Review

The Role of Cannabinoids in Neuroanatomic Alterations in Cannabis Users

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ABSTRACT

The past few decades have seen a marked change in the composition of commonly smoked cannabis. These changes primarily involve an increase of the psychoactive compound Δ^9-tetrahydrocannabinol (THC) and a decrease of the potentially therapeutic compound cannabidiol (CBD). This altered composition of cannabis may be linked to persistent neuroanatomic alterations typically seen in regular cannabis users. In this review, we summarize recent findings from human structural neuroimaging investigations. We examine whether neuroanatomic alterations are 1) consistently observed in samples of regular cannabis users, particularly in cannabinoid receptor–high areas, which are vulnerable to the effects of high circulating levels of THC, and 2) associated either with greater levels of cannabis use (e.g., higher dosage, longer duration, and earlier age of onset) or with distinct cannabinoid compounds (i.e., THC and CBD). Across the 31 studies selected for inclusion in this review, neuroanatomic alterations emerged across regions that are high in cannabinoid receptors (i.e., hippocampus, prefrontal cortex, amygdala, cerebellum). Greater dose and earlier age of onset were associated with these alterations. Preliminary evidence shows that THC exacerbates, whereas CBD protects from, such harmful effects. Methodologic differences in the quantification of levels of cannabis use prevent accurate assessment of cannabis exposure and direct comparison of findings across studies. Consequently, the field lacks large "consortium-style" data sets that can be used to develop reliable neurobiological models of cannabis-related harm, recovery, and protection. To move the field forward, we encourage a coordinated approach and suggest the urgent development of consensus-based guidelines to accurately and comprehensively quantify cannabis use and exposure in human studies.

Keywords: Cannabidiol, Cannabinoids, Cannabis, CBD, Hippocampus, Prefrontal, THC

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Although cannabis has existed for thousands of years, the past few decades have seen a marked increase in the prevalence of highly potent cannabis strains [1]. These strains have a high proportion of the psychoactive constituent Δ^9-tetrahydrocannabinol (THC) [2], which exerts persistent adverse effects on cognition, mental health, and the brain [3,4]. In parallel, there are decreasing levels of other constituent cannabis compounds, such as cannabidiol (CBD), which has been touted as a potential therapeutic agent for conditions ranging from chronic pain and seizures to psychiatric symptoms [5–7]. These recent changes in the composition of "street" cannabis create a new and complex landscape for investigators endeavoring to understand the neurobiological harm and the therapeutic potential of cannabis products.

Specific cannabinoid compounds have distinct effects on mental health and brain function. The psychoactive and addictive properties of cannabis are primarily due to THC [8]. Increased availability of cannabis varieties that are high in THC (e.g., "skunk") have been consistently linked to accelerated onset of psychosis [9,10], increased cannabis-related hospital admissions [11], and increased anxiety symptoms and psychotic-like experiences [12–15]. Preclinical studies showed that THC is neurotoxic to brain areas rich in cannabinoid type

1 receptors, including the hippocampus [16–20], amygdala [20], striatum [21], and prefrontal cortex (PFC) [21–23]. In contrast, CBD has been found to have anxiolytic, antipsychotic, and therapeutic properties [24–27]. There is evidence suggesting that CBD is neuroprotective, mitigating the neurotoxic effects of THC [28–30].

The compounds THC and CBD have also been shown to have opposing effects on the functional activity and connectivity between brain regions that are high in cannabinoid receptors, such as the hippocampus, amygdala, striatum, cerebellum, and PFC [12–14,31–36]. These changes in brain function, documented using functional magnetic resonance imaging (MRI), may modulate the effects of THC on anxiety and psychotic-like experiences in humans [5,32,37]. Similar processes may underpin the protective effects of CBD on such experiences [5,6,27,32,37]. Participants pretreated with CBD do not experience the psychotogenic and anxiogenic effects of THC [12–14,32–37].

The recent changes in the relative composition of cannabinoids found within commonly available cannabis increase the potential for psychological and neurobiological harm in the current generation of cannabis users. However, the relative contribution of the two major compounds of cannabis (i.e.,

THC and CBD) to such damage is unclear (37). In this review, we summarize the current literature on neuroanatomic alterations reported in regular cannabis users, which includes nine additional studies relative to the most recent review on the topic, reflecting an increased focus on this field of research and warranting a need to integrate the most recent findings (38–46). We present a novel focus on the emerging evidence for differential roles of specific cannabinoids in neuroanatomic abnormalities (41,43,47,48). First, we provide an overview of findings and stratify them according to brain regions. Second, we examine the link between neuroanatomic alterations and levels of cannabis use, with a specific focus on the cannabinoid compounds THC and CBD. Finally, we identify major limitations of current research, particularly in relation to the measurement of cannabis use and cannabinoid compounds. These methodologic inadequacies limit the ability to develop evidence-based models of the effects of cannabis on neuroanatomy, whereby specific patterns (and types) of cannabis use are associated with discrete alterations in defined neural circuits. We suggest that a coordinated approach is required to move the field forward, and we offer preliminary guidelines to develop a standardized protocol to measure levels of cannabis use.

METHODS AND MATERIALS

We performed a PubMed search on April 7, 2015, using the keywords "Cannabis OR Marijuana" AND "MRI OR Computed Tomography OR Neuroimaging" and identified 492 articles. We screened these studies according to the following inclusion criteria: 1) use of structural neuroimaging techniques and 2) examination of regular cannabis users (as defined by each study protocol). We excluded nonempirical studies and samples including any other regular substance use or major psychopathologies. We included 32 studies in this review for further inspection (30,38–46,49–70), of which 23 were described previously (47). Nine additional studies conducted since 2012 were identified (38–46). The newest studies add to the literature five investigations of the PFC (38–42,44) and of the hippocampus (39,40,44–46); four investigations of the amygdala (39,41,44,46); three investigations of the striatum (39,41,43); two investigations of the insula (40,41); and single investigations of the parietal and occipital cortices (41), cerebellum (39), and pituitary gland (38).

RESULTS

Characteristics of Samples Included in Structural MRI Studies

Key characteristics of the reviewed samples are summarized in Table 1 and Figure 1. The total sample sizes included between 15 and 30 participants [range, 8 (63) to 62 (42) control subjects and 10 (70) to 57 (65) cannabis users]. Mean ages of cannabis users were between 17 years (49,54) and 40 years (38,45,50,58). The age distribution varied within samples, ranging from 16 years (49,54) to 60 years (38,45,50,58).

All samples of cannabis users smoked cannabis regularly, on a daily (30,39,40,42–44,49,51,62,68–70) or almost daily (38,41,45,50,53,55,58,61,63) basis. Some studies did not provide information on frequency of use but estimated the

number of smoking episodes (52,54,56,57,60,64) and joints (38,45,50,58,59,65–67). Most cannabis users started smoking between age 15 and 17 years. Participants in a few samples started smoking 1 or 2 years earlier [14 years (43,52)] or later [18–20 years (38,42,45,50,53,58,64)]. Duration of use varied greatly across all examined samples and ranged from 2 years (54,60) to 23 years (62,69) of regular use. Lifetime exposure to cannabis was computed in cumulative number of joints, cones (standard cannabis unit, with 1 joint = 3 cones, 1 g = 12 cones; for other conversions, see guidelines from the National Cannabis Prevention and Information Centre at https://ncpic.org.au/media/1593/timeline-followback.pdf) (red triangles in Figure 2), or smoking episodes (blue squares in Figure 2), which was available for all but a few studies (39,43,64,66,67,69,70).

