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Lorenzetti, V; Batalla, A.; Cousijn, J.

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Cannabis Use Disorders and Altered Brain Morphology: Where Is the Evidence?

Valentina Lorenzetti[1] · **Albert Batalla**[2,3] · **Janna Cousijn**[4]

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Abstract Cannabis use disorders (CUDs) affect 13.1 million individuals worldwide. Brain morphology specific to CUDs may mediate the adverse behavioral outcomes of CUDs. We reviewed findings from 20 human neuroimaging studies on grey and white matter morphology in cannabis users that specifically included CUD assessments. There is evidence for CUD-specific morphological abnormalities within the striatum, medial temporal lobe, prefrontal cortex, cerebellum, and corpus callosum. Factors that may aggravate morphological abnormalities associated with CUDs include earlier onset age, higher lifetime exposure, and CUD-associated problems, while abstinence may result in (partial) recovery. These observations suggest that the neural substrates of compulsive cannabis use (e.g., striatum) may be distinct from those linked to cannabinoid exposure (e.g., hippocampus). The lack of studies examining individuals with a diagnosed CUD prevents drawing strong conclusions on CUD-specific morphological abnormalities. Comparing cannabis users with and without CUD is essential to delineate the neurobiology and inform new treatment strategies.

Keywords Addiction · Brain morphology · Cannabis · Cannabis use disorder · Grey matter · White matter

Introduction

Cannabis use disorders (CUDs) are associated with significant societal and personal harms. CUDs represent the highest burden of disease in drug treatment services in Oceania and Africa and the second highest in Europe and South America [1]. An estimated 30 % of all cannabis users develop a CUD [2] but less than one third of those individuals seek help [3]. CUDs are associated with high relapse rates (~52–70 %) that are comparable to those of other substance use disorders (SUDs) [4, 5]. The high number of individuals with a CUD and the high relapse rates warrant the development of better treatment and prevention strategies. Unfortunately, a small number of studies investigate the neurobiological processes in individuals with a diagnosed CUD, which may drive underestimating the personal and societal harms of CUDs [6]. Nevertheless, CUDs are linked to significant harms to executive functions such as planning, organizing, problem solving, decision-making, memory, and emotional control [7, 8], and mental health, with high comorbidity with depression, anxiety, and psychotic disorders [9••]. Currently, little is known about the neurobiological mechanisms underlying

Valentina Lorenzetti and Albert Batalla shared first authorship

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✉ Valentina Lorenzetti
valentina.lorenzetti@monash.edu

Albert Batalla
a.batallacases@gmail.com

Janna Cousijn
j.cousijn@gmail.com

[1] Brain & Mental Health Laboratory, Monash Institute of Cognitive & Clinical Neurosciences and School of Psychological Sciences, Monash University, Melbourne, Australia

[2] Department of Psychiatry, Radboud University Medical Centre, Nijmegen, The Netherlands

[3] Nijmegen Institute for Scientist-Practitioners in Addiction (NISPA), Radboud University, Nijmegen, The Netherlands

[4] Department of Developmental Psychology, University of Amsterdam, Amsterdam, The Netherlands

CUDs. Most studies investigating the neurobiology underlying cannabis (ab)use involve chronic cannabis users who may not necessarily experience problems with their use [6]. A history of regular cannabis use does not necessarily differentiate between cannabis users with and without a CUD [9••]. As such, neurobiological correlates of cannabis use in chronic cannabis users may not necessarily relate to CUD-related problems [6].

The cognitive and mental health harms of CUDs may be ascribed to the detrimental neurobiological effects of both addiction-related processes and long-term cannabinoid exposure. Research in SUDs shows that brain areas that play a prominent role in the development of addiction include subcortical regions like the ventral tegmental area (VTA), nucleus accumbens (NAcc), amygdala, hippocampus, and dorsal striatum and also regions of the prefrontal cortex (PFC) [10–12]. Most of the brain regions relevant to SUDs (e.g., striatum, amygdala, hippocampus, and PFC [13]) are also rich in endogenous cannabinoid receptors-1 (CB1). These regions mediate the psychoactive effects of cannabinoids, including delta 9-tetrahydrocannabinol (THC), which have consistently demonstrated dose-dependent neurotoxic changes in brain regions rich with CB1 in animal studies [14].

