

Cannabis Use Disorders and Brain Morphology

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Abbreviations

ACC Anterior cingulate cortex
CUD Cannabis use disorder
DLPFC Dorsolateral prefrontal cortex
DSM *Diagnostic and Statistical Manual of Mental Disorders*
NAcc Nucleus accumbens
OFC Orbitofrontal cortex
PFC Prefrontal cortex
SUD Substance use disorder
THC Δ^9 -Tetrahydrocannabinol
VTA Ventral tegmental area

INTRODUCTION

The past decades have been marked by an increase in the awareness of the addictive properties of cannabis, which parallels the rise in prevalence rates of cannabis use disorders (CUDs) (Degenhardt et al., 2013). CUDs currently have the highest burden of disease in drug treatment services in Oceania and Africa and the second highest in Europe and South America (UNODC, 2010). Approximately 30% of all cannabis users develop a CUD (Swift, Hall, & Teesson, 2001), but less than one-third of individuals with a CUD seek help (Stinson, Ruan, Pickering, & Grant, 2006). Moreover, relapse rates of CUDs range between 52% and 70% and are comparable to those of other substance use disorders (SUDs) (Budney, Vandrey, Hughes, Thostenson, & Bursac, 2008; Chauchard, Septfons, & Chabrol, 2013). The significant societal and personal harms associated with CUDs are alarming and warrant the development of new treatment and intervention strategies. These harms may be ascribed to the detrimental impact of addiction-related processes and of long-term cannabinoid exposure on the brain. Elucidating the brain correlates of CUDs is an important step that may help identify new treatment targets. However, in contrast to other SUDs like alcohol and cocaine, relatively little is known about the neurobiological mechanisms underlying CUDs. Most neuroimaging studies that investigate the effects of cannabis on the brain examine groups of heavy cannabis users rather than groups with a diagnosed CUD specifically. This chapter presents a

narrative review of structural neuroimaging findings on gray matter abnormalities associated with CUDs. We summarize the existing studies on gray matter morphology in CUDs in an attempt to dissociate the potential adverse effects of cannabis use versus CUDs on gray matter morphology. Moreover, we discuss caveats of existing studies and offer suggestions for future work in this area. To provide a theoretical background for the discussion of the structural brain correlates of CUDs we start this chapter with a description of the nosology of CUDs and the neurocognitive processes associated with CUDs, including the related brain systems.

NOSOLOGY OF CANNABIS USE DISORDER

CUDs are similar to other SUDs in that they are characterized by compulsive substance use despite awareness of its harmful consequences (Leshner, 1997). In the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-V), a CUD is diagnosed when the individual meets at least 2 of 11 criteria within a period of 12 months (APA, 1996). Diagnostic criteria of CUDs are similar to those of other SUDs and are clustered alongside four dimensions: loss of control, social problems, pharmacological consequences of cannabis use, and high-risk use (see Table 1).

Given the introduction of the DSM-V in May 2013, the structural neuroimaging studies discussed in this review investigated cannabis abuse and dependence as defined in the DSM-IV. In contrast to the DSM-IV, the DSM-V does not distinguish between cannabis abuse and dependence. Moreover, the DSM-V includes craving and cannabis withdrawal as diagnostic criteria and three stages of severity based on the number of diagnostic criteria that are met (mild, two or three criteria; moderate, four or five criteria; severe, six or more). These changes in diagnostic criteria raise questions on how the reviewed neurobiological findings on CUD as defined by the DSM-IV can be related to CUD as defined by the DSM-V. In this regard, Bailey, DuPont, and Teitelbaum (2014) noted that a moderate or severe CUD DSM-V diagnosis approximates cannabis dependence in the DSM-IV, while a mild CUD DSM-V diagnosis approximates cannabis abuse in the DSM-IV. Additional features of CUD include its gender-dependent clinical profile, psychiatric comorbidity, and low psychosocial outcomes. Males have a higher

TABLE 1 DSM-V Criteria for Cannabis Use Disorders

At least two of the following symptoms

Loss of control

- Cannabis is often taken in large amounts or over a longer period than was intended;
- Persistent desire to stop or cut down cannabis use or unsuccessful efforts in doing so;
- Craving or the strong urge or desire to use cannabis;
- Spending a great deal of time obtaining, using, or recovering from the use of cannabis.

Social problems

- Recurrent cannabis use resulting in a failure to fulfill obligations at home, school, or work;
- Recurrent cannabis use despite having persistent or recurrent social or interpersonal problems due to cannabis use;
- Important social, work, or recreational activities are given up or reduced owing to cannabis use.

Pharmacological consequences of cannabis use

- Withdrawal from the effects of cannabis, which is taken to relieve or avoid withdrawal symptoms;
- Tolerance to the effects of cannabis: more cannabis is needed to achieve the desired effect.

High-risk use

- Recurrent cannabis use in physically hazardous situations;
- Cannabis use is continued despite knowledge of physical and psychological problems.

chance of developing a CUD (UNODC, 2010), but craving appears to be more severe in females (King et al., 2011). Comorbid substance use and psychiatric disorders including depression, anxiety, and psychosis are common among individuals with a CUD (van der Pol et al., 2013). Finally, an earlier onset of cannabis use is associated with more severe outcomes with regard to psychiatric health, neurocognitive functioning, socioeconomic status, and academic achievements (Stinson et al., 2006; Swift et al., 2001).

NEUROCOGNITIVE ASPECTS OF CANNABIS USE DISORDER

Contemporary addiction models highlight the role of an imbalance between strong automatically triggered motivations to use and compromised cognitive control (disinhibition) in the transition from impulsive and recreational substance use toward compulsive substance use (e.g., Everitt & Robbins, 2005; Koob & Volkow, 2010; Robinson & Berridge, 2003; Wiers et al., 2007). Automatically triggered motivations—including craving, attention, and approach action tendencies—are thought to reflect sensitized and conditioned responses toward substance-related stimuli that develop during the development of SUDs. Exposure to cannabis-related versus neutral cues can induce craving (Gray, LaRowe, Watson, & Carpenter, 2011; Lundahl & Johanson, 2011), automatically capture attention (Asmaro, Carolan, & Liotti, 2014; Cousijn, Watson, et al., 2013), and activate approach tendencies (Cousijn, Goudriaan, & Wiers, 2011; Field, Eastwood, Bradley, & Mogg, 2006) in individuals with a CUD compared to non-cannabis-using controls (henceforth referred to as controls). Moreover, individuals with a CUD show impairments in executive functions like planning, organizing, problem solving,

decision-making, memory, and emotional control (Solowij & Battisti, 2008). Cognitive impairments may already (mildly) emerge in recreational cannabis users and exacerbate as the CUD progresses (Martin-Santos et al., 2010). Some cognitive impairment may predate the onset of cannabis use and/or CUD, constituting a risk factor for CUD (Cousijn, Wiers, et al., 2013).