Lifetime episodes of cannabis use ranged from 402 (60) to 5625 (42). Lifetime cumulative cannabis dosage (dosage × smoking days × duration of regular use) ranged from 5322 cones (30) to 68,000 cones (68). Most studies measured cannabinoid compounds, with three exceptions (39,55,62). In 20 studies, urinalysis was used to detect cannabinoid compounds. Eight studies reported the levels of cannabinoid metabolites. Mean values for 11-nor-9-carboxy-THC (THC-COOH) (green circles in Figure 2) were reported from toxicology analyses of urine samples in eight studies (38,40,45,49,50,54,58) and analyses of hair samples in one study (30). In 11 studies, positive [three studies (44,53,63,64)] or negative [eight studies (51,56,57,59–61,65)] returns were reported from toxicologic analysis of urine samples without quantification.

The reviewed studies used various specimens to detect cannabinoids or their metabolites, including urine samples in 19 studies (30,38,40–43,45,49,50,52,54,56–60,63,64,71), oral fluid (40) and blood samples (40) in single studies, and hair in 2 studies (30,44), only one of which reported the outcome of the assessment (30) (Table 1). Some studies used several specimens [i.e., hair and urine (30,44), blood and oral fluid (40)]. Breathalyzers were used in five studies to screen for acute intoxication (52,56,57,59,60). Several studies controlled for the confounding effects of alcohol (n = 18) and tobacco use (n = 13) (Table 1) by covarying for their influence in group comparisons or reanalyzing the data after excluding participants with concurrent alcohol and tobacco use.

Neuroanatomic Alterations in Regular Cannabis Users Relative to Control Subjects

Neuroanatomic alterations were reported in several brain regions (Table 2 and Figure 3A). Abnormalities in cannabis users, relative to control subjects, emerged most consistently in the hippocampus [seven studies (30,40,45,51,58,63)]. Several studies reported alterations in the volume (i.e., sum of all voxels that are included within the boundaries of the region of interest) and gray matter density (i.e., amounts of gray or white matter concentration in each voxel) within the amygdala and striatum (41,43,52,58,63), PFC (40–42,49,55,70), parietal cortex (41,49,55), insular cortex (40,41,49), and cerebellum (50,53,56). Single studies reported alterations within the fusiform gyrus (63), temporal pole, superior temporal gyrus, and occipital cortex (41).

Table 1. Sample Characteristics of Structural Magnetic Resonance Imaging Studies of Regular Cannabis Users

Study	Sample N (Males) CB	HC	Age (Years) CB	HC	Duration (Years)	Age of Onset (Years)[a]	Dosage[b]	Frequency[c]	Specimens	Alcohol CB	Alcohol HC	Control for	Tobacco CB	Tobacco HC	Control for
Lorenzetti et al., 2015 (38)	15 (15)	16 (16)	40 ± 9	36 ± 10	20 ± 7	20 ± 7	Ep./life.: 62,000; Cone/past 1 year: 77,816 ± 66,542; Cone/life.: 186,184 ± 210,022	Days/month 28 ± 5	Urine	SD/week: 10 ± 6	SD/week: 7 ± 5	Yes (cov.)	Cig./day: 17 ± 9	Cig./day: 8 ± 9	Yes (cov.)
Weiland et al., 2015 (39)	29 (16)	29 (16)	28 ± 7	27 ± 7	—	—	—	Daily	—	SD/month 7 ± 3; AUDIT 12 ± 7	SD/month 7 ± 3; AUDIT 12 ± 8	Yes (cov.)	Cig./day 11 ± 8	Cig./day 8 ± 8	Yes (cov.)
Battistella et al., 2014 (40)[d]	Reg.: 25 (0)	—	23 ± 2	—	7 ± 3	16 ± 2	—	Occ./month 63 ± 23	Urine, blood, and oral fluid	SD/week 10 ± 5	—	Yes (regr.)	—	—	—
	Occ.: 22 (0)		25 ± 2		8 ± 3	17 ± 2		Occ./month 4±2		SD/week 5 ± 2					
Filbey et al., 2014 (42)	CB, tobacco, alcohol: 48 (33)	62 (39)	28 ± 8	30 ± 8	10 ± 8	18 ± 3	Occ./week: 11 ± 1; Ep./life.[e]: 5,720	Almost daily	—	n = 21 drinkers	—	Yes (excl. users)	n = 21 smokers	—	Yes (excl. users)
	CB only 27 (17)		28 ± 9		9 ± 9	19 ± 3	Occ./week: 11 ± 1; Ep./life.[e]: 5,148			No drinkers			No smokers	No smokers	
Gilman et al., 2014 (41)	20 (9)	20 (9)	21 ± 2	21 ± 2	6 ± 3	17 ± 2	Joints/week: 11 ± 10; Life. cone[e]: 10,296	4 ± 2	Urine	SD/week 5 ± 5; AUDIT 6 ± 2	SD/week 3 ± 2; AUDIT 3 ± 2	Yes (cov.)	n = 7 occ.; n = 1 daily	No smokers	Yes (cov.)
Yip et al., 2014 (43)[f]	Abst. 21 days: 13	20 (0)	27 ± 2	29 ± 2	14 ± 3	13 ± 1	Ep./life.[e]: 2,688	Days/month 16 ± 3	Urine	Days/month 4 ± 2; n = 1 abuse; n = 4 past use disorder	—	No	n = 8 smokers	n = 2 smokers	No
	Current: 7				9 ± 2	14 ± 1	Ep./life.[e]: 3,840	Days/month 20 ± 4		Days/month 3 ± 1; n = 0 abuse; n = 4 past use disorder			n = 7 smokers		
Batalla et al., 2013 (44)	29 (29)	28 (28)	21 ± 2	22 ± 3	6 ± 2	15 ± 1	Joints/day: 3 ± 2; Joints/life.: 5,203 ± 4,192; Cone/life.[e]: 15,609 ± 12,576	Daily	Hair, urine	SD/week: 5 ± 4; Age onset: 16 ± 2; duration years: 6 ± 2	SD/week: 3 ± 3; Age onset: 16 ± 2; duration years: 6 ± 3	No	n = 27 smokers; Cig./day: 6 ± 5	n = 9 smokers; Cig./day: 2 ± 6	No
Solowij et al., 2013 (45)	15 (15)	16 (16)	40 ± 9	36 ± 10	20 ± 7	20 ± 7	Ep./life.: 62,000; Cone/past 1 year: 77,816 ± 66,542; Cone/life.: 186,184 ± 210,022	Days/month 28 ± 5	Urine	SD/week: 10 ± 6	SD/week: 7 ± 5	Yes (cov.)	Cig./day: 17 ± 9	Cig./day: 8 ± 9	Yes (cov.)
Schacht et al., 2012 (46)	37 (14)	37 (14)	28 ± 8	27 ± 8	10 ± 9	18 ± 3	—	6 ± 1 days/week	—	Days/month: 7 ± 7; SD/drinking day: 3 ± 2	n = 5 smokers	Yes (cov.)	Days/month: 3 ± 4; SD/drinking day: 2 ± 1	No smokers	Yes (cov.)
McQueeny et al., 2011 (52)	35 (27)	47 (36)	18 ± 1	18 ± 1	3; Abst. days: 28	14	Ep./life.: 446	12 ep./week; 10 hits/ep.	Urine, Breathalyzer	Ep./life.: 24 ± 44	Ep./life.: 212 ± 175	Yes (cov.)	FTND: 0 ± 0	FTND: 0.2 ± .4	Yes (cov.)
Cousijn et al., 2012 (53)	33 (12)	42 (16)	21 ± 2	22 ± 2	3 ± 2	19 ± 2	Grams/week: 3 ± 2; Joints/life.: 1580 ± 1425; Cone/life.[e]: 4740 ± 4725	5 ± 2 days/week	Urine	AUDIT 6 ± 3	AUDIT 5 ± 3	Yes (regr.)	FTND: 3 ± 2; Cig./day: 7 ± 7; Duration: 4 ± 4 years	FTND: 1 ± 1; Cig./day: 1 ± 4; Duration: 1 ± 2 years	Yes (cov.)