In line with contemporary addiction models, morphological abnormalities of the ventral striatum are apparent in *early* stages of addiction [15] and thus may already be evident in regular cannabis users before the onset of CUDs. On the other hand, morphological abnormalities of the dorsal striatum are implicated in *compulsive*, *chronic* substance use [15]. Thus, dorsal striatal abnormalities may only be evident in individuals with a CUD. Similarly, given the role of excessive disinhibition in SUDs, morphological abnormalities of the PFC, which is primarily implicated in cognitive control, may be prominent in individuals with a CUD [16]. For treatment and prevention, it is essential to specifically uncover the neurobiology underlying CUDs, thereby differentiating between the effects of chronic cannabinoid exposure and CUD-related problems.

Here, we provide a critical overview of the existing structural neuroimaging evidence on grey and white matter volume abnormalities in CUDs (Table 1). Previous systematic reviews on the relationship between cannabis use and brain morphology revealed differences in structure of prefrontal, medial temporal (hippocampus, amygdala), and cerebellar regions in chronic cannabis users relative to non-cannabis using controls [17••]. Unfortunately, these reviews do not differentiate between regular cannabis use with and without a CUD [18, 19]. We therefore specifically attempt to dissociate the neurobiology of regular cannabinoid exposure and that of CUDs. From the available structural neuroimaging studies in cannabis users, we included only those studies that used a measure of CUD. First, we describe socio-demographic characteristics of the samples included in the reviewed studies, and the methods that were employed to measure CUDs. We then review the findings on the association between grey and white matter morphology and CUD and discuss (1) group differences between individuals with a CUD diagnosis and controls, (2) associations with CUD severity, (3) the role of abstinence and treatment, and (4) the role of gender. Finally, we discuss limitations of existing studies and offer suggestions for future work in this area.

Grey Matter Differences between CUDs and Controls

We reviewed findings separately for all regions in which an association with CUDs was reported, including the striatum, amygdala, hippocampus, PFC, and cerebellum.

Striatum Striatal grey matter morphology was examined in three studies with mixed findings. Cousijn and colleagues [16] found no differences in striatal volume in regular cannabis users, of which 38 % of the sample met the criteria for CUD, compared to controls [16]. In contrast, Yip and colleagues [20] found that cannabis-dependent participants, compared to controls, had smaller volume (i.e., sum of all voxels that are included within the boundaries of the region of interest) of the dorsal (i.e., caudate), but not other, striatal subregions [20]. Conversely, Gilman and colleagues [21] found larger grey matter density (i.e., amounts of gray or white matter concentration in each voxel) in the ventral striatum (i.e., NAcc) in non-dependent regular cannabis users relative to non-cannabis using controls (but no group difference for NAcc volume) [21]. In sum, the neuroanatomy of the ventral striatum was different in non-dependent cannabis users [21] whereas that of the dorsal striatum (caudate) was different in dependent cannabis users [20] compared to controls. These findings are in line with the model of Koob and Volkow [11], which postulates a transition from ventral striatum (e.g., NAcc) to dorsal striatum (e.g., caudate) as drug use becomes more compulsive [11].

Amygdala Four studies examined amygdala grey matter: two in individuals with CUDs [22, 23]; one in cannabis users with mixed levels of problem severity [16]; and one in cannabis users without any CUD [21]. These studies showed mixed findings. Smaller amygdala volumes were found in male chronic cannabis abusers versus their control counterpart [23]. In contrast, larger amygdala volumes were found in CUD females compared to both control females and CUD males [22]. No difference in amygdala volume was found in non-dependent regular cannabis users [21] and in users with varying levels of problem severity [16] compared to controls. Amygdala shape differences were however observed in the latter study, suggesting that regular cannabis use is associated

Table 1 Structural neuroimaging studies of grey and white matter morphology in regular cannabis users assessed for cannabis use disorders