Cognitive deficits in CUD overlap with those observed in other SUDs (Fernández-Serrano, Pérez-García, & Verdejo-García, 2011). However, compared to other SUDs, neurocognitive and neurobiological research in CUD is still in its infancy. Yet, preliminary findings support similar neurobiological mechanisms underlying CUD and other SUDs. Brain areas that play a prominent role in the development of SUDs include subcortical regions such as the ventral tegmental area (VTA), nucleus accumbens (NAcc), amygdala, hippocampus, dorsal striatum, and regions of the prefrontal cortex (PFC) (see Figure 1; Everitt & Robbins, 2005; Koob & Volkow, 2010; Wilson, Sayette, & Fiez, 2004). SUD-associated brain areas (striatum, amygdala, hippocampus, and PFC (Burns et al., 2007)) are rich in endogenous cannabinoid receptor 1 (CB1), which mediates the psychoactive effects of cannabinoids including Δ^9 -tetrahydrocannabinol (THC).

The VTA modulates the hedonic response to drug cues through the firing threshold of its dopamine neurons. The hedonic response to drug cues is thought to change as the addiction progresses, resulting in increased firing in response to substance-related cues (Koob & Volkow, 2010). VTA dopamine neurons project to the ventral striatum (e.g., NAcc), which mediates reward seeking by connecting motivational aspects of salient stimuli to motor actions (Everitt & Robbins, 2005). Neurobiological changes in the VTA and ventral striatum occur during recreational substance use, before the development of SUDs (Koob & Volkow, 2010). The dorsal striatum mediates the formation of habitual and compulsive substance use (Belin & Everitt, 2008; Everitt & Robbins, 2005). Notably, there is a shift from ventral to dorsal striatum involvement during the transition from controlled to compulsive substance use, but this evidence remains to be replicated in CUD (Everitt & Robbins, 2013).

The hippocampus and amygdala are also important in the development of cue-induced conditioned responses, such as craving and attention. The amygdala is involved in attributing emotional salience to cues and mediating approach and avoidance behavior (Schneider et al., 2001). The PFC is one of the main substrates involved in cognitive control and is therefore crucially involved in SUDs. Key components of the PFC that have been linked to cognitive control deficits in SUDs include the dorsolateral PFC (DLPFC), anterior cingulate cortex (ACC), and orbitofrontal cortex (OFC) (Koob & Volkow, 2010; Mansouri, Tanaka, & Buckley, 2009). More specifically, the ACC is involved in attention, conflict monitoring, and assessing salience of motivational information (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). The OFC is key for reward evaluation and, together with the ACC, in the integration of motivational information into cognitive processes (Koob & Volkow, 2010; Mansouri et al., 2009).

STRUCTURAL NEUROIMAGING STUDIES INVESTIGATING CANNABIS USE DISORDER

Morphological alterations within the aforementioned brain regions have been observed in various SUDs including alcohol, opiate, and

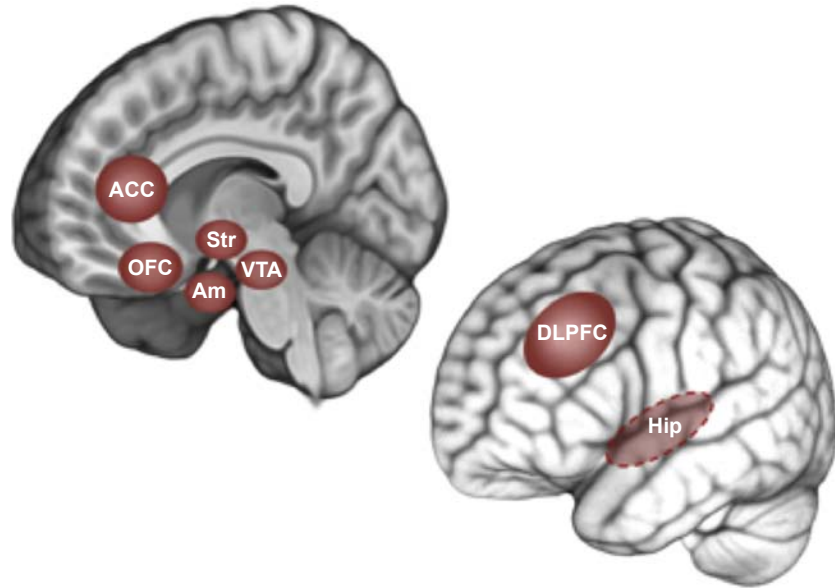


FIGURE 1 Brain regions implicated in addiction. ACC, anterior cingulate cortex; OFC, orbitofrontal cortex; DLPFC, dorsolateral prefrontal cortex; Str, striatum; Am, amygdala; VTA, ventral tegmental area; Hip, hippocampus.

cocaine use disorders (Everitt & Robbins, 2005; Koob & Volkow, 2010; Wilson et al., 2004). Given that CUD and other SUDs share neurocognitive deficits, the morphology of SUD-associated regions such as the VTA, striatum, hippocampus, amygdala, ACC, DLPFC, and OFC may also be affected in CUD. Morphological abnormalities of the ventral striatum (implicated in early stages of addiction) may already be evident in regular cannabis users before the onset of CUD, whereas morphological abnormalities of the dorsal striatum (implicated in compulsive, chronic substance use) may be evident only in individuals with a CUD. Similarly, given the role of disinhibition in SUDs, morphological abnormalities of the PFC may be prominent in individuals with a CUD (Cousijn et al., 2012).

Over the past decade, a growing number of neuroimaging studies examined gray matter morphology in regular cannabis users, but not specifically in individuals with a CUD (for reviews see Batalla et al., 2013; Lorenzetti, Solowij, Fornito, Lubman, & Yucel, 2014; Rocchetti et al., 2013). Notably, a history of regular cannabis use does not necessarily differentiate between cannabis users with and without a CUD (van der Pol et al., 2013). While the structural neuroimaging evidence in regular cannabis users is critical to characterize brain alterations associated with chronic cannabinoid exposure, neuroanatomical alterations specific to CUD remain largely unknown. This section summarizes structural neuroimaging findings on gray matter morphology in CUD specifically. First, we describe sociodemographic characteristics of the reviewed samples and the methods that were employed to measure CUDs. We then review the existing findings on the association between gray matter morphology and CUD and discuss (1) group differences between individuals with a CUD diagnosis and controls, (2) associations with CUD problem severity, (3) the role of abstinence and treatment, and (4) the role of gender. We identified a total of 16 studies in regular cannabis users that reported using instruments to assess diagnosis and/or severity of CUD (see Table 2). These studies were selected from those identified in a systematic literature review on brain morphology in

regular cannabis users (Lorenzetti et al., 2014) and include additional studies that were published since January 2013.