Cannabinoid Compounds and Neuroanatomy

Table 1. Continued

Study	Sample N (Males) CB	HC	Age (Years) CB	HC	Cannabis Duration (Years)	Age of Onset (Years)[a]	Dosage[b]	Frequency[c]	Specimens	Alcohol CB	HC	Control for	Tobacco CB	HC	Control for
Lopez-Larson et al., 2011 (49)	18 (16)	18 (16)	17 ± 1	17 ± 8	Reg. use: 19 ± 1; Heavier use (months): 19 ± 14	16 ± 1	Ep./week: 10 ± 8; Ep./life.: 1346 ± 1372; THC ng/mL: 455 ± 352	Daily	Urine	n = 3 drinks > once/week	—	No	Occ./week: 10 ± 4; Occ./life.: 1,346 ± 1,371	—	No
Solowij et al., 2011 (50)	15 (15)	16 (16)	40 ± 9	36 ± 10	20 ± 7	20 ± 5	Cone/month: 636 ± 565; cone past 10 years: 77,816 ± 66,542	28 ± 5	Urine	SD/week: 10 ± 6	SD/week: 7 ± 5	Yes (cov.)	Cig./day: 17 ± 9	Cig./day: 8 ± 9	Yes (cov.)
Ashtari et al., 2011 (51)	14 (14)	14 (14)	19 ± 0.8	19 ± 1	5 ± 2; Abst. months: 7 ± 4	13 ± 2	Daily joints: 6 ± 3; Joints/life.: 11,220; Cone/life.[e]: 33,660	Daily	—	n = 5 abuse	Ep./life.: <5	No	n = 8 abuse/ dependence	Ep./life.: <5	No
Churchwell et al., 2010 (54)	18 (16)	18 (12)	17 ± 1	17 ± 1	2[e]	First try: 15 ± 0.3; Reg.: 16 ± 0.2	Ep./life.: 1353 ± 323; Dose THC ng/mL: 429 ± 85	Ep./week: 9 ± 2	Hair, urine	n = 2 abuse	—	No	n = 4 current use	—	No
Demirakca et al., 2010 2011 (30)	11 (11)	13 (13)	22 ± 2	23 ± 2	5	16 ± 2	Daily THC grams: 0.3; Cone/life.[e]: 5322	Daily	Urine	Drinks/day = 1.5	Drinks/day = 0.3	Yes (cov.)	n = 6 smokers	n = 1 smoker	Yes (cov.)
Mata et al., 2010 (55)	30 (23)	44 (25)	26 ± 5	26 ± 6	8 ± 9	17 ± 4	Cone/week: 27 ± 21; Cone/life.: 11,619 ± 9387	Almost daily	—	n = 23 drinkers	n = 23 drinkers	Yes (cov.)	n = 25 smokers	n = 17 smokers	Yes (cov.)
Medina et al., 2010 (56)	16 (12)	16 (10)	18 ± 1	18 ± 1	3±2; Abst. days: 107 ± 33	15[e]	Ep./life.: 476 ± 269	—	Urine, Breathalyzer	Ep./life.: 195 ± 137	Ep./life.: 23 ± 47	Yes (regr.)	Cig./month: 29 ± 74	Cig./month: 5 ± 20	No
Medina et al., 2009 (57)	16 (12)	16 (10)	18 ± 1	18 ± 1	3 ± 2; Abst. days: 107 ± 33	15[e]	Ep./life.: 476 ± 269	—	Urine, Breathalyzer	Ep./life.: 230 ± 128	Ep./life.: 25 ± 51	Yes (cov.)	Ep./life.: <25	Ep./life.: <5	No
Yücel et al., 2008 (58)	15 (15)	16 (16)	40 ± 9	36 ± 10	20 ± 7	20 ± 7	Ep./life.: 62,000; Cone/ past 1 year: 77,816 ± 66,542; Cone/life.: 186,184 ± 210,022	Days/month 28 ± 5	Urine	SD/week: 10 ± 6	SD/week: 7 ± 5	Yes (regr.)	Cig./day: 17 ± 9	Cig./day: 8 ± 9	Yes (regr.)
Medina et al., 2007 (60)	26 (19)	21 (14)	18 ± 1	18 ± 1	2 years[e]	15[e]	Ep./life.: 402 ± 260	Ep./month: 14 ± 11	Urine, Breathalyzer	Ep./life.: 152 ± 185	Ep./life.: 8 ± 16	Yes (cov.)	n = 9 smoked past month; Cig./day: 3 ± 3	n = 1 smoked past month; Cig./day: 1	No
Medina et al., 2007 (59)	16 (12)	16 (11)	18 ± 1	18 ± 1	3 ± 2; Abst. days: 28	15[e]	Ep./life.: 476 ± 269	—	Urine, Breathalyzer	Ep./life.: 230 ± 128	Ep./life.: 25 ± 51	Yes (regr.)	Ep./life.: <25	Ep./life.: <5	No
Jager et al., 2007 (61)[g]	20 (13)	20 (13)	25 ± 5	24 ± 4	8 ± 5	16[e]	Joints/life. (median): 1900; Joints past 1 year (median): 333	Almost daily	—	SD/week: 10	SD/week: 6	Yes (cov.)	Cig./week: 10	Cig./week: 0	Yes (cov.)
Tzilos et al., 2005 (62)	22 (16)	26 (19)	38 ± 6	30 ± 9	Reg.: 23 ± 6; Daily: 19 ± 8	16 ± 4	Ep./life.: 20,140 ± 13,866	Daily	—	Drinks/life.: 6,524 ± 5,934	—	No	Life. cig. packs: 2,727 ± 2,981	—	No
Matochik et al., 2005 (63)	11 (11)	8 (8)	30 ± 5	25 ± 5	8 ± 6; Abst. days: 20	16 ± 3	Joints/week: 35 ± 18; Cone/life.[e]: 40,599	Almost daily	Urine	SD/week: 2 ± 2	SD/week: 1 ± 2	No	—	—	No
Block et al., 2000 (64)	18 (8)	13 (6)	22 ± 1	23 ± 1	4 ± 0.4	18[e]	—	Ep./week: 18 ± 2	Urine	Drinking days, past month & 2 years: 6 ± 1	Drinking days, past month 4 ± 1 & and past 2 years: 3 ± 1	No	—	—	No

Table 1. Continued

Study	Sample N (Males) CB	HC	Age (Years) CB	HC	Cannabis Duration (Years)	Age of Onset (Years)[a]	Dosage[b]	Frequency[c]	Specimens	Alcohol CB	HC	Control for	Tobacco CB	HC	Control for
Wilson et al., 2000 (65)	57 (25); CB onset: early 16 (13), late 9 (19)	—	31 ± 7	—	R = 11–26; Early onset: 15 ± 6; Late onset: 14 ± 7	17 ± 4; Early onset: ≤17; late onset: >17	Joints/year; Early onset: 194 ± 169; Late onset: 164 ± 387	—	—	n = 48 drinkers; n = 2 former drinkers	—	Yes (cov.)	n = 27 smokers; n = 3 former smokers	—	No
Hannerz and Hindmarsh, 1983 (66)	12 (8)	12 (8)	26	26	10	—	—	—	—	—	—	—	—	—	—
Kuehnle et al., 1977 (67)	19 (19)	19 (19)	24	—	Inward study: 5 days abst.; 21 days CB use; 5 abst. days	—	—	Outward monthly joints: 35; Inward study, total joints: 111	—	—	—	—	—	—	—
Co et al., 1977 (68)	12 (12)	34 (34)	24	26	7	Occ.: 16; Reg.: 17	—	Joints/day: 9	—	—	—	—	—	—	—
Stefanis, 1976 (69)	47 (47)	40 (40)	40	42	23	—	—	Daily	—	—	—	—	—	—	—
Campbell et al., 1971 (70)	10 (10)	13 (7)	23	20	7	16	—	Daily	—	—	—	—	—	—	—

Values for all measures are mean (SD).

abst., abstinence; AUDIT, Acohol Use Disorder Identification Test; CB, cannabis users or cannabis; cig., cigarettes; cone, standardized cannabis unit; cov., covariate; ep., episodes; excl. users, excluded users with comorbid alcohol or tobacco use (or both); FTND, Fagerström Test for Nicotine Dependence scores; HC, healthy non–cannabis using control subjects; life., lifetime; occ., occasional use; past 1 year, over the past 12 months; R, range; reg., regular cannabis use; regr., regressor; SD, standard deviation; THC, Δ9-tetrahydrocannabinol.