Author (year)	Sample total *N* (males)	Age, years		In treatment	Abuse		Dependence		Results	
		CB	HC		Assessed	Report	Assessed	Reported	Group comparison	Association with abuse/ dependence symptoms
Battistella (2014) [30]	25 regular vs. 22 occasional users. All males	25 (2)	23 (2)	No	Diagnosis, symptoms	No	No	N/A	Regular < occasional users for grey matter volume in temporal cortex/pole, para-hippocampus, insula, OFC Regular > occasional for cerebellar grey matter volume	None performed (with abuse)
Gilman (2014) [21]	20(9) CB vs. 20(9) HC	21 (2)	21 (2)	No	Diagnosis	No	Diagnosis	None met criteria	CB > HC for left NAcc volume (trend) and density. Shape difference in left NAcc and right amygdala	N/A
Yip (2014) [20]	20 CUD, of which 13 abstained for 21 days, vs. 20 HC. All males	27 (2)	29 (2)	Yes	No	N/A	Diagnosis, symptoms	All dependent	CUD > HC and abstinent > non-abstinent CUD for caudate volume CUD = HC for putamen volume	None performed (with abstinence days and addiction severity)
Zalesky (2012) [34••]	59 (28) CB vs. 33 (14) HC	33 (11)	31 (12)	No	Diagnosis	No	Diagnosis, SDS	SDS 5.5 (4)	CB impaired axonal connectivity in the right fimbria of the hippocampus (fornix), splenium of the corpus callosum, and commissural fibers	None performed (with SDS)
Gruber (2011) [35]	15 (14) CUD vs. 15 (14) HC	25 (9)	25 (8)	No	Diagnosis	All CUDs	Diagnosis	All CUDs	CUDs increased MD in the right genu and reductions in left frontal FA	N/A
McQueeny (2011) [22]	35 (27) CUD after 28 days abstinence vs. 47 (36) HC	18 (1)	18 (1)	No	Diagnosis, symptoms	Diagnosis endorsed in 65 % of sample. Symptoms not reported	Diagnosis	Endorsed in 65 % of sample	CUD = HC and CUD female > HC female, CUD male for amygdala volume	None performed (with withdrawal symptoms, substance related life problems).
Kumra (2012) [39]	16 (8) CUD vs. 51 (26).	17 (2)	16 (2)	Yes	Diagnosis	All CUDs	Diagnosis	All CUDs	CUD < HC for superior parietal cortex GM volume	N/A
Cousijn (2012) [16]	33 (12) CUD vs. 42 (16) HC	21 (1)	22 (2)	No	Diagnosis, symptoms	Symptom severity exceeds abuse cutoff	Diagnosis, symptoms	Symptom severity suggests dependence	CUD > HC for anterior cerebellum. CUD = HC for volume of hippocampus, amygdala, OFC, ACC, striatum	Neg. corr. problem severity and amygdala volume No corr use and hippocampal volume
Ashtari (2011) [25]	14 CUD after 7 months abstinence vs. 14 HC. All males	19 (1)	19 (1)	Yes	No	N/A	Diagnosis	Dependence early full remission	CUD < HC for hippocampus volume CUD = HC for amygdala volume	None performed (with abstinence duration)
Ashtari (2009) [36]				Yes		N/A		Dependence early full remission	CB decreased FA in bilateral posterior internal capsule/thalamic radiation, the left middle temporal gyrus, and the right superior temporal gyrus.	None performed (with abstinence duration)
Churchwell (2011) [28]	18 (16) CUD vs. 18 (12) HC	17 (1)	17 (1)	No	Diagnosis	All endorsed	Diagnosis	No	CUD < HC for right OFC. CUD = HC for left OFC.	N/A
Mata (2010) [31]	30 (23) CB vs. 44 (25) HC	26 (5)	26 (6)	No	Diagnosis	No	No	N/A	CB < HC for frontal sulcal concavity CB > HC for frontal thickness	N/A
Medina (2010) [32]	16 (12) CB 28-day abstinence vs. 16 (12) HC	18 (1) 18 (1)		No	Diagnosis, symptoms	No	Diagnosis, symptoms	No	CB > HC for cerebellar vermis and inferior posterior lobules XIII-X	N/A
Medina (2009) [29]				No		*N* = 2.2(3.1) DSM symptoms		*N* = 2.2(3.1) DSM symptoms	CB female > HC female for PFC volume CB male < HC controls for PFC volume	No corr. abuse/dependence symptoms and PFC (anterior, posterior, total GM and WM, total ICV)
Arnone (2008) [37]	11 (11) CB vs. 11 (11) HC	25 (3)	23 (3)	No	Diagnosis	No	Diagnosis	No	CB increased MD in corpus callosum	N/A
Yücel (2008) [23]		40 (9)	36 (10)	No	Diagnosis	All endorsed	No	N/A		N/A

Table 1 (continued)