Sample Characteristics and Diagnostic Instruments

Sample Size, Age, and Gender Distributions

Table 2 provides an overview of the characteristics of the reviewed studies. Most investigations used relatively small samples of regular cannabis users: only three studies included >30 participants (Cousijn et al., 2012; Mata et al., 2010; McQueeney et al., 2011). Moreover, most studies investigated young adults or adolescents. Only two investigations examined adults between 30 and 40 years of age (Tzilos et al., 2005; Yücel et al., 2008). CUDs are more prevalent in males (UNODC, 2010), which is reflected in the characteristics of the reviewed samples: most studies investigated samples that were composed of mostly males or exclusively of males.

Recruitment Sites of Regular Cannabis Users

The study of non-treatment-seeking regular cannabis users dominates the literature to date. Most investigations ($n=11$, see Table 2) recruited regular cannabis users from the general community, educational institutions, or Dutch coffee shops (outlets where legal cannabis can be bought). Only three studies recruited treatment-seeking, regular cannabis users from treatment services (Ashtari et al., 2011; Kumra et al., 2012; Yip et al., 2014).

Assessment of CUD Diagnosis and Symptoms

Assessment of CUD according to the DSM-IV (APA, 1996) was reported in all reviewed investigations. Specifically, the studies reported screening for any current or past psychiatric disorder and not excluding participants who endorsed cannabis abuse or

TABLE 2 Structural Neuroimaging Studies of Gray Matter Morphology in Regular Cannabis Users Assessed for Cannabis Use Disorder

Author (Year)	Sample Total <i>n</i> (Males)	Age, years (SD)		Recruitment Site	In Treatment	Abuse		Dependence		Results	
		CB	HC			Assessed	Reported	Assessed	Reported	Group Comparison	Association with Abuse/ Dependence Symptoms
Battistella et al. (2014)	25 regular vs 22 occasional users. All males.	25 (2)	23 (2)	General community and university	No	Diagnosis, symptoms	No	No	N/A	Regular < occasional users for gray matter volume in temporal cortex/pole, parahippocampus, insula, OFC. Regular > occasional for cerebellar gray matter volume.	None performed (with abuse)
Gilman et al. (2014)	20 (9) CB vs 20 (9) HC	21 (2)	21 (2)	Not specified	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 et al. (2014)	20 CUD, of which 13 abstained for 21 days, vs 20 HC. All males.	27 (2)	29 (2)	Treatment service (out-patients)	Yes	No	N/A	Diagnosis, symptoms	All dependent	CUD > HC and abstinent > nonabstinent CUD for caudate volume. CUD = HC for putamen volume.	None performed (with abstinence days and addiction severity)
McQueeney et al. (2011)	35 (27) CB after 28 days abstinence vs 47 (36) HC	18 (1)	18 (1)	Local schools	No	Diagnosis, symptoms	Diagnosis endorsed in 65% of sample. Symptoms not reported.	Diagnosis	Endorsed in 65% of sample.	CB = HC and CB female > HC female, CB male for amygdala volume.	None performed (with withdrawal symptoms, substance-related life problems).
Kumra et al. (2012)	16 (8) CUD vs 51 (26)	17 (2)	16 (2)	Treatment service	Yes	Diagnosis	All CUDs	Diagnosis	All CUDs	CUD < HC for superior parietal cortex GM volume.	N/A
Cousijn et al. (2011)	33 (12) CUD vs 42 (16) HC	21 (1)	22 (2)	Coffee shops	No	Diagnosis, symptoms	Symptom severity exceeds abuse cutoff	Diagnosis, symptoms	Symptom severity suggests dependence	CB > HC for anterior cerebellum. CB = HC for volume of hippocampus, amygdala, OFC, ACC, striatum.	Neg. corr. between problem use and amygdala volume. No corr. between problem use and hippocampus, OFC, ACC, cerebellum.
Ashtari et al. (2011)	14 CUD after 7 months abstinence vs 14 HC. All males.	19 (1)	19 (1)	Therapeutic community (inpatients)	Yes	No	N/A	Diagnosis	Dependence early full remission	CUD < HC for hippocampus volume, CUD = HC for amygdala volume.	None performed (with abstinence duration).

Churchwell, Lopez-Larson, and Yurgelun-Todd (2010)	18 (16) CUD vs 18 (12) HC	17 (1)	17 (1)	General community	No	Diagnosis	All endorsed	Diagnosis	No	CUD<HC for right OFC. CUD=HC for left OFC.	N/A
Mata et al. (2010)	30 (23) CB vs 44 (25) HC	26 (5)	26 (6)	General community	No	Diagnosis	No	No	N/A	CB<HC for frontal sulcal concavity. CB>HC for frontal thickness.	N/A
Medina, Nagel, and Tapert (2010)	16 (12) CB 28 day abstinence vs 16 (12) HC	18 (1)	18 (1)	High school, colleges	No	Diagnosis, symptoms	No	Diagnosis, symptoms	No	CB>HC for cerebellar vermis and inferior posterior lobules XIII–X.	N/A
Medina et al. (2009)					No		<i>n</i> = 2.2 (3.1) DSM symptoms		<i>n</i> = 2.2 (3.1) DSM symptoms	CB=HC for PFC volume. CB female>HC female for PFC volume. CB male<HC controls for PFC volume.	No corr. between abuse/dependence symptoms and PFC (anterior, posterior, total gray and white matter, total ICV)
Yücel et al. (2008)	15 CUD vs 16 HC. All males	40 (9)	36 (10)	General community	No	Diagnosis	All endorsed	No	N/A	CB<HC for hippocampus and amygdala volumes.	N/A
Medina, Schweinsburg, et al. (2007)	26 (19) CB vs 21 (14) HC	18 (1)	18 (1)	General community, high schools, university	No	Diagnosis, symptoms	<i>n</i> = 2.2 (3.1) DSM symptoms	Diagnosis, symptoms	<i>n</i> = 2.2 (3.1) DSM symptoms	CB=HC for hippocampal volume.	Pos. corr. between abuse/dependence symptoms and hippocampal volume and left>right asymmetry.
Medina, Nagel, et al. (2007)	16 (12) CB following 28-day abstinence vs 16 (11) HC	18(1)	18(1)		No		No		No	CB=HC for hippocampal volume.	N/A
Jager et al. (2007)	20 (13) CB abstinent for 7 days vs 20 (16) HC	25 (5)	24 (4)	General community, coffee shops, university	No	Diagnosis	No	No	N/A	CB=HC for parahippocampus gray and white matter density.	N/A
Tzilos et al. (2005)	22 (16) CUD vs 26 (19) HC	38 (6)	30 (9)	Not specified	No	No	N/A	Diagnosis	All endorsed	CUD=HC for hippocampus volume.	N/A