[a]Age of cannabis use initiation (occasional, regular, or heavy).

[b]Measures of cannabis dosage (smoking episodes, cones, joints, grams).

[c]Measures of cannabis use frequency (daily, weekly, monthly).

[d]For Battistella et al. (40), median and median absolute deviation values are provided.

[e]Estimated values based on published data.

[f]For Yip et al. (43), mean and SE values are provided.

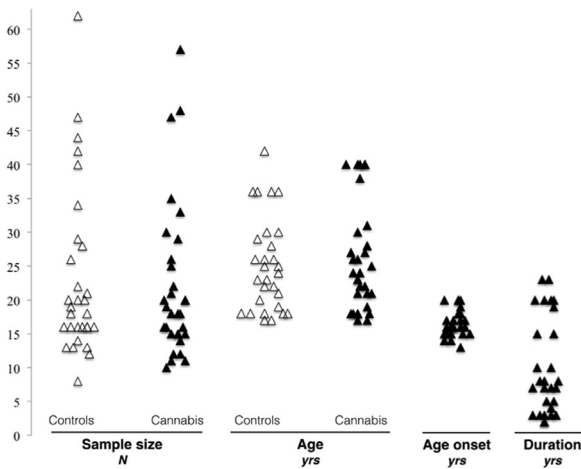[g]For Jager et al. (61), mean values are provided.

Figure 1. Summary of sample size, mean age, and mean cannabis use characteristics of the samples included in structural magnetic resonance imaging studies of cannabis users.

Overall, neuroanatomical alterations included most consistently 1) volumetric reductions in all regions, with the exception of the cerebellum and striatum, where larger volumes were also observed (41,50,53); 2) higher gray matter density in most regions (amygdala, PFC, parietal cortex, striatum), with the exception of one study that found lower prefrontal gray matter density in cannabis users relative to control subjects (41)—this exception may result from noise or reflect a true change demonstrating complex effects of cannabis on gray matter density; 3) altered shape, sulcal-gyral anatomy; and 4) cortical thickness (49). There is substantial overlap between the location of the neuroanatomic alterations in cannabis users (blue heat map, Figure 3A) and the location of high-density concentration of cannabinoid type 1 receptors (green heat map, Figure 3B) (31).

Most studies found abnormalities within the hippocampus, which has a very high cannabinoid receptor density relative to other brain regions [i.e., 1680 binding sites across all hippocampal subregions (31)]. Neuroanatomic abnormalities also

were found in prefrontal regions with very high densities of cannabinoid receptors [i.e., 627 and 518 binding sites within the lateral PFC and anterior cingulate cortex, respectively (31)]. Also, the amygdala and cerebellum, brain regions that show consistent abnormalities, have a high density of cannabinoid receptors [i.e., 102 and 137 binding sites, respectively (31)]. There appears to be an intriguing link between the concentration of cannabinoid receptor density in the brain and the consistency with which studies detect abnormal neuroanatomy in regular cannabis users.

Associations With Levels of Cannabis Use

The link between neuroanatomy and cannabis use levels was examined in 21 studies (Figure 4) (30,38–42,44,45,49–55, 57,58,62–65). Cannabis dosage was most consistently associated with the neuroanatomy of the hippocampus (30,51, 53,58) and PFC (44,49,57) and less consistently with the neuroanatomy of the amygdala, striatum (41), parahippocampal gyrus, insula, and temporal pole (40). Age of onset was most consistently associated with prefrontal neuroanatomy (49,54) and less consistently with the neuroanatomy of the parahippocampal gyrus, temporal cortex (40), and global brain measures (49). Duration of regular use was associated with the neuroanatomy of the PFC (57) and hippocampus (63) but not with the neuroanatomy of the amygdala (51), parahippocampal gyrus (40,44,63), cerebellum (44,52), and striatum (41). Most studies did not examine the association between cannabis use measures and neuroanatomy (Figure 4).

Associations Between Quantified Cannabinoid Levels and Neuroanatomy

Five studies examined the link between quantified cannabinoid levels and the neuroanatomy of the hippocampus (30,45,58), PFC (38,49), and amygdala (58) as well as the cerebellum in a sixth additional study [cited by Lorenzetti *et al.* (48)]. Four studies found significant associations (30,49).

Demirakca *et al.* (30) found a significant association between higher ratio of THC/CBD (but not THC, measured as ng/mg hair, mean .31 ng/mg, SD .2 ng/mg) and smaller
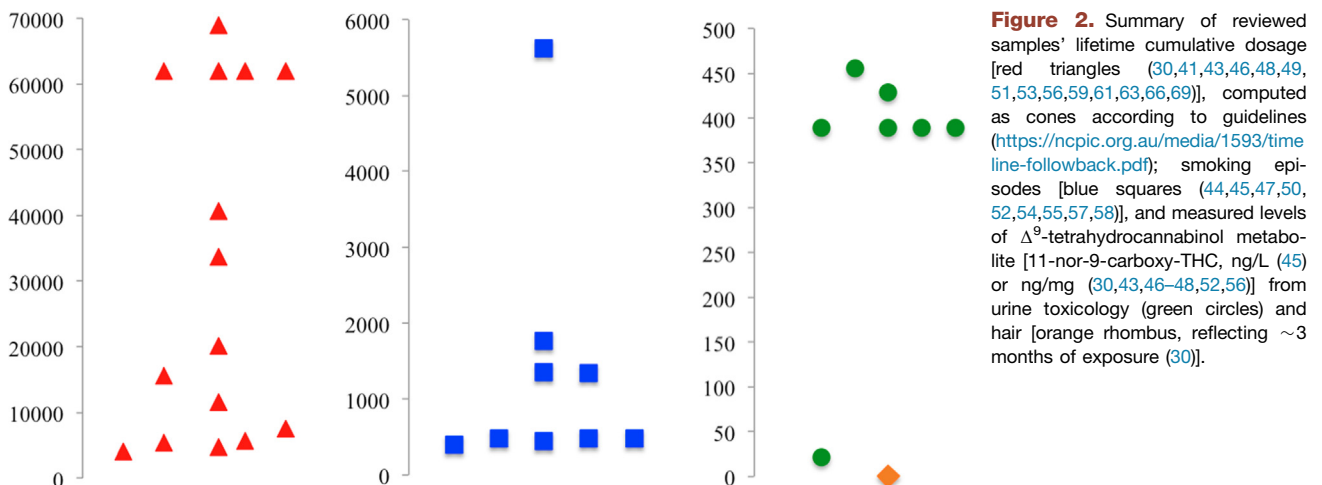

Figure 2. Summary of reviewed samples' lifetime cumulative dosage [red triangles (30,41,43,46,48,49, 51,53,56,59,61,63,66,69)], computed as cones according to guidelines (https://ncpic.org.au/media/1593/time line-followback.pdf); smoking episodes [blue squares (44,45,47,50, 52,54,55,57,58)], and measured levels of Δ^9-tetrahydrocannabinol metabolite [11-nor-9-carboxy-THC, ng/L (45) or ng/mg (30,43,46–48,52,56)] from urine toxicology (green circles) and hair [orange rhombus, reflecting ~3 months of exposure (30)].