Author (year)	Sample total *N* (males)	Age, years		In treatment	Abuse		Dependence		Results	Association with abuse/ dependence symptoms
		CB	HC		Assessed	Report	Assessed	Reported	Group comparison	
	15 CUD vs. 16 HC. All males								CB < HC for hippocampus and amygdala volumes	
Medina et al. (2007) [26]	26 (19) CB vs. 21(14) HC	18 (1)	18 (1)	No	Diagnosis, symptoms	*N* = 2.2(3.1) DSM symptoms	Diagnosis, symptoms	*N* = 2.2(3.1) DSM symptoms	CB = HC for hippocampal volume	Pos. corr. abuse/dependence symptoms and hippocampal volume and left > right asymmetry
Medina et al. (2007) [38]	16 (12) CB following 28-day abstinence vs. 16(11) HC	18 (1)	18 (1)	No	Diagnosis, symptoms	No	Diagnosis, symptoms	No	CB = HC for hippocampal volume	N/A
Jager (2007) [48]	20 (13) CB abstinent for 7 days vs. 20 (16) HC	25 (5)	24 (4)	No	Diagnosis	No	No	N/A	CB = HC for para-hippocampus grey and white matter density	N/A
Tzilos (2005) [24]	22 (16) CUD vs. 26 (19) HC	38 (6)	30 (9)	No	No	N/A	Diagnosis	All endorsed	CUD = HC for hippocampus volume	N/A

Studies on regular cannabis users, with no known outcomes for assessment of cannabis use disorders (blank rows); with diagnosed cannabis use disorders (light grey rows) and treatment seeking (dark grey rows); *Courtesy of Valentina Lorenzetti and Janna Cousijn. Elsevier Inc., 2014*

CB regular cannabis users, *CUD* participants diagnosed with a cannabis use disorder (i.e., abuse or dependence), *HC* non-cannabis using controls, *Neg.* negative, *Corr.* correlation, *Pos.* positive, *ICV* intracranial volume. *N/A* not applicable, *FA* fractional anisotropy, *OFC* orbitofrontal cortex, *NAcc* nucleus accumbens

with abnormal amygdala morphology *before* the onset of CUDs, representing a preexisting risk factor or neurotoxic effects of cannabis use. Nevertheless, the correlation between amygdala volume and problem severity [16] suggests that amygdala volume may differentiate between cannabis users with and without a CUD.

Hippocampus Five studies examined hippocampal grey matter [16, 23–26]. Only two studies found reduced volume in chronic cannabis users and in dependent cannabis users in early remission compared to healthy controls [23, 25]. Although hippocampal volume did not differ between cannabis users and controls on the group level, it correlated negatively with weekly cannabis use in cannabis users with a CUD [16] and positively with CUD symptom severity in cannabis users with mixed levels of CUD severity [26]. No morphological abnormalities of the hippocampus were observed in cannabis users with a CUD [24]. Notably, although these findings are somewhat mixed, hippocampal volume *reduction* is the most consistently reported finding in regular cannabis users without a CUD [27]. Reductions in hippocampal volume may thus reflect neurotoxic effects of chronic cannabinoid exposure rather than addiction-related processes in CUD [16, 25].

Prefrontal cortex The three studies that investigated PFC grey matter also showed mixed results. Churchwell and colleagues [28] found smaller PFC volumes in CUD versus control participants [28], a finding that was replicated in male CUD participants, but found larger PFC volumes in female participants with a CUD compared to female controls [29]. In contrast, Cousijn and colleagues [16] observed no differences in PFC (ACC and orbitofrontal cortex (OFC)) volume in cannabis users with a CUD compared to controls [16]. Interestingly, all these studies investigated young adults. However, the cannabis users that exhibited morphological abnormalities were aged between 16 and 18 years [28, 29], slightly younger than those users aged between 18 and 25 years that showed no PFC abnormalities [16]. Similarly, other investigations of cannabis users aged between 23 and 25 years [30] and around 26 years [31] also found no PFC abnormalities. In sum, diagnosis of a CUD during adolescence, rather than adulthood, may have a specific detrimental impact on PFC development (see section on age of onset below). This notion is yet to be fully tested, as some investigations of PFC morphology failed to report whether cannabis users met the criteria for CUD [30, 31] and longitudinal developmental studies are missing.

Cerebellum Two studies showed larger cerebellar grey matter volumes in CUDs versus controls [16, 32]. These findings are consistent with studies in regular cannabis users in which CUDs were not assessed. Battistella and colleagues [30] found larger cerebellar grey matter in regular versus occasional

cannabis users [30]. In contrast, Solowij and colleagues [33] failed to observe differences in cerebellar grey matter (but found reduced white matter volume) between chronic cannabis users and controls [33]. The cerebellum contains a high concentration of CB1 [13] and is not commonly associated with SUDs. Larger cerebellar grey matter volume may therefore specifically relate to cannabis use, not to the use of other substances of abuse or the development of addictive behaviors. Future longitudinal studies are needed to determine whether cerebellar grey matter alterations are specific to regular cannabis use regardless of CUD severity.

White Matter Differences between CUDs and Controls

Four studies examined the integrity of white matter in individuals with CUDs compared to controls reporting morphological differences in various brain regions. In chronic cannabis abusers relative to controls, axonal connectivity was impaired in the right fimbria of the hippocampus (fornix), splenium of the corpus callosum, and commissural fibers extending to the precuneus [34••]. Similarly, cannabis users without a CUD compared to controls showed increased mean diffusivity (MD), a measure of structural integrity, in the corpus callosum [33]. Differences were also found in cannabis users with a CUD compared to controls by Gruber and colleagues [35]. They reported increased MD in the right genu as well as reductions in left frontal fractional anisotropy (FA; a measure of white matter tract coherence). Moreover, Ashtari and colleagues [36] found decreased FA in the bilateral posterior internal capsule/thalamic radiation, the left middle temporal gyrus, and the right superior temporal gyrus [36]. Overall, the corpus callosum and fronto-temporal white matter circuits were most consistently impaired in CUDs.

Associations between Brain Morphology and Age of Onset

Onset of regular cannabis use was found to be associated with grey matter morphology of the PFC, such that an earlier age of onset was associated with reduced PFC volume and thickness [18]. Age of onset was also associated with microstructural white matter morphology in both chronic cannabis abusers and cannabis users without a CUD [34••, 37]. In the study of Zalesky and colleagues [34••], radial and axial diffusivities were both positively associated with the age at which chronic cannabis abuse commenced. Gruber and colleagues [35] also examined white matter integrity in the frontal lobe in cannabis users with a CUD, showing associations between higher FA and higher impulsivity [35] and higher FA, lower MD, and a later age of onset of cannabis use [35]. These findings preliminarily suggest that earlier initiation of cannabis use negatively affects grey and white matter morphology, especially in the PFC, a CB1 receptor-rich lobe that undergoes major development over the course of adolescence toward adulthood.

Associations with CUD Severity

Three studies explored the linear association between symptoms of cannabis abuse/dependence and grey matter morphology [16, 26, 38]. The only study that investigated amygdala volume found that, despite a lack of significant group differences between cannabis users and controls, smaller volumes were associated with higher levels of CUD-related problems [16]. Higher levels of CUD-related problems were associated with larger hippocampal volumes [26], but this effect was not replicated in another study [16]. CUD-related problems were not associated with striatal, PFC, and cerebellar morphology [16, 29]. These findings require replication, but suggest that CUD-related problems selectively affect the neuroanatomy of medial temporal regions. None of the studies reviewed investigated the association between white matter morphology and CUD severity.

Abstinence and Treatment

Several studies examined individuals with a CUD who were abstinent for longer than 3 weeks [20, 22, 25, 29, 38]. Hippocampal volume was reduced in one [25] but intact in a different sample of abstinent cannabis users [29]. Other brain regions were examined in single studies only. These demonstrated morphological abnormalities within the caudate [20] and cerebellum [32], but not within the putamen [20], amygdala [22], PFC [29], or in white matter integrity [36].

Notably, the MRI assessments on abstinent samples were conducted at different stages of the abstinence period across studies. Participants were scanned prior to abstinence in one investigation [20], but following prolonged abstinence in other studies [22, 25, 29]. It is unclear whether neuroanatomical abnormalities observed in abstinent cannabis users reflect either vulnerabilities preexisting the onset of cannabis use [20], subacute effects of ongoing regular cannabis use [16], or neurobiological recovery following prolonged abstinence [25].

Longitudinal studies are required to investigate the neurobiological trajectories of change (and potentially recovery) during prolonged abstinence. Based on the existing (preliminary and cross-sectional) evidence, alterations within specific brain regions may recover during prolonged abstinence. Reduced hippocampal, but not amygdala, volume was found in 7-month abstinent cannabis users [25]. Notably, amygdala volume reductions were also reported in

current users [23] that correlated with cannabis use-related problems [16]. This suggests that neuroanatomical abnormalities within the amygdala recover following abstinence, while those within the hippocampus may not [27].

Gender Effects

Few studies examined gender effects and reported mixed findings. Two investigations reported group × gender effects, with larger PFC and amygdala volumes in females compared to males with a CUD [22, 29]. No gender effect was reported in the striatum [16, 21], PFC [16, 31], medial temporal regions [16, 21], superior parietal regions [39], or the integrity of white matter tracts [34••, 35]. The scarcity of studies investigating gender effects is to no surprise given the small sample sizes and male predominance of CUD groups. However, it contrasts with the strong preclinical evidence on the role of sex hormones in problematic cannabinoid consumption [40], warranting future investigations in larger CUD samples with a balanced gender ratio.

Discussion

This systematic review shows emergent associations between gray and white matter morphology and CUDs, particularly within the striatum, amygdala, hippocampus, PFC and cerebellum. These findings may reflect neuroadaptations related to the development of addictive behaviors, which could exacerbate morphological abnormalities already observed in regular cannabis users without a CUD. Alternatively, these observations could represent (neurotoxic) alterations of brain morphology as a consequence of regular cannabinoid exposure, independent of CUD severity. An additional interpretation is that morphological characteristics of certain brain areas predate the development of a CUD. Unfortunately, the evident lack of studies comparing cannabis users with and without a diagnosed CUD and the absence of longitudinal neuroimaging studies preferably starting before the onset of cannabis use prevent us from drawing conclusions on causal relationships between cannabis use, CUDs, and brain morphology. Nevertheless, we observed several region-dependent trends, which suggest that different brain regions are relevant for different aspects and stages of CUDs.

Morphological abnormalities within the amygdala (i.e., reduced volumes and altered shape) and the dorsal striatum (i.e., larger volumes) may be specific to the development of addictive behaviors in CUDs and exacerbate with the progress of the addiction. These abnormalities would occur in regular cannabis users without a CUD and exacerbate as CUD symptoms become more severe, as suggested for the amygdala [16]. Consistent with recent theoretical models of a ventral to dorsal striatal shift as the SUD progresses [11], individuals with a CUD exhibited enlargement of the dorsal striatum [20] and volume reductions in various prefrontal [28] and parietal regions [39]. However, the paucity of neuroimaging studies of striatal morphology in cannabis users with and without a CUD hinders strong conclusions.

Morphological abnormalities within the ventral striatum, hippocampus, and cerebellum may reflect effects of cannabis exposure and not changes in brain morphology related to the development of CUD-related problems. These abnormalities may be evident across cannabis users with and without a CUD. For instance, neuroanatomical alterations within the ventral striatum are reported specifically in cannabis users without a CUD [21], which is also in line with widely accepted addiction models. Hippocampal alterations in participants with a CUD (i.e., reduced volume) are less consistently reported than in regular cannabis users where a CUD diagnosis was not reported (i.e., the presence of a CUD cannot be verified [27]). Hence, the hippocampus could be affected by the neurotoxic effects of chronic cannabinoid exposure, and these effects might not linearly exacerbate with increasing CUD-related problems. Hippocampal alterations may mediate the memory impairments specifically observed in cannabis users, in which nicotine exposure might also play a role [41]. Similarly, larger cerebellar volume was reported across regular cannabis users with and without a CUD [16, 32].

We did not observe morphological abnormalities in grey and white matter specifically associated with treatment status. This may be due to the fact that different brain regions were examined by studies investigating treatment-seeking [20, 25, 36, 39] versus non-treatment-seeking cannabis users. Unfortunately, only four studies recruited treatment-seeking regular cannabis users from treatment services [20, 25, 36, 39]. Not surprisingly, these studies showed contradictory results that lack replication, limiting a reliable integration of the findings to date. The paucity of studies in treatment-seeking cannabis users, and the concurrent abundance of studies in regular cannabis users with varying levels of CUD-related problems, may lead to underestimate of the effects of CUDs on brain morphology and prevent to elucidate if the neuroanatomical alterations reported in regular cannabis users are (partially) driven by addiction-related processes rather than by cannabinoid exposure per se.

Additional demographic characteristics (e.g., gender and age), onset of (heavy) cannabis use, and cannabis use patterns may moderate the relationship between CUDs and brain morphology. Gender played a role in abnormalities within the amygdala and OFC, which differentially affected male compared to female individuals with a CUD [22, 23, 29]. Participants' age moderated abnormalities within the PFC, where reduced volume was apparent in late adolescents but not in young adults. CUDs may detrimentally affect PFC morphology in earlier stages of adolescent neurodevelopment, when significant PFC remodeling occurs [42].

The few studies exploring the integrity of white matter in cannabis users with and without CUDs, relative to controls, have also shown evidence of potential enduring effects of cannabis use—including higher MD and lower FA. These effects might be directly related to demyelination or axonal damage or indirectly by delaying normal brain development [34••]. The notion that adolescence is a vulnerable period for the development of adverse outcomes from cannabis use is supported by the reported associations between age of cannabis use onset and PFC grey matter abnormalities [18] and white matter integrity [19].

It should be emphasized that our interpretation of the mechanisms mediating morphological abnormalities specific to CUDs and/or common to all regular cannabis users (with and without a CUD) are speculative. There are insufficient studies that specifically examine CUD, and no study directly compared cannabis users with and without a CUD. Studying the commonalities and differences between regular cannabis users with and without a CUD and between regular cannabis users and individuals with a similar psychopathological profile is needed to understand the neurobiological mechanisms underlying CUDs. Such studies are required to aid the development of new intervention and treatment strategies that target functioning of specific brain systems.

The lack of neuroimaging studies in CUDs is in sharp contrast with the growing body of studies in regular cannabis users [18]. Individuals with similar levels of cannabis exposure (i.e., dosage, age of onset, frequency, and duration) can vary greatly in the use-related problems they experience [9••]. Studies in regular cannabis users lack CUD assessments and therefore cannot identify potential CUD-specific effects, emphasizing the lack of knowledge about the neurobiological mechanisms underlying CUDs.

The neurobiology of CUDs may overlap with that of other SUDs. Yet, neuroimaging and neurocognitive behavioral studies in long-time regular cannabis users show relatively mild or absent neurocognitive deficits. We cannot conclude that neurobiological and neurocognitive effects of CUDs are less severe than those of other SUDs, given the paucity of neuroimaging studies in cannabis users with CUDs. The relatively mild neurocognitive effects and low addictive potential of cannabis, compared to other substances like cocaine and

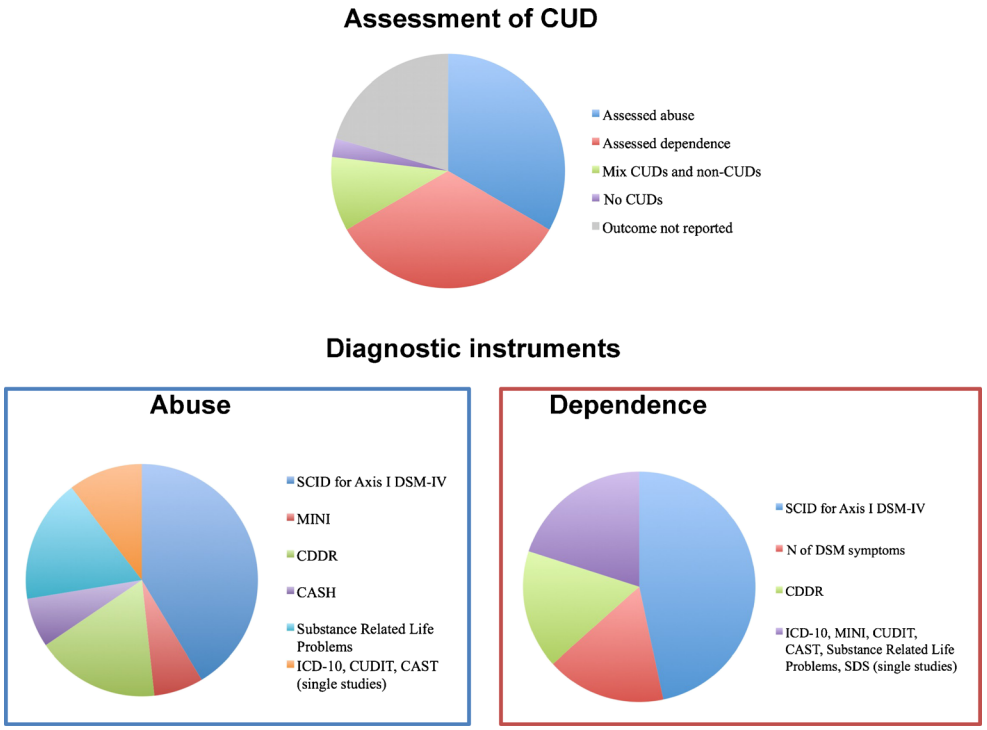

Fig. 1 Summary of instruments employed to diagnose the cannabis use disorders. **Abuse**. *SCID* Structured Clinical Interview for Axis I DSM-IV Disorders [20, 21, 24–27, 30, 32, 34••, 35, 38, 39]; *ICD-10* [47] International Classification of Diseases 10 [37]; *MINI* Substance Abuse Scales of the Mini International Neuropsychiatric Interview of the DSM [18, 48]; *CDDR* Customary Drinking and Drug Use Record [20, 21, 32, 34••, 38]; *CASH* Comprehensive Assessment of Symptoms History screening [22, 48]; *CUDIT* Diagnostic Threshold of the Cannabis Use Disorder Identification Test [18]; *CAST* Cannabis Abuse Screening Test [29]; Substance Related Life Problems [20, 21, 32, 34••, 38]. **Dependence**. *SCID* Structured Clinical Interview for Axis I DSM-IV Disorders [20, 21, 23, 24, 26–28, 30, 32, 34••, 35, 36, 38, 39]; *ICD-10* International Classification of Diseases 10 [37]; *MINI* Substance Abuse Scales of the Mini International Neuropsychiatric Interview of the DSM [18]; number of DSM-IV endorsed symptoms [20, 21, 28, 32, 38]; *CDDR* Customary Drinking and Drug Use Record [20, 21, 32, 34••, 38]; *CASH* Comprehensive Assessment of Symptoms History screening; *CUDIT* Diagnostic Threshold of the Cannabis Use Disorder Identification Test [18]; *CAST* Cannabis Abuse Screening Test [30]; Substance Related Life Problems [34••]; *SDS* Severity of Dependence Scale [24]

heroin, does not imply that the problems an individual can experience from a CUD are less severe than those experienced from another SUDs.

Limitations of Current Studies and Future Directions

This review of structural neuroimaging studies highlights a number of limitations, including the lack of information about whether CUDs were endorsed in the examined samples. Most studies that screened for CUDs in their samples did not report whether cannabis users actually endorsed a CUD diagnosis and did not report symptom severity.

Other prominent limitations include the following: the use of heterogeneous instruments to assess CUDs; the lack of studies in treatment-seeking cannabis users or longitudinal studies; and small sample sizes with limited age ranges (mainly young adults and adolescents). Examination of the neurobiology underlying CUDs requires the comparison of regular cannabis users with a CUD in treatment with regular cannabis without a CUD, while matching for other psychological problems. The reviewed studies examined samples that were composed mostly of participants with comorbid psychopathologies and medication [20, 25, 36, 39], which is consistent with epidemiological evidence of high comorbidity between CUDs and other psychiatric disorders [9••, 43–45]. Findings in individuals with a CUD without any comorbid psychopathologies may therefore not extend to both treatment- and non-treatment-seeking cannabis users [46]. Even though psychiatric comorbidity complicates the study of CUDs, more investigations of ecologically valid clinical and subclinical groups are needed. To differentiate between abnormalities specific to CUDs or general to multiple psychopathologies, studies could include clinical control groups matched on psychopathological symptoms other than CUDs.

The comparability of findings across studies is hindered by the heterogeneity of instruments employed to assess diagnosis and severity of CUDs (Fig. 1). Standardized and validated measures of the severity of CUDs are currently lacking, highlighting the need to develop objective, evidence-based measures of CUDs [9••, 49]. Differences between the new DSM-5 [50] criteria for CUDs and older versions of the DSM like the commonly used DSM-IV [51] should also be noted. The DSM-5 no longer distinguishes between cannabis abuse and dependence, but introduces craving and withdrawal as diagnostic criteria and three stages of CUD severity. The DSM-5 criteria for cannabis dependence may provide a more standardized instrument to measure severity of dependence. Future studies could benefit from investigating the association between CUD symptom severity, as reported in the DSM5, and brain morphology [50].

Finally, only a few investigations examined CUD participants after prolonged abstinence and there were no prospective longitudinal studies that mapped neurobiological pathways preceding the onset of CUDs. An important step in understanding the neurobiology of CUDs is to dissociate causal and consequential effects and to determine trajectories of change following prolonged cannabinoid abstinence, treatment, and recovery from CUDs.

Conclusions

This systematic review of structural neuroimaging studies of brain morphology in CUDs identifies critical limitations in current investigations of regular cannabis users. From a clinical perspective, identification of brain structural brain anomalies that relate to CUD severity may reveal targets important for treatment. In the quest to unravel the neurobiology of CUDs, the limited literature to date provides valuable hypotheses and lessons that should guide future studies. We believe that studying the commonalities and differences between cannabis users with and without a CUD while matching for other comorbid psychopathological problems is an essential next step.

Compliance with Ethical Standards

Conflict of Interest Valentina Lorenzetti, Albert Batalla, and Janna Cousijn declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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