CB, regular cannabis users; CUD, participants diagnosed with a CUD (i.e., abuse or dependence); HC, non-cannabis-using controls; Neg., negative; corr., correlation; Pos., positive; ICV, intracranial volume. N/A, not applicable; OFC, orbito-frontal cortex; NAcc, nucleus accumbens.

Diagnostic instruments, cannabis abuse

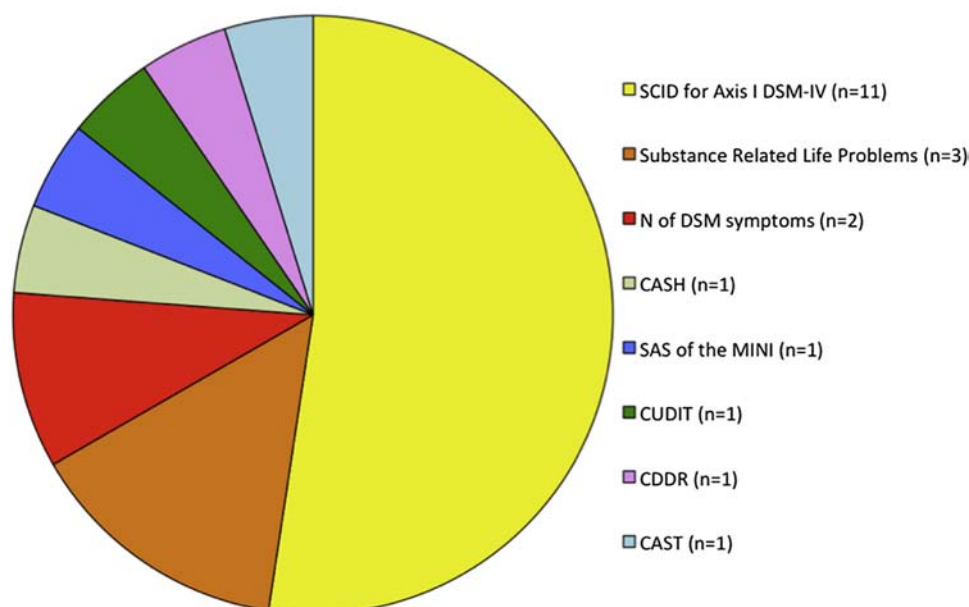


FIGURE 2 Summary of instruments employed to diagnose cannabis abuse. SCID, Structured Clinical Interview for Axis I DSM-IV Disorders (Ashtari et al., 2011; Churchwell et al., 2010; Gilman et al., 2014; Kumra et al., 2012; McQueeney et al., 2011; Medina et al., 2009, 2010; Medina, Nagel, et al., 2007; Medina, Schweinsburg, et al., 2007; Yip et al., 2014; Yücel et al., 2008); Substance-related life problems (McQueeney et al., 2011; Medina et al., 2009; Medina, Nagel, et al., 2007); number of DSM-endorsed symptoms (Medina et al., 2009; Medina, Schweinsburg, et al., 2007); CASH, Comprehensive Assessment of Symptoms History screening (Jager et al., 2007); SAS of the MINI, Substance Abuse Scales of the Mini International Neuropsychiatric Interview of the DSM (Jager et al., 2007); CUDIT, diagnostic threshold of the Cannabis Use Disorder Identification Test (Cousijn et al., 2012); CDDR, Customary Drinking and Drug Use Record (McQueeney et al., 2011); CAST, Cannabis Abuse Screening Test (both diagnosis and symptoms; Battistella et al., 2014).

dependence (see Table 2). The three investigations that examined treatment-seeking cannabis users, however, included mostly participants with comorbid psychopathologies and medication (Ashtari et al., 2011; Kumra et al., 2012; Yip et al., 2014). Only five studies were composed exclusively of individuals with a CUD diagnosis (Ashtari et al., 2011; Churchwell et al., 2010; Kumra et al., 2012; Tzilos et al., 2005; Yip et al., 2014), and four samples were composed of cannabis users with and without CUDs (Cousijn et al., 2012; McQueeney et al., 2011; Medina et al., 2009; Medina, Schweinsburg, Cohen-Zion, Nagel, & Tapert, 2007).

Thirteen investigations assessed cannabis abuse with a variety of instruments (see Table 2 and Figure 2), but only four reported the outcome of the diagnostic assessment. Seven studies assessed severity of cannabis abuse (Battistella et al., 2014; Cousijn et al., 2012; McQueeney et al., 2011; Medina et al., 2009; Medina, Nagel, Park, McQueeney, & Tapert, 2007; Medina et al., 2010; Medina, Schweinsburg, et al., 2007). Eleven studies examined cannabis dependence (see Figure 3) and seven studies the severity of dependence (see Figure 4; Cousijn et al., 2012; McQueeney et al., 2011; Medina et al., 2009, 2010; Medina, Nagel, et al., 2007; Medina, Schweinsburg, et al., 2007; Yip et al., 2014).

Cannabis Abstinence and Withdrawal

A total of six CUD samples were studied following prolonged abstinence from cannabinoids (>21 days, see Table 2). Most of the

other samples abstained from cannabis for approximately 12 to 3 h. Several studies measured cannabis withdrawal as a criterion of CUD ($n=5$; McQueeney et al., 2011; Medina et al., 2009, 2010; Medina, Nagel, et al., 2007; Medina, Schweinsburg, et al., 2007), but the severity of withdrawal was not reported.

Cannabis Use Disorders Compared to Controls

This section summarizes the findings of studies that compared gray matter morphology between CUD and control participants. We reviewed findings separately for the striatum, amygdala, hippocampus, PFC, and cerebellum, all regions in which an association with CUD was reported.

Striatum

Striatal gray matter morphology was examined in three studies that showed mixed findings. Yip et al. (2014) found a smaller volume of some (i.e., caudate), but not all, parts of the striatum in cannabis-dependent participants compared to controls. In contrast, Cousijn et al. (2012) found no differences in striatal volume in regular cannabis users (of which most endorsed a CUD diagnosis) compared to controls. Interestingly, Gilman et al. (2014) found larger gray matter density in the NAcc (but no significant volume differences) in nondependent regular cannabis users. It is

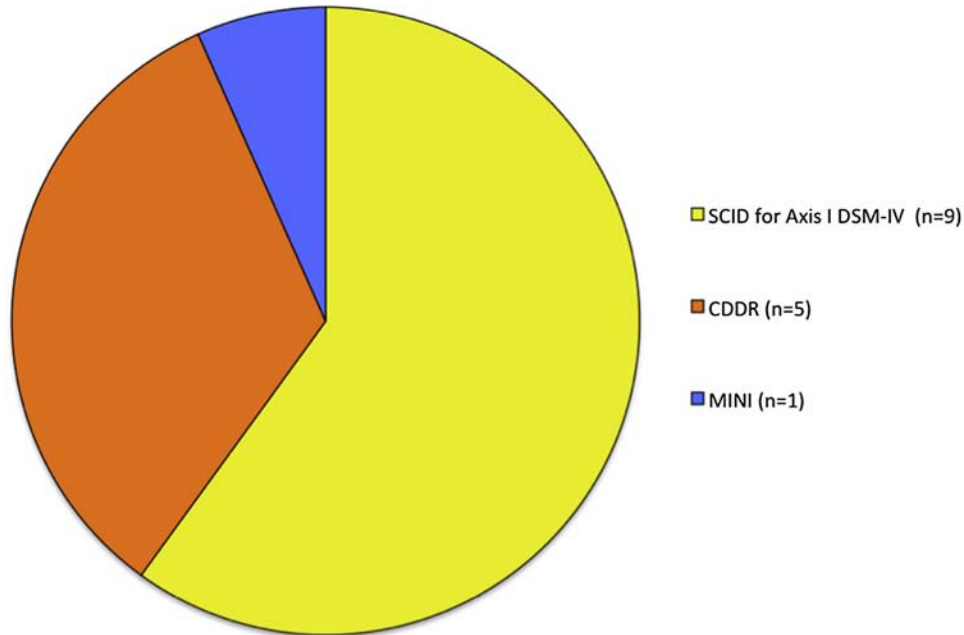
Diagnostic instruments, cannabis dependence

FIGURE 3 Summary of instruments employed to diagnose cannabis dependence. SCID, Structured Clinical Interview for Axis I DSM-IV Disorders (Ashtari et al., 2011; Churchwell et al., 2010; Gilman et al., 2014; McQueeney et al., 2011; Medina et al., 2009, 2010; Medina, Nagel, et al., 2007; Medina, Schweinsburg, et al., 2007; Yip et al., 2014); CDDR, Customary Drinking and Drug Use Record (McQueeney et al., 2011; Medina et al., 2009, 2010; Medina, Nagel, et al., 2007; Medina, Schweinsburg, et al., 2007); MINI, Mini International Neuropsychiatric Interview of the DSM (Cousijn et al., 2012).

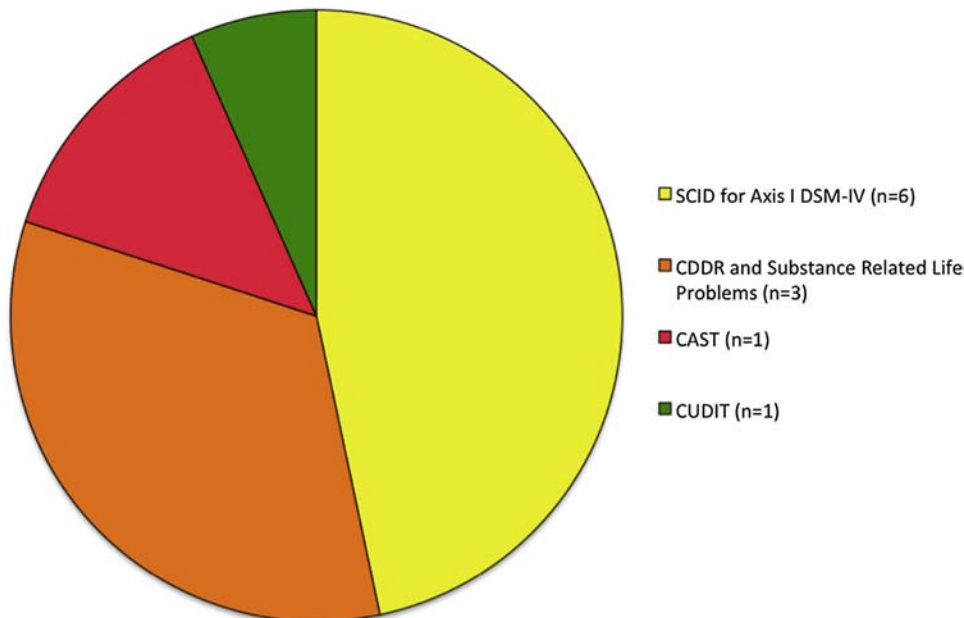
Instruments, cannabis dependence symptoms

FIGURE 4 Summary of instruments employed to measure symptoms of cannabis dependence. SCID, Structured Clinical Interview for Axis I DSM IV Disorders (Churchwell et al., 2010; Gilman et al., 2014; McQueeney et al., 2011; Medina et al., 2009, 2010; Medina, Nagel, et al., 2007); Substance-related life problems and CDDR, Customary Drinking and Drug Use Record (McQueeney et al., 2011; Medina et al., 2009, 2010; Medina, Nagel, et al., 2007); CAST, Comprehensive Assessment of Symptoms History screening (Yip et al., 2014); CUDIT, Cannabis Use Disorder Identification Test (Cousijn et al., 2012).

notable that the NAcc was affected in nondependent cannabis users (Gilman et al., 2014), whereas the dorsal striatum (caudate) was affected in dependent users (Yip et al., 2014). These findings are in line with the model of Koob and Volkow (2010), which postulates a transition from ventral striatum (e.g., NAcc) to dorsal striatum (e.g., caudate) as drug use becomes compulsive (Koob & Volkow, 2010). However, the paucity of neuroimaging studies investigating striatal morphology in dependent and nondependent cannabis users prevents drawing conclusions about this issue.

Amygdala

Four studies examined gray matter morphology of the amygdala in samples endorsing cannabis dependence (McQueeney et al., 2011), cannabis abuse (Yücel et al., 2008), mixed levels of problem severity (Cousijn et al., 2012), and no CUD (Gilman et al., 2014). These studies showed mixed findings, with smaller volumes in male cannabis abusers vs male controls (Yücel et al., 2008) and larger volumes in CUD females compared to control females and CUD males (McQueeney et al., 2011). Gilman et al.'s (2014) investigation of nondependent regular cannabis users found no volumetric reduction, but a significant shape alteration of the amygdala, suggesting subtle detrimental effects of regular cannabis use predating CUD onset.

Hippocampus

Five studies examined hippocampal gray matter morphology (Ashtari et al., 2011; Cousijn et al., 2012; Medina, Schweinsburg, et al., 2007; Tzilos et al., 2005; Yücel et al., 2008). While hippocampal volume reduction is the most consistently reported finding in regular cannabis users (Rocchetti et al., 2013), only two studies found reduced volume in chronic cannabis abusers and in dependent individuals in early remission (Ashtari et al., 2011; Yücel et al., 2008). Hippocampal alterations are probably related to neurotoxic effects of chronic cannabinoids exposure rather than specific to CUD (Ashtari et al., 2011; Cousijn et al., 2012).

Prefrontal Cortex

Three studies investigated PFC gray matter morphology and showed mixed results. Churchwell et al. (2010) found smaller PFC volumes in CUD versus control participants. Medina et al. (2009) replicated this finding in male CUD participants, but found an effect in the opposite direction in females with CUD, who showed larger PFC volumes compared to female controls. In contrast, Cousijn et al. (2012) observed no alteration in PFC regions (ACC and OFC) in participants with CUD. While all these studies investigated samples of young adults, the samples in which group effects were found were between 16 and 18 years of age (Churchwell et al., 2010; Medina et al., 2009), slightly younger than the 21- to 22-year-old CUD participants who showed no PFC alterations (Cousijn et al., 2012). Other investigations of cannabis users between 23 and 25 years of age (Battistella et al., 2014) and around 26 years (Mata et al., 2010) also found PFC alterations, but failed to report whether cannabis users endorsed a CUD diagnosis. While it is unclear if PFC alterations relate to either chronic cannabis exposure or CUD, these findings preliminarily suggest that adolescent- versus adult-onset CUD may more strongly affect

PFC morphology. The PFC plays a prominent role in cognitive control together with superior parietal brain regions. Interestingly, Kumra et al. (2012) showed smaller superior parietal cortex volumes in CUD, suggesting that impairments occur in cognitive control regions.

Cerebellum

Two studies investigated cerebellar gray matter and observed larger volumes in CUD versus controls (Cousijn et al., 2012; Medina et al., 2010), which is consistent with evidence in regular cannabis users (that did not report on CUD). Battistella et al. (2014) found larger cerebellar gray matter in regular versus occasional cannabis users, while Solowij et al., (2011) failed to observe differences in cerebellar gray matter (but found reduced white matter volume) between chronic cannabis users and controls. The cerebellum contains a high concentration of CB1 (Burns et al., 2007) and is not commonly associated with SUDs. Larger cerebellar gray matter volumes may therefore be specific to users of cannabis vs other substances. Reporting on diagnostic outcomes of CUD assessments in future studies will determine whether cerebellar gray matter alterations are specific to regular cannabis users either with or without a CUD.

Associations with Cannabis Use Disorder Severity

Three studies explored the linear association between symptoms of cannabis abuse/dependence and brain morphology (Cousijn et al., 2012; Medina, Nagel, et al., 2007; Medina, Schweinsburg, et al., 2007). Only one study investigated this in the amygdala, and although volume of this region did not differ between cannabis users and controls, smaller amygdala volumes were associated with higher levels of CUD-related problems (Cousijn et al., 2012). Regarding the hippocampus, one study observed that larger volumes were associated with higher levels of CUD-related problems (Medina, Schweinsburg, et al., 2007), but this effect was not replicated in another study (Cousijn et al., 2012). Striatal, PFC, and cerebellar morphology was not significantly associated with CUD-related problems (Cousijn et al., 2012; Medina et al., 2009). These findings require replication, but suggest that increases in CUD-related problems affect neuroanatomy.

Abstinence and Treatment

Several studies examined individuals with a CUD who were abstinent for more than 3 weeks (Ashtari et al., 2011; McQueeney et al., 2011; Medina et al., 2009; Medina, Nagel, et al., 2007; Yip et al., 2014). No systematic trend emerged across these investigations, as they examined different brain regions. Studies examining the hippocampus reported both reductions (Ashtari et al., 2011) and no differences in abstinent cannabis users versus controls (Medina et al., 2009). Other brain regions were investigated in single studies only, which demonstrated alterations in the caudate (Yip et al., 2014) and cerebellum (Medina et al., 2010), but not in the putamen (Yip et al., 2014), amygdala (McQueeney et al., 2011), and PFC (Medina et al., 2009). Notably, magnetic resonance imaging assessments were conducted prior to abstinence in one study

(Yip et al., 2014) but following prolonged abstinence in others (Ashtari et al., 2011; McQueeney et al., 2011; Medina et al., 2009). Thus, group differences may constitute preexisting vulnerabilities (Yip et al., 2014), subacute effects of cannabis use (Cousijn et al., 2012), or recovery after abstinence (Ashtari et al., 2011). For example, Ashtari et al. (2011) found reduced hippocampal but not amygdala volumes in 7-months-abstinent cannabis users. Thus, amygdala volume reductions, which were reported in current users (Yücel et al., 2008) and correlated with cannabis use-related problems (Cousijn et al., 2012), may recover following abstinence. In contrast, hippocampal volume reductions, the most consistently reported finding in regular cannabis users (Rocchetti et al., 2013), may persist after abstinence. Longitudinal studies are required to elucidate the neurobiological trajectories of change (and potentially recovery) after prolonged abstinence.

Patterns of neuroanatomical alterations associated with seeking treatment could not be noted, as different brain regions were examined by studies investigating treatment-seeking (Ashtari et al., 2011; Kumra et al., 2012; Yip et al., 2014) versus non-treatment-seeking cannabis users.

Gender Effects

A few studies examined gender effects and reported mixed findings. This is to no surprise given the predominance of small sample sizes and male dominance in the reviewed studies. However, two investigations reported group $\times$ gender effects, with larger brain volumes in females compared to males with a CUD (McQueeney et al., 2011; Medina et al., 2009). Medina et al. (2009) found larger PFC volumes in female cannabis users compared to female controls, while male cannabis users showed smaller volumes than male controls. Similarly, McQueeney et al. (2011) found larger amygdala volumes in female cannabis users compared to male cannabis users and female controls. Yet, two other studies did not replicate these effects (Cousijn et al., 2012; Gilman et al., 2014). No gender effect was reported on striatal (Cousijn et al., 2012; Gilman et al., 2014), PFC (Cousijn et al., 2012; Mata et al., 2010), medial temporal (Cousijn et al., 2012; Gilman et al., 2014), and superior parietal regions (Kumra et al., 2012). The scarcity of studies investigating gender effects contrast with strong preclinical evidence on the role of sex hormones in problematic cannabinoid consumption (Winsauer et al., 2011), warranting future investigations in larger CUD samples with a balanced male to female ratio.

DISCUSSION

This narrative review shows a lack of research and understanding of the neurobiological substrates underlying CUDs. The conducted studies often investigated relatively small samples of regular cannabis users with varying levels of CUD-related problems. Perhaps not surprisingly, these studies generally showed contradictory results that lack replication, hindering a proper and reliable integration of the findings to date. Yet, the reported significant associations between gray matter morphology and CUD are in line with contemporary addiction models and indicate structural alterations in different brain regions at different stages of CUD. Moreover, age of onset, gender, cumulative cannabis

consumption, abstinence duration, CUD-related problem severity, and gender may be important moderators of the relation between CUD and gray matter morphology. In this section, we summarize the associations between gray matter morphology and CUDs and then discuss the implications of these findings for furthering the current understanding of the neurobiology of CUDs. Moreover, we will discuss important issues and limitations that became evident from the reviewed literature and suggest how these could be addressed by future studies.

Summary of Regional Alterations Associated with Cannabis Use Disorder

There are emerging trends for gray matter abnormalities in CUD samples within the striatum, amygdala, hippocampus, PFC, and cerebellum. Consistent with theoretical models of a ventral-to-dorsal striatal shift as the SUD progresses (Koob & Volkow, 2010), cannabis users without a CUD showed an altered ventral striatum (Gilman et al., 2014), while cannabis users with a CUD exhibited alterations within the dorsal striatum (Yip et al., 2014). Gender may moderate the effect of CUD on the brain, as the amygdala and OFC were differentially affected in male and female individuals with a CUD (McQueeney et al., 2011; Medina et al., 2009; Yücel et al., 2008). Hippocampal alterations in CUD participants are less consistently reported than in regular cannabis users (Rocchetti et al., 2013), suggesting that alterations within this region are related to neurotoxic effects of chronic cannabinoid exposure and may not exacerbate with increasing CUD-related problems. Similarly, larger cerebellar volume may be shared across regular cannabis users with and without a CUD (Cousijn et al., 2012; Medina et al., 2010). In contrast, more severe CUD symptoms may aggravate structural alterations in the amygdala (Cousijn et al., 2012). Within the PFC, alterations were apparent in late adolescents but not in young adults, suggesting that CUD detrimentally affects PFC morphology in earlier stages of adolescent neurodevelopment when significant PFC remodeling occurs (Gogtay et al., 2004). These region-dependent trends suggest that different brain regions are relevant for different aspects and stages of CUD. This notion remains speculative given the paucity of studies. Notably, the lack of neuroimaging studies in CUD is in sharp contrast with the growing body of studies in regular cannabis users (Lorenzetti et al., 2014). 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 (van der Pol et al., 2013). Studies in regular cannabis users lack CUD assessments and thereby cannot identify potential CUD-specific effects, emphasizing the lack of knowledge about the neurobiological mechanisms underlying CUDs.

Cannabis Use Disorder and Comorbid Psychopathologies

To study the neurobiology underlying CUD, one should preferably compare regular cannabis users with a CUD in treatment with regular cannabis users with nonsignificant psychological problems. These samples may even be matched on the level of cannabis use (van der Pol et al., 2013). Unfortunately, only three

studies recruited participants from treatment services. While most investigations examined daily or almost daily cannabis users without comorbid diagnosable or subthreshold psychiatric problems, the three studies of treatment-seeking cannabis users examined samples that were composed mostly of participants with comorbid psychopathologies and medication (Ashtari et al., 2011; Kumra et al., 2012; Yip et al., 2014). This is consistent with epidemiological evidence of high comorbidity between CUD and other psychiatric disorders, including anxiety, depression, attention-deficit hyperactivity disorder, and psychotic disorders (Dorard, Berthoz, Phan, Corcos, & Bungener, 2008; Moore et al., 2007; Skinner, Conlon, Gibbons, & McDonald, 2011; van der Pol et al., 2013). To control for comorbid psychiatric symptoms, exclusion of participants with a diagnosed disorder other than CUD is common in the reviewed studies that investigated nonclinical samples. Findings in CUD without comorbid psychopathologies may not extend to both treatment- and non-treatment-seeking cannabis users, as a substantial part of them suffer from comorbid psychopathologies. Even though psychiatric comorbidity complicates the study of CUD, more investigations of ecologically valid clinical and subclinical groups are needed. To differentiate between abnormalities specific to CUD or general to multiple psychopathologies, studies could include clinical control groups matched on psychopathological symptoms other than CUD.

Limitations of Existing Studies and Recommendations for Future Studies

This review of structural neuroimaging studies highlights a number of limitations, including the lack of information about whether CUD was endorsed in the examined samples, the heterogeneous instruments used to assess CUD, the lack of studies in treatment-seeking cannabis users, the lack of longitudinal studies, and the small sample sizes with limited age ranges (mainly young adults and adolescents). First, most studies that screened for CUD in their samples did not report whether cannabis users endorsed a CUD diagnosis and did not examine the symptom severity. Thus, the literature on the neurobiology of regular cannabis users may be partly entrenched with CUD-related processes that do not occur in regular users who do not experience problems with their use. Moreover, the lack 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 an underestimation of the effects of CUD on brain morphology. As highlighted in the previous sections, the progress of addiction determines profound changes in brain functioning, independent of drug-specific neurotoxic effects, particularly within the striatum and PFC, with alterations shifting from the ventral to the dorsal portion of the striatum and from the medial to the lateral portion of the PFC (Koob & Volkow, 2010). 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, will help to understand the neurobiological mechanisms underlying CUDs. This may especially prove fruitful in the development of new intervention and treatment strategies that target the functioning of specific brain systems.

A variety of instruments were employed to assess diagnosis and severity of CUD, which limits the direct comparability of findings across studies. Standardized and validated measures of the severity of cannabis dependence are currently lacking, and this issue highlights the need to develop objective measures of CUD (van der Pol et al., 2013). Moreover, differences between the new DSM-V criteria for CUD and older versions of the DSM should be noted, as the former no longer distinguishes between cannabis abuse and dependence, introduces craving and withdrawal as diagnostic criteria, and describes three stages of CUD severity. In light of these issues, future studies could benefit from investigating the association between brain morphology and CUD symptom severity as reported in the DSM-V (American Psychiatric Association, 2013). The DSM-V criteria of cannabis dependence can thereby provide a more standardized instrument to measure severity of dependence.

Finally, an important step in understanding the neurobiology of CUD is to dissociate causal and consequential effects and to determine potential neurobiological trajectories of recovery. Only a few investigations examined CUD participants after prolonged abstinence and no longitudinal studies are currently missing. The reviewed preliminary evidence suggests that the amygdala may recover to normal levels, while the hippocampus shows persistent reductions despite cannabis use cessation. Future studies may elucidate the neurobiological trajectories of change (and potentially recovery) after prolonged cannabinoid abstinence by performing magnetic resonance examinations of cannabis users prior to and following abstinence treatment.

APPLICATIONS TO OTHER ADDICTIONS AND SUBSTANCE MISUSE

The neurobiology of CUD may overlap with that of other SUDs. Yet neuroimaging and neurocognitive behavioral studies in long-time regular cannabis users show relatively mild to even absent neurocognitive deficits. While it is tempting to conclude that neurobiological and neurocognitive effects of CUD are less severe than those of other SUDs, such conclusion cannot be drawn (yet) given the paucity of neuroimaging studies in cannabis users with CUD. Moreover, it is essential to note that the potential mild neurocognitive effects and low addictive potential of cannabis compared to other substances like cocaine and heroin do not imply that the problems an individual can experience from a CUD are less severe than those experienced from another SUD.

CONCLUDING KEY FACTS ON THE ASSOCIATION BETWEEN GRAY MATTER AND CANNABIS USE DISORDER

- Our review highlights an urgent need for a better understanding of the neurobiological correlates of CUD.
- CUD may exacerbate adverse neurobiological outcomes of regular cannabis use, affecting additional brain regions.
- The few significant associations between gray matter morphology and CUD are consistent with contemporary addiction models.
- Age of onset, gender, cumulative cannabis consumption, abstinence, and CUD-associated problems may be important moderators in the association between CUD and brain morphology.

- Studying the commonalities and differences between ecologically valid samples of regular cannabis users with and without a CUD will be an important next step to understanding the neurobiological mechanisms underlying CUD and developing new treatment strategies.

DEFINITION OF TERMS

Cannabis use disorder This refers to the problematic use of cannabis and includes harms such as loss of control over use, social problems in relation to use, pharmacological consequences (tolerance and withdrawal), and high-risk use.

Substance use disorder This refers to problematic use of substances, including cannabis, that have progressive detrimental effects that pervade all aspects of the individual's personal, social, and work life.

Cannabinoids These are the chemical compounds of cannabis, including over 480 natural compounds, which have a variety of properties. Only a minority of cannabinoids are psychoactive.

Δ⁹-Tetrahydrocannabinol This is the main psychoactive compound of cannabis and has been linked to the neurotoxic effects of cannabis on the central nervous system.

CB1 This refers to the cannabinoid type 1 receptor to which THC binds. CB1 receptors are located in the central nervous system, in presynaptic terminals. They are part of the endogenous cannabinoid system and have been described to mediate the effects of cannabis on brain and behavior.

Striatum This is an area of the brain implicated in processing reward. It is subdivided into a dorsal and a ventral portion, which mediate impulsive and compulsive behavior, respectively.

Prefrontal cortex This is a brain area involved in mediating cognitive control functions, including planning, decision-making, and conflict monitoring.

Hippocampus This is a region of the brain that mediates learning and memory.

Amygdala This is a brain area that mediates the regulation of emotion.

Diagnostic and Statistical Manual of Mental Disorders This manual is the standard used to classify psychopathologies by mental health professionals. It outlines diagnostic classifications, diagnostic criteria to endorse disorders, and their descriptions.

KEY FACTS OF THE STRIATUM

- The striatum is a deep-brain nucleus that links motivation to motor movements involved in the execution of simple motor tasks as well as more complex cognitive tasks, such as reward processing, decision-making, and social interactions.
- In medicine, the term “striatum” was initially used to refer to a variety of regions of the brain. The currently accepted definition of the term striatum has been used since 1941.
- The term “corpus striatum” originates from Latin and it means “striped mass” of gray and white matter.
- Gray matter regions of the striatum include the caudate nucleus and the putamen, which are separated by the white matter internal capsule and the NAcc.
- The dorsal striatum comprises the caudate and putamen, while the ventral striatum includes the NAcc and the ventromedial portions of the caudate and putamen.
- The main input regions of the striatum are the somatosensory and motor cortices, which project to the putamen; the PFC, which innervates the caudate; and the VTA, which projects to the NAcc.
- Drug and behavioral addictions affect the plasticity of the striatum. In recreational drug use and at the initial stages of addiction, impulsive reward seeking and the experience of pleasure are mediated by the ventral striatum. As addiction develops, habitual and compulsive use is mediated by the dorsal striatum.
- The striatum has also been implicated in mediating low levels of motivation in psychopathologies such as schizophrenia and depression.
- Alterations in the striatum are observed in neurodegenerative disorders such as Parkinson disease, characterized by degeneration of striatal dopaminergic innervations, and Huntington disease, which is accompanied by reduced striatal gray matter.

SUMMARY POINTS

- CUDs affect 13.1 million individuals worldwide and represent the most vulnerable portion of cannabis users.
- Neuroanatomical alterations may mediate the adverse outcome of CUD.
- This review summarizes findings from 16 neuroimaging studies of gray matter morphology in CUD.
- CUD-specific alterations emerged within the striatum, medial temporal lobe, PFC, and cerebellum.
- Age of onset, gender, cumulative cannabis consumption, abstinence, and CUD-associated problems may moderate the association between CUD and brain morphology.
- The paucity of conducted studies prevents drawing conclusions about CUD-specific alterations.
- Studying the commonalities and differences between cannabis users with and without a CUD is an important next step to understanding the neurobiological mechanisms underlying CUDs.

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