Table 2. Neuroanatomical Alterations in Regular Cannabis Users by Brain Region

Brain Region/Study	Volume		Cohen's d^a	Gray Matter Density	Gyrification	Thickness	Shape
		% Change					
Hippocampus							
Battistella et al., 2014 (40)	↓	NA	>1	—	—	—	—
Solowij et al., 2013 (45)	—	NA	NA	—	—	—	Altered
Schacht et al., 2012 (46)	↓	−6%	0.7	—	—	—	—
Demirakca et al., 2011 (30)	↓	NA	—	—	—	—	—
Ashtari et al., 2011 (51)	↓	−13%	1.3	—	—	—	—
Yücel et al., 2008 (58)	↓	−12%	1.2	—	—	—	—
Matochik et al., 2005 (63)	↓	NA	NA	—	—	—	—
Amygdala							
Gilman et al., 2014 (41)	—	NA	NA	↑	—	—	Altered
Yücel et al., 2008 (58)	↓	−7%	0.9	—	—	—	—
Schacht et al., 2012 (46)	↓	−5%	0.5	—	—	—	—
Striatum/Thalamus							
Accumbens							
Gilman et al., 2014 (41)	↑	NA	NA	↑	—	—	Altered
Caudate							
Yip et al., 2014 (43)	↓	NA	NA	—	—	—	—
Thalamus							
Matochik et al., 2005 (63)	—	NA	NA	↑	—	—	—
Prefrontal Cortex							
OFC							
Filbey et al., 2014 (42)	↓	NA	NA	—	—	—	—
Battistella et al., 2014 (40)	↓	NA	NA	—	—	—	—
Medial frontal gyrus							
Gilman et al., 2014 (41)	—	NA	NA	↑ ↓	—	—	—
DLPFC, frontal pole							
Gilman et al., 2014 (41)	—	NA	NA	↓	—	—	—
PFC							
Mata et al., 2010 (55)	—	NA	NA	—	Altered	—	—
Campbell et al., 1971 (70)	—	NA	NA	—	Altered	—	—
Caudal middle, superior frontal							
Lopez-Larson et al., 2011 (49)	—	NA	NA	—	—	↓	—
Parietal Cortex							
Precuneus, postcentral							
Gilman et al., 2014 (41)	—	NA	NA	↑	—	—	—
Parietal, paracentral							
Matochik et al., 2005 (63)	—	NA	NA	↑	—	—	—
Inferior parietal, lingual, paracentral gyri							
Lopez-Larson et al., 2011 (49)	—	NA	NA	—	Altered	↓	—
Parietal							
Mata et al., 2010 (55)	—	NA	NA	—	Flatter sulci	—	—
Insula							
Gilman et al., 2014 (41)	—	NA	NA	↑	—	—	—
Battistella et al., 2014 (40)	↓	NA	NA	NA	—	—	—
Lopez et al., 2011 (49)	—	NA	NA	—	—	↓	—
Cerebellum							
Medina et al., 2010 (56)	↓	+7%	0.7	—	—	—	—
Solowij et al., 2011 (50)	↑	−27%	−1.6	—	—	—	—
Cousijn et al., 2012 (53)	↑	+20%	0.6	—	—	—	—

DLPFC, dorsolateral prefrontal cortex; NA, not applicable; OFC, orbitofrontal cortex; PFC, prefrontal cortex; ↑, cannabis users > control subjects; ↓, cannabis users < control subjects; —, not measured or lack of significant difference between cannabis users and control subjects.
^{a}Cohen's d, measure of effect size, with medium effect size ranging between $d = .5$ and $.8$ and large effect size $d > .9$.
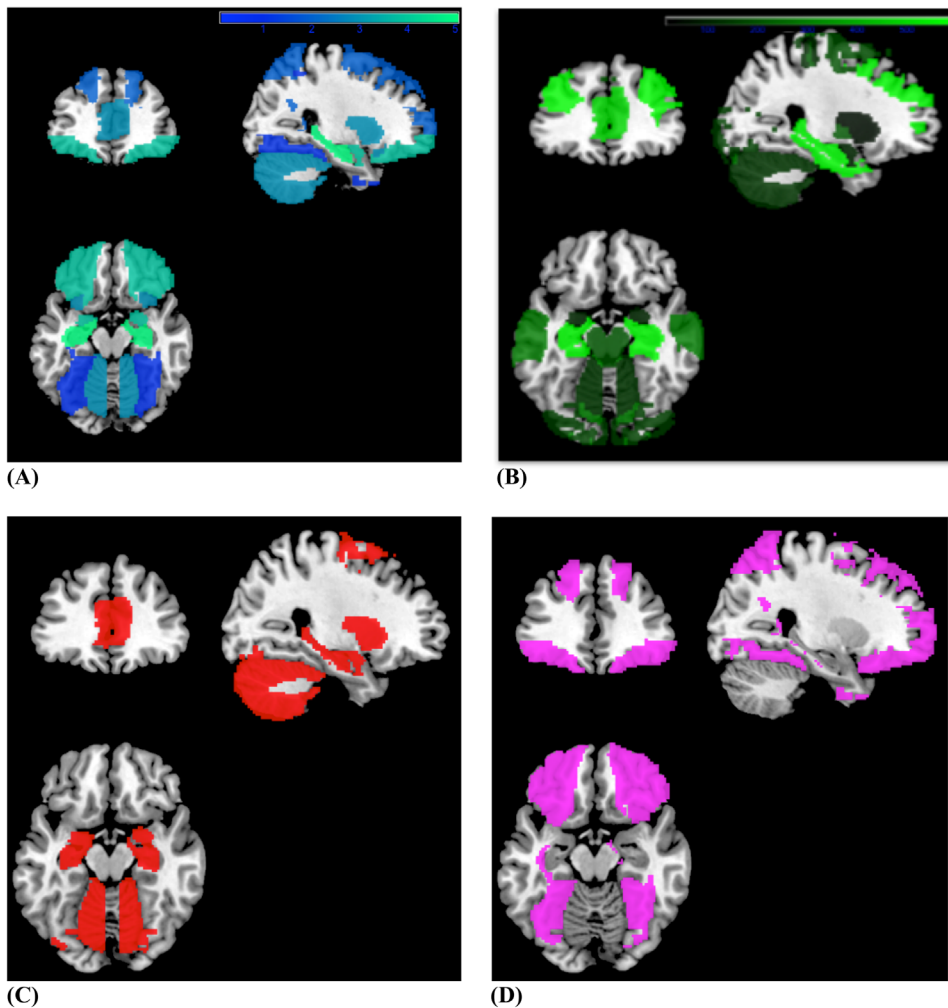
Figure 3. Weighted color maps. **(A)** Neuroanatomical alterations in cannabis users (blue-green), relative to control subjects (two to six studies). **(B)** Brain map with regional distribution of cannabinoid receptor density [dark-light green; range, 40–1680 density of receptor binding sites, measured via autoradiographic techniques (3)]. Lighter colors indicate evidence from more studies and greater density of receptors. **(C)** Binary map (red) illustrates overlap between **(A)** and **(B)**, including regions high in cannabinoid receptors that also show neuroanatomical alterations. **(D)** Binary map (violet) illustrates nonoverlap between **(A)** and **(B)**, including areas that showed neuroanatomic alterations and are low in cannabinoid receptors.

right hippocampal volumes and bilateral hippocampal gray matter concentration. A similar finding was reported in a separate sample of cannabis users with reduced hippocampal volume relative to controls (72); a subgroup of users with high levels of THC (and no detectable levels of CBD) in hair showed more marked reductions relative to control subjects than the other users, who had detectable levels of THC and CBD (72).

Two studies examined the association between prefrontal neuroanatomy and urinary THC metabolite levels (38,49), with one finding being a significant association between higher levels of THC-COOH (mean 455 mg/mL, SD 352 mg/mL) and the thickness of prefrontal (and parietal) cortices (49). In light of findings suggesting a role for THC metabolites in neuroanatomic alterations, N. Solowij, Ph.D., et al. (personal communication, April 2015) re-examined a data set on cerebellar neuroanatomy (50). They found that higher levels of THC-COOH in urine measured the night before (Spearman $\rho = -.577$, $p = .049$) and on the day of the MRI scan (Spearman $\rho = -.790$, $p = .002$) (Figure 5, left plot) were associated with reduced cerebellar gray matter in cannabis users. The latter relationship was strengthened with the removal of three

cannabis users with very high levels of urinary cannabinoid metabolites (Spearman $\rho = -.87$, $p = .002$) (Figure 5, right plot).

Only one study examined the link between CBD and neuroanatomy in cannabis users (30). The CBD levels (ng/mg hair, mean .13 ng/mg, SD .12 ng/mg) were associated with higher hippocampal gray matter concentration (but not volume). Similarly, we recently found that cannabis users with high levels of CBD showed no hippocampal volume abnormalities [i.e., were comparable to control subjects (72)]. In contrast, the whole group of cannabis users, particularly users with high THC and no detectable levels of CBD, showed significant hippocampal reductions relative to control subjects (72).

DISCUSSION

The reviewed literature demonstrates that regular exposure to cannabis is associated with neuroanatomic alterations in several brain regions, most consistently within the hippocampus (reduced volumes and gray matter density, altered shape), followed by the amygdala and striatum, orbitofrontal
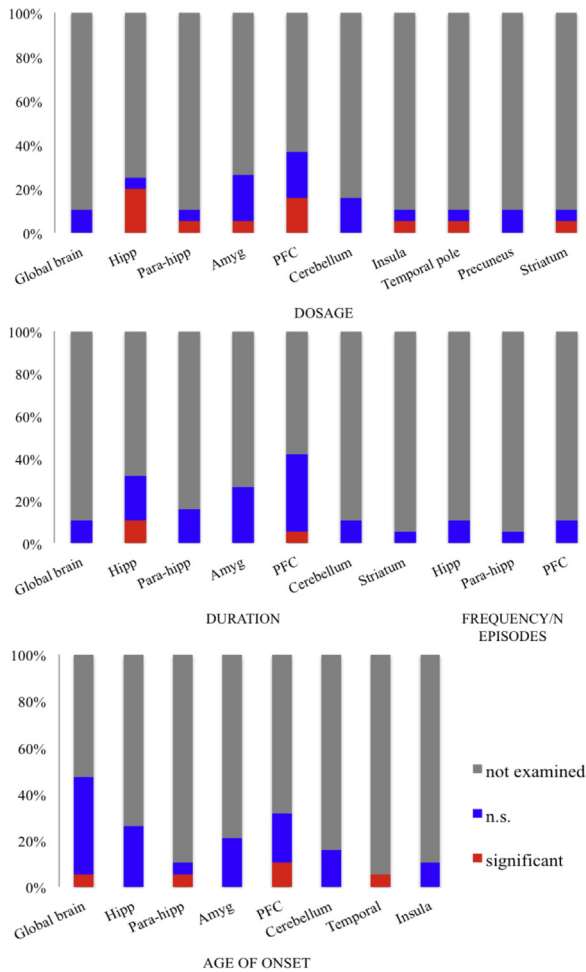
Figure 4. Percentage of studies reporting associations between regional neuroanatomy and cannabis use measures. Significant associations (red), nonsignificant associations (n.s.; blue), and associations unexamined (gray). Amyg, amygdala; Hipp, hippocampus; Para-hipp, parahippocampal gyrus; PFC, prefrontal cortex.

cortex, parietal cortex, insular cortex, and cerebellum. Some associations emerged between higher cannabis dosage and hippocampal alterations and between earlier age of onset and

PFC alterations. These trends (i.e., hippocampal volumetric reduction) were previously observed (47), although there is now increasing evidence for alteration within other regions (i.e., striatum, orbitofrontal cortx, parietal cortex, insular cortex, cerebellum). There was also preliminary evidence that neuro-anatomic alterations within the hippocampus, cerebellum, prefrontal, and lingual regions were associated with THC and CBD levels specifically, suggestive of an adverse effect of THC and a protective effect of CBD (from THC-related damage).

Neuroanatomic abnormalities were most reliably found in regions that have a high concentration of cannabinoid type 1 receptors, to which THC binds to exert its psychoactive effects (31). Cannabis plants that are typically used for drug production have high levels of THC (17%–20%) (73) but low levels of CBD (1). According to preclinical findings, THC accumulates in neurons (74) and with chronic exposure becomes neurotoxic (18). Neuroanatomic abnormalities may result from the adverse effects of direct and chronic exposure to high levels of THC found in commonly available "street" cannabis. Although CBD may be neuroprotective (24,25) and mitigate the adverse effects of THC (47,85), it is seldom found in high levels (1). As one of the regions of highest density of cannabinoid type 1 receptors (3), damage to the hippocampus may be related to THC-induced neurotoxicity.

Putative Mechanisms

Neuroanatomic alterations in areas that are high or low in cannabinoid receptors may result from distinct mechanisms. Alterations within regions high in cannabinoid type 1 receptors (hippocampus, amygdala, cerebellum, anterior cingulate cortex) may involve 1) accumulation of THC and its metabolites in neurons (74) that leads to THC-induced neurotoxicity [e.g., shrinkage of neuronal cell nuclei and bodies (19,20), reduced synapse number (20), and reduced pyramidal cell density (16,76)]; 2) downregulation, adaptation, and molecular and signaling changes downstream of cannabinoid receptors (77–82); and 3) changes in vascularity, and reductions in glia and neuronal dendrites, which are associated with gray matter volumes (83–85).

Chronic cannabinoid-induced alterations of neural oscillations in cannabinoid receptor–high regions [i.e., shown in preclinical studies of the hippocampus (86,87) and amygdala (88,89)] may propagate (90) to functionally and structurally
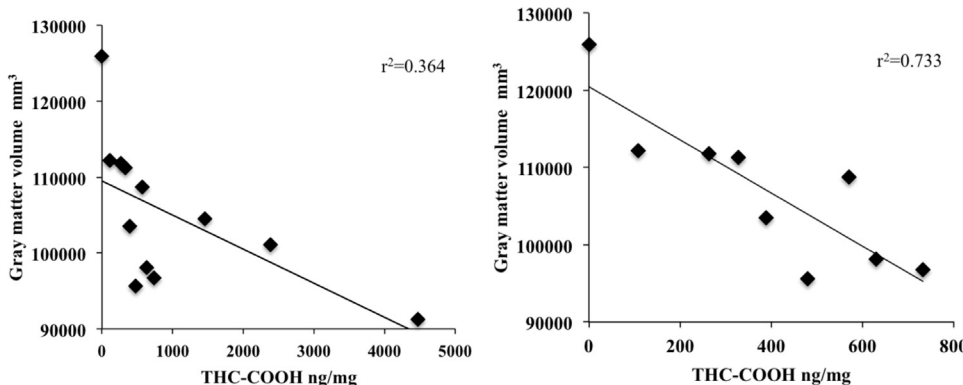

Figure 5. Association between urinary 11-nor-9-carboxy-THC (THC-COOH; ng/mg) (x axis) and cerebellar gray matter volume (mm³) (y axis) before (left) and after removal of three outliers (right).

connected cannabinoid receptor–low regions [e.g., parietal cortex (91–93) and orbitofrontal cortex (94)] and lead to neuroanatomic alterations of the latter. Previous studies in neurodegenerative disorders showed a direct link between alteration of connectivity (i.e., synchrony of activity) between functionally and structurally related regions and alteration of gray matter volumes in the same areas (95). Cannabis users show impaired functional (34,96) and structural (97) connectivity between cannabinoid receptor–high regions (i.e., hippocampus) and cannabinoid receptor–low regions (i.e., parietal cortex, inferior frontal gyrus). In this review, cannabis users showed neuroanatomic alterations in both regions. These regions are integral components of the brain reward (98), memory (99), and executive-attention systems (100,101) and may mediate the deficits that cannabis users show in these domains (93,98,99–104).

The compound CBD may counteract THC-induced damage to neuroanatomy, as it has been shown to alleviate neurodegeneration, reverse brain ischemic damage in mice (24), and modulate the effects of THC by blocking cannabinoid type 1 receptors (105–107). The molecular mechanisms by which CBD counteracts the effects of THC are unclear (24,105). It may be that CBD, via attenuating THC-induced effects on brain function (13,14,34,36), prevents the onset of molecular mechanisms that would trigger neurotoxicity and lead to neuroanatomic abnormalities in cannabis users. Multimodal imaging studies in cannabis users that carefully examine levels of THC and CBD (prior proportional exposure from hair analysis and circulating levels in urine, blood, and oral fluid samples) would help elucidate the potential neurotoxic, neuroadaptive, or neuroprotective mechanisms involving different cannabinoids.

Limitations of Reviewed Literature

There are major gaps in the measurement of cannabinoids and cannabis use levels [e.g., dose, duration, frequency, age of onset (47,75,108)]. The development of standardized methods to characterize cannabis users and to identify the effects of specific cannabinoids on the brain is warranted.

Measurement of Cannabinoid Levels. Hypotheses and interpretation concerning neuroanatomic alterations in cannabis users often postulate that THC drives these effects. However, few studies have tested this model directly by obtaining quantified measures of THC-specific exposure. Quantifying cannabinoid levels in hair could provide levels of THC and CBD to which cannabis users have been exposed cumulatively over a few months (109,110). Also, metabolites in blood or urine measure circulating cannabinoids, which reflect exposure over recent hours, days, or weeks, and, in daily or near-daily users, indicate typically circulating levels. Although methods exist for quantifying cannabinoid exposure, such indices are underreported. The role of cannabinoid compounds in causally driving neuroanatomic alterations in cannabis users cannot be ascertained.

Improvements in the time frame and reliability of toxicology tests are warranted (111). For example, hair analyses inform the past ~3 months of exposure and rely on length of hair available (1 cm of hair = 1 month of exposure), which most

(but not all) participants can provide (109,110). We need better reliability and validity studies for toxicology analyses, as there is limited and contradictory evidence on this topic [e.g., urine toxicology tests may not match positive self-reports of cannabis use (111)]. Development of further measures of cannabinoid metabolites that enable more reliable detection of CBD in urine and other relevant cannabinoid metabolites that have longer time windows may help in the objective measurement of cannabinoid exposure. Finally, cannabinoid compounds from specimens collected from participants may not be stable over time (e.g., use of different varieties, breeds, or parts of the cannabis plant). Although it would be difficult to systematically control for this, assaying cannabinoid content from specimens, particularly in prospective studies, may inform future work on their neurobiological impact.

Underreporting Key Aspects of Cannabis Use. Key aspects of cannabis use are often not measured or reported, including the 1) type of cannabis predominantly used by the sample, the potency of which varies between marijuana [~1%–20% THC (1)], hashish (~10%), and hashish oils [up to 50% (112)]; 2) use of tobacco in cannabis preparations, which can almost double the release of THC compared with smoking pure cannabis (113); and 3) usual dosage and days of use, age of onset of regular use, and problems associated with use (114). The underreporting of levels of exposure limits our understanding of the effects of cannabis use levels on the human brain.

Noisy Measurements. Measuring levels of cannabis use is an inherently difficult task. Self-reported levels of use are compromised by retrospective accounts including difficulties in remembering changes in use over the years, which are exacerbated by memory deficits in cannabis users (102, 115–117). Studies measure differently levels of cannabis dosage (e.g., joints, smoking occasions, grams), frequency (e.g., smoking either occasions or days), and age of onset (e.g., of either first try or of regular use). Levels of use are estimated over distinct time windows (i.e., "usual" use; past 1–6 months, past 1 year, 10 years, lifetime), and duration and cumulative exposure measures often do not account for periods of prolonged abstinence. These issues prevent a direct comparison of findings across studies.

Lack of a Comprehensive Tool. No single instrument captures all key aspects of exposure to cannabis use and cannabinoids (Table 3). Research groups often develop their own in-house tools, which are not validated and standardized to perform accurate measurements of the history of use [e.g., periods of prolonged abstinence or of heavier use (50,58)]. The studies reviewed employed different instruments (114), obviating direct comparisons in the level of use across the reviewed samples. Methodologic issues in measuring cannabis use preclude the development of evidence-based neurobiological models of cannabis-related harm in humans, which rely on preclinical evidence (130,131) that cannot be replicated in humans, given the interspecies differences in neuroanatomy (132) and different routes of administration in animal studies

Table 3. Measurement of Cannabis Use Levels and Problems

Patterns of Use	Outcome Measures	Instruments	Period Over Which Measured
Type	Marijuana, hashish, cannabis oils, spice, mixed with tobacco	In-house, DSM, CUDIT, CAST	Currently or usually (no detail about period over which it is measured), not measured
Quantity (how much)	Number of grams, joints, bongs, blunts, standard cannabis units (NCPIC guidelines)	Self-reported	Cumulative (accumulated over a specified period of time) or average (divided by a given period of time)
		In-house, NCPIC guidelines, CUDIT, CDDR	Currently or usually (no detail about period over which it is measured), monthly or past month, yearly or past year, past 10 years, lifetime
	THC, THC-COOH, CBD, (quantified levels, positive vs. negative outcomes)	Toxicology tests from:	Detection windows, for smoked cannabis (118):
		Hair	~90 days (109,110)
		Urine	Single dose, 1.5–4 days; Chronic use, up to 2 weeks and longer >25 days (119)
		Oral fluid	1–4 hours, also up to 16 hours (120)
		Blood or plasma	~20–57 hours (occasional), 3–13 days (regular users)
		Breathalyzer	~2 minutes, up to 12 hours (121)
Frequency (how often)	Days per week, per month; Occasions per day, per week	In-house, NCPIC guidelines, CUDIT	Usually, past month, past year, past 10 years, lifetime
Duration (how long)	Current age minus age of first use; age of regular use; prolonged abstinence periods	In-house, NCPIC guidelines, CUDIT	Lifetime
Age of onset	Regular use, first use	In-house, CUDIT, CDDR, ASI	Lifetime
Problem use	Cannabis use disorder diagnosis, severity, symptoms	DSM (122,123)	Past 6 months, and if endorsed in the past
	Severity of problem use, addiction and dependence	In-house semi-structured interviews (38,45,50,58)	Lifetime
		CDDR (adolescents), ASI	Lifetime, past 3 months
		CAST	Lifetime, past 30 days
		CUDIT, SAS of the MINI	Past 6 months
		SDS	Past 3 months
	Withdrawal symptoms	MWCL	Since last use

ASI, Addiction Severity Index (127); CAST, Cannabis Abuse Screening Test (125); CBD, cannabidiol; CDDR, Customary Drinking and Drug Use Record (126); CUDIT, Cannabis Use Disorder Identification Test (124); MWCL, Marijuana Withdrawal Checklist; NCPIC, National Cannabis Prevention and Intervention Centre guidelines (available from https://ncpic.org.au/media/1593/timeline-followback.pdf); SAS of the MINI, Substance Abuse Scales of the Mini International Neuropsychiatric Interview of the DSM (128); THC, Δ^9-tetrahydrocannabinol; THC-COOH, 11-nor-9-carboxy-THC; SDS, Severity of Dependence Scale (129).

Table 4. Recommended Set of Minimum Criteria

Type of cannabis used and whether it is mixed with tobacco
Ages of onset of first use and of regular use
Recent (i.e., past month) and lifetime levels of use
Duration of regular use, accounting for prolonged abstinence periods
Standardized dosage measure (e.g., https://ncpic.org.au/media/1593/timeline-followback.pdf)
Cumulative dosage—accounting for periods of prolonged abstinence, and increases/decreases in dosage and smoking days
Cannabis use disorder severity, determined with Cannabis Use Disorders module of the DSM-5 (123)
Severity of dependence and problem use [e.g., Cannabis Use Disorder Identification Test (124), Addiction Severity Index (127)]
Use of interview techniques that aid memory of past events [e.g., TimeLine Follow Back procedure (134)]
Toxicology tests—Breathalyzer, and urine and hair toxicology analyses to assess recent use and measure cannabinoids in the few weeks before assessment
Assay of samples brought by the participant would provide information on the cannabinoid composition of at least recent exposure (135,136)[a]
Measure key confounders associated with cannabis use [e.g., alcohol use with the Alcohol Use Disorder Identification Test (137), and tobacco use with the Fagerström Tolerance Questionnaire (138)]

[a]While ideal, this raises ethical/legal challenges that need further consideration.

(i.e., oral, consistent doses) and human studies (i.e., inhaling cannabis smoke or vapors, variable doses), which create different models of metabolizing THC (76).

We propose the development of internationally agreed-on standards for quantifying exposure levels as a necessary step to develop evidence-based neurobiological models of cannabis use. The platform PhenX Toolkit previously took steps in this direction to improve the standard of research in substance use (133). In this review, we incorporate these useful guidelines (i.e., lifetime/recent use, age of onset, diagnostic assessment for problem use) and include additional items that are specific to cannabis use research. Table 4 lists recommended criteria for assessing regular cannabis use as a starting point for further discussion and consensus around improving standardization of measurements within the international community of cannabis researchers. We acknowledge that it will prove difficult, if not impossible, to determine the exact amount of THC that cannabis users may be exposed to over significantly varying periods of time and drug availabilities. However, an attempt at a more standardized approach is necessary to isolate factors that may cause brain alterations.

CONCLUSIONS

Regular cannabis users show abnormalities within brain regions that are high in cannabinoid type 1 receptors, particularly the hippocampus and the PFC. These abnormalities are associated with higher levels of cannabis use (dosage, age of onset, duration). The psychoactive compound THC may be responsible for neuroanatomic damage in cannabis users, whereas the potentially therapeutic compound CBD may protect from such damage. Further evidence is needed to verify this hypothesis. To develop evidence-based neurobiological models of cannabis-related harm, objective measurement of cannabinoid compounds and the development of standardized measures of levels of cannabis use are necessary next steps. Objective measurements also need to keep up to date with the continually changing cannabinoid compounds (e.g., CP-55940, WIN) in increasingly available synthetic cannabinoids [e.g., K2, Spice (139)], which mimic the psychoactive effects of THC, causing significant mental health harm (140,141) and unknown effects on the brain.

The mechanisms by which distinct cannabinoid compounds harm (and benefit) the brain are unclear. Research on the neurobiology of cannabinoids is not keeping up to date with ongoing public policy debates on the legalization as well as the therapeutic potential of the drug. To bridge this gap, we urgently need to develop standardized measurements of cannabis use levels and evidence-based neurobiological models of cannabinoid exposure.

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ARTICLE INFORMATION

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REFERENCES

1. Swift W, Wong A, Li KM, Arnold JC, McGregor IS (2013): Analysis of cannabis seizures in NSW, Australia: Cannabis potency and cannabinoid profile. PloS One 8:e70052.
2. Gaoni Y, Mechoulam R (1971): The isolation and structure of delta-1-tetrahydrocannabinol and other neutral cannabinoids from hashish. J Am Chem Soc 93:217–224.
3. Volkow ND, Baler RD, Compton WM, Weiss SRB (2014): Adverse health effects of marijuana use. N Engl J Med 370: 2219–2227.
4. Di Forti M, Marconi A, Carra E, Fraietta S, Trotta A, Bonomo M, et al. (2015): Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. Lancet Psychiatry 2:233–238.
5. Bhattacharyya S, Atakan Z, Martin-Santos R, Crippa JA, McGuire PK (2012): Neural mechanisms for the cannabinoid modulation of cognition and affect in man: A critical review of neuroimaging studies. Curr Pharm Des 18:5045–5054.
6. Zuardi AW, Crippa JAS, Hallak JE, Bhattacharyya S, Atakan Z, Martin-Santos R, et al. (2012): A critical review of the antipsychotic effects of cannabidiol: 30 years of a translational investigation. Curr Pharm Des 18:5131–5140.
7. Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R (2009): Non-psychotropic plant cannabinoids: New therapeutic opportunities from an ancient herb. Trends Pharmacol Sci 30:515–527.
8. Lupica CR, Riegel AC, Hoffman AF (2004): Marijuana and cannabinoid regulation of brain reward circuits. Br J Pharmacol 143: 227–234.
9. United Nations Office on Drugs and Crime (2009): Why does cannabis potency matter? In: World Drug Report 2009. New York: United Nations.
10. Di Forti M, Sallis H, Allegri F, Trotta A, Ferraro L, Stilo SA, et al. (2014): Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. Schizophr Bull 40:1509–1517.
11. Substance Abuse and Mental Health Services Administration (2013): Drug Abuse Warning Network, 2011: National Estimates of Drug-Related Emergency Department Visits. HHS Publication No. (SMA) 13-4760, DAWN Series D-39. Rockville, MD: Substance Abuse and Mental Health Services Administration.
12. Martin-Santos R, Crippa JA, Batalla A, Bhattacharyya S, Atakan Z, Borgwardt S, et al. (2012): Acute effects of a single, oral dose of Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) administration in healthy volunteers. Curr Pharm Des 18:4966–4979.
13. Fusar-Poli P, Allen P, Bhattacharyya S, Crippa JA, Mechelli A, Borgwardt S, et al. (2010): Modulation of effective connectivity during emotional processing by delta-9-tetrahydrocannabinol and cannabidiol. Int J Neuropsychopharmacol 13:421–432.
14. Bhattacharyya S, Morrison PD, Fusar-Poli P, Martin-Santos R, Borgwardt S, Winton-Brown T, et al. (2010): Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology 35: 764–774.
15. Crippa JA, Zuardi AW, Martín-Santos R, Bhattacharyya S, Atakan Z, McGuire P, et al. (2009): Cannabis and anxiety: A critical review of the evidence. Hum Psychopharmacol 24:515–523.

16. Lawstone J, Borella A, Robinson JK, Whitaker-Azmitia PM (2000): Changes in hippocampal morphology following chronic treatment with the synthetic cannabinoid WIN 55,212-2. Brain Res 877:407–410.

17. Chan GCK, Hinds TR, Impey S, Storm DR (1998): Hippocampal neurotoxicity of Δ^9-tetrahydrocannabinol. J Neurosci 18:5322–5332.

18. Landfield PW, Caldwallader LB, Vinsant S (1988): Quantitative changes in hippocampal structure following long-term exposure to Δ9-tetrahydrocannabinol: Possible mediation by glucocorticoid systems. Brain Res 443:47–62.

19. Scallet AC, Uemura E, Andrews A, Ali SF, McMillan DE, Paule MG, et al. (1987): Morphometric studies of the rat hippocampus following chronic delta-9-tetrahydrocannabinol (THC). Brain Res 436:193–198.

20. Heath RG, Fitzjarrell AT, Fontana CJ, Garey RE (1980): Cannabis sativa: Effects on brain function and ultrastructure in rhesus monkeys. Biol Psychiatry 15:657–690.

21. Kolb B, Gorny G, Limebeer CL, Parker LA (2006): Chronic treatment with delta-9-tetrahydrocannabinol alters the structure of neurons in the nucleus accumbens shell and medial prefrontal cortex of rats. Synapse 60:429–436.

22. Downer E, Boland B, Fogarty M, Campbell VCA (2001): Delta-9-tetrahydrocannabinol induces the apoptotic pathway in cultured cortical neurons via activation of the CB1 receptor. Neuroreport, 12, 3973–3978.

23. Harper JW, Heath RG, Myers WA (1977): Effects of Cannabis sