegmental area (VTA; reward network) with frontal, temporal, and limbic regions. These WM-related functional connectivity alterations in fronto-temporal and reward-related regions should be replicated with larger samples.

Effective connectivity via dynamic causal modelling indicates the direction of communication between regions. Individuals with CUD showed smaller WM-related changes in effective connectivity between the right dorsolateral prefrontal cortex (DLPFC) and left caudate and larger changes in effective connectivity between the left DLPFC and left caudate, right DLPFC and right caudate, and the right ventrolateral prefrontal cortex (VLPFC) and left caudate compared to controls during a picture N-back task [39]. Individuals with early compared to late-onset CUD showed greater WM-related changes in effective connectivity between the left and right DLPFC and smaller changes in effective connectivity between left VLPFC and right DLPFC. Effective connectivity in individuals with CUD was not associated with task performance.

A Sternberg spatial working memory task with a cue-delay-target structure was used to disentangle activity during the encoding, maintenance, and retrieval phases of the N-back task [40]. Users and controls did not differ in activity, but posterior parietal cortex (PPC) activity during the encoding phase was negatively associated with age of onset of cannabis use. Additionally, PPC activity during encoding mediated the association between age of onset and reaction times. Furthermore, heavier cannabis use was associated with higher right DLPFC activation during the maintenance and retrieval phases.

Decision-Making and Inhibition

Examining risk-taking behavior and effective functional connectivity during a BART task, both cannabis users and controls exhibited activity in regions associated with risk-taking behavior and reward (e.g., dorsal ACC, NAc, and insula, [41]). While no group differences in risk-taking-related activity were observed, effective connectivity analyses between the dorsal ACC, NAc, and insula indicated an absence of inhibitory effects of the dorsal ACC on the NAc in the cannabis group which was present in the controls.

Looking at whole brain inhibition (Go-NoGo task)-related activity, 2-week abstinent cannabis users showed higher activity in the left MFG, left SFG, and left ACC during correct inhibitions compared to controls (lifetime use < 51, past year use < 6) [42]. This association was not moderated by gender.

Reward, Error, and Time Processing

In a monetary incentive delay task, weekly cannabis users showed higher activity in the frontal pole, SMG, and angular gyrus during feedback compared to controls [43•]. Furthermore, adolescent cannabis users showed higher feedback-related activity in the SFG than adult cannabis users, but no group differences in reward anticipation–related activity were observed, and analyses assessing age (adolescent/adults) effects showed no significant effects. Predefined regions of interest (left ventromedial prefrontal cortex (PFC) and ventral striatum) based on an earlier meta-analysis of the same monetary incentive delay task did not show any effects [44].

Similarly, in adolescent cannabis users, activity during a monetary incentive delay task in the bilateral ventral striatum was not associated with CUDIT scores [45]. However, CUDIT scores were negatively associated with lingual gyrus and putamen activity during inaccurate trials (compared to accurate trials) and ACC and dorsomedial PFC activity

during punished inaccurate trials (compared to other trial types). These results suggest more severe cannabis use, and related problems are linked to reduced responsiveness to errors.

In a novelty task, the tendency to seek novel stimuli was positively associated with reward prediction error–related activity in attention-related regions (IPL, dorsomedial PFC, and STG) in adolescents with low CUDIT scores, but this association was negative in adolescents with high CUDIT scores [46]. These findings indicate altered attentional response to novel stimuli in adolescents with more severe cannabis use and related problems.

Looking at the brain processes underlying the processing of affective negative and positive future events, those with higher CUDIT scores showed less activity in the ACC and PCC, STG, fusiform gyrus, and putamen when presented with high-intensity future events, suggesting blunted responsiveness to affective future events in those with more severe use and related problems [47]. Similarly, cannabis users exhibited lower cerebellar, MTG, STG, fusiform gyrus, and lateral occipital cortex activity when envisioning future events compared to controls [48].

The effect of cannabis dependence on social reward processing in heterosexual cannabis-dependent men who were abstinent for 28 days before assessment was assessed with an interpersonal pleasant touch paradigm [49]. Controls exhibited greater right dorsal striatal and putamen activity in response to female compared to male touch, while cannabis users showed relatively lower activity, which was associated with heavier lifetime cannabis use.

Emotion and Face Processing

Emotion and face processing have gained attention in addiction research as evidence emerged that socio-emotional processes are important in dependence and recovery. Adolescent cannabis users with higher CUDIT scores displayed reduced responsiveness to faces in the left superior-medial PFC and ACC, regardless of the emotion presented [50]. The valence of stimuli may also be important, as 28-day abstinent cannabis users displayed altered responses to negative but not positive emotional stimuli compared to controls [51]. Specifically, the cannabis group showed higher right medial OFC activity and higher functional connectivity with the left dorsal striatum and left amygdala, even after prolonged abstinence.

Focusing on the link between emotional and cognitive brain processes, emotional brain responses (response to angry or fearful faces vs. shapes) were correlated with cognitive brain responses (high load working memory vs. recognition) in cannabis users with CUD but not non-dependent users or controls [52]. Similarly, only the cannabis users with CUD showed a correlation between cognitive and emotional task performance on a behavioral level. Reduced segregation of emotional and cognitive processes might affect cognitive function when presented with emotionally demanding situations.

Cue-Reactivity

Cannabis cue-reactivity—the brain's response to cannabis stimuli—is considered a key factor in cue-induced craving and drug-seeking behavior (e.g., [53••]). Cannabis-using late adolescents (aged 17–21) rated cannabis images as more rewarding than neutral images and exhibited higher activity in regions involved in salience and reward processes (including the precuneus, thalamus, PCC, and the MFG and SFG) in response to cannabis relative to neutral images [54]. However, increased cue-reactivity was not associated with heaviness of use, and no control group was included. Similar results were observed in weekly cannabis-using adults using a multimodal cue-exposure paradigm [55]. Cannabis users compared to controls showed higher activity in reward-related regions (including the VTA, insula, and pallidum) in response to visual and odor cannabis cues compared to neutral cues, but not when compared to flower cues. Bimodal conditions—in which both visual and odor cues were presented simultaneously—showed similar results but also showed higher activity in the SPL in cannabis users compared to controls for cannabis cues compared to flower cues. Higher cue-reactivity for bimodal cannabis compared to neutral cues in the cingulate gyrus, left insula, and occipital lobe was also associated with higher craving after cue-exposure.

Visual cannabis cue-reactivity in male-dependent cannabis users has been compared to heavy non-dependent users and controls [56]. While all cannabis users showed higher visual cannabis cue-reactivity in the ventral striatum (as well as prefrontal, cingulate, and parietal clusters), higher cue-activity in the dorsal striatum was specific to the dependent users, which was also associated with higher craving in this subgroup.

As tobacco co-use is common in cannabis users [29], Kuhns et al. (2020) assessed cannabis cue-reactivity in heavy cannabis users and matched controls in which 50% of each group also smoked cigarettes daily [57]. Complex interactions between cannabis use status and cigarette use status were observed in the IFG, frontal pole, ACC, striatum, and amygdala. Non-cigarette-using cannabis users showed increased cue-reactivity in the amygdala compared to non-cigarette-using controls. However, cannabis and cigarette co-users did not show increased cannabis cue-reactivity compared to the cigarette-using controls. Cigarette-using controls showed increased cannabis cue-reactivity in the striatum and amygdala compared to non-cigarette-using controls and cannabis and cigarette co-users, as well as higher cannabis cue-reactivity in the ACC compared to cannabis

and cigarette co-users. These results suggest that tobacco use may modulate cannabis cue-reactivity and that co-use should be considered when assessing cannabis cue-reactivity.

Highlights and Challenges

Differences Between Heavy Use and Cannabis Use Disorder

Although crucial to distinguish cannabis exposure effects from CUD-related effects, direct empirical comparisons between heavy use and CUD are still scarce [8, 9•]. Chye et al. (2019) showed that individuals with CUD had reduced hippocampal volume compared to heavy users [14] but no differences in cortical surface morphology [17]. Furthermore, CUD status was associated with cannabis cue-induced activity in the striatum: heavy cannabis use in a sample of males was associated with ventral striatal activity, while dependent use in a sample of males was associated with dorsal striatal activity [56]. The dorsal striatum has been suggested to mediate the shift towards habit formation and subsequently CUD [8, 56]. These findings are a step in the right direction and emphasize the importance of exploring the neurobiological mechanisms underlying heavy compared to dependent use in other domains.

Quantification of Cannabis Exposure

Although the studies included in this review reported on the heaviness of use and whether individuals were suffering from CUD, there was a lack of studies which quantified cannabis exposure. This includes stating the type of cannabis used, ratios of THC and CBD, as well as the potency of THC. This raises an important limitation of the research to date, as there is accumulating evidence to suggest differential effects of THC and CBD [58] as well as THC potency effects [59] on brain structure and function. Future studies should include a biochemical quantification of cannabis exposure to address some of the fundamental questions on the pharmacokinetics of different cannabinoids, and how they differentially impact the brain.

Age Matters

While it is often proposed that the adolescent brain is more vulnerable to the potential negative effects of cannabis than adults [60••], direct comparisons of adolescents and adults remain rare. Cannabis use has shown age-related effects on cortical thinning of the prefrontal cortex [25], and an earlier onset of use has been associated with larger increases in several cerebellar lobules [28•] and thinner hippocampi, once cannabis users reach adulthood [61]. However, findings on the effects of adolescent cannabis use on structural brain changes are inconsistent [26•]. Focusing on reward-related processes, adolescent cannabis users exhibited higher feedback-related activity in the SFG than adults, but age did not affect reward anticipation–related activity [43•]. Interestingly, cannabis use might have protective effects in older age as older cannabis users showed higher RSFC between the left cerebellum and left hippocampus compared to controls, similar to non-using younger individuals [35].

Despite the abundance of reviews on the effects of cannabis in specific age groups, particularly adolescence [e.g., 60••, 62••, 63••, 64••, 65], only one review evaluated studies directly comparing adolescents and adults [66••]. The evidence suggested that adolescents are more susceptible to the effects of cannabis use on aspects of cognition, especially in heavy and dependent users. There is also preliminary evidence of resilience during adolescence, as intoxicated adolescents were found to have increased spatial memory ability and decreased cognitive disorganization. While evidence is still limited, these findings suggest age-dependent effects of cannabis on the brain and cognition in several domains, highlighting the importance of direct age group comparisons in future studies.

Sex and Gender Differences

A growing body of evidence examined sex differences in the impact of cannabis use on the brain and cognition [67], but the effects of gender identity are unclear. As the sex gap in cannabis use is narrowing, research should aim to include equal numbers of men and women and collect data on gender identity to enable direct comparisons.

Preliminary evidence suggests that males exhibit heightened WM-related activity in the SFG compared to females [36], while sex did not moderate heightened inhibition-related activity in cannabis users compared to controls [68]. A recent systematic review and meta-analysis of sex-related differences in cortical gray matter volume found that a higher proportion of females in the included studies were associated with increased grey matter volume in the middle occipital gyrus in adolescent cannabis users versus controls [62••]. When investigating sex effects in adults, a recent systematic review found mixed findings, as the majority of included studies found no evidence of an interaction between sex and cannabis use on brain structure or function although there was evidence to suggest that adult females may be more susceptible to cannabis' neurotoxic effects in the frontal and occipital cortex [69••].

Another important consideration is the effects of sex and gender on dual diagnoses [70••]. Preliminary evidence suggests that long-term cannabis use is associated with an increased vulnerability to the development of psychosis and anxiety in females and increased vulnerability to

the development of depressive symptoms in males [70••]. Among female cannabis users, anxiety symptoms were correlated with larger amygdala volume [71]. Taken together, these findings indicate sex differences in vulnerability to psychiatric disorders associated with cannabis use, emphasizing the importance of considering comorbidity in the neurobiological impact of cannabis use.

Co-use of Tobacco

Co-use of tobacco and cannabis is highly prevalent, particularly in Europe [29], but is often under-reported or not controlled for in analyses. This is particularly concerning due to the evidence of potential interaction effects of tobacco and cannabis on the brain and aspects of cognition. For example, cannabis-only users showed heightened cannabis cue-reactivity in several reward-related regions, but no differences were found in co-users of cannabis and cigarettes [57]. Effects of cannabis use on brain structure should also consider cigarette use, as alterations in grey matter volume were found in both co-users of cannabis and tobacco and non-cannabis-using tobacco smokers [30]. This suggests similarities in the impact of cannabis and tobacco on the structure of the brain, highlighting the need to consider tobacco use history to better understand the unique and combined neurobiological mechanisms by which both drugs impact the brain.

There is also a high incidence of co-use of cannabis and alcohol [72]; however, to date, most studies have investigated the effects of alcohol or cannabis use on change in brain structure and function without considering co-use patterns [73]. Of the studies investigating the effects of co-use, the majority do not include an alcohol-only comparison group, and even less include a cannabis-only comparison group. In the limited studies which have compared co-users and single drug users, there is evidence of differential activity and connectivity between co-users and alcohol users [74], but further studies exploring brain structural and functional differences are necessary. In future studies, it will be important to include co-users, as well as single drug users, and non-using controls to draw conclusions on whether the effects are unique to a particular drug or co-use.

Causality and Evidence for Lasting Effects: Longitudinal Studies and Recovery After Abstinence?

Few longitudinal studies have investigated the causal relationship between cannabis use and brain structure, with even fewer exploring brain function. In a 5-year longitudinal study in adolescents [25], only cortical thickness at follow-up (and not baseline) was associated with lifetime cannabis use at follow-up; suggesting changes in cortical thickness are dependent on current use rather than preceding use. Furthermore, Meier et al. (2019) found that cannabis use trajectories in a sample of male adolescents did not affect grey matter volume and cortical thickness in adulthood (age 30–36, [26•]), whereas Burggren et al. (2018) showed thinner hippocampi in late adulthood (age 57–75) after adolescent cannabis use [61].

Additionally, limited research investigated recovery of brain structure and function after a period of abstinence. Some studies indicated persistent problems after two (inhibition, [43•]) to four (reward processing, [49]) weeks of abstinence. These findings align with a recent meta-analysis that found functional alterations persisting up to 25 days post-abstinence [75]. However, studies examining longer abstinence periods are crucial to determine long-term effects.

Conclusions

In conclusion, this review highlights the mounting evidence indicating that frequent cannabis use and CUD have apparent effects on brain structure and functioning. The findings reinforce previous research by confirming volumetric changes, particularly in the OFC and hippocampus, among regular and heavy users as well as those with CUD that might be associated with cognitive performance. Altered RSFC within and between various networks and regions was found in heavy users and those with CUD, compared to controls, but these alterations are more commonly found to be associated with measures of use and dependence in those with CUD. Task-based fMRI studies revealed altered WM and emotion as well as face processing–related activity and connectivity in cannabis users compared to controls. Limited evidence points towards cannabis use–related alterations of inhibition and decision-making-related brain activity. No group differences in reward-related brain activity were observed, but more severe use and related problems appear to be associated to altered processing of novel stimuli and reduced responsiveness to errors. Finally, heavy cannabis users and those with CUD show heightened cannabis cue-reactivity in reward-related regions compared to controls.

To date, the causal relationship between cannabis use and brain structure and functioning remains elusive. However, evidence suggests the persistence of alterations even after a period of abstinence lasting up to 25 days, highlighting the need for further investigation into the long-term effects following an extended period of abstinence. This review demonstrated the accumulating body of evidence supporting the impact of heavy use and CUD on brain structure, function, and cognition. However, findings also emphasize the necessity for studies to consider dependence status, age, sex, gender, tobacco and alcohol co-use, and tobacco and alcohol

use histories when examining the effects of cannabis on the brain. By addressing these factors comprehensively, future research can provide a more complete understanding of the complex relationship between cannabis use and the brain.

Author Contribution EK was responsible for the design and project supervision. EK and KCP conducted the literature search and wrote the manuscript text. CR prepared Table 1. JC, LK, and CR were involved in reviewing and editing the manuscript. All authors reviewed and approved the final version.

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Declarations

Competing Interests The authors declare no competing interests.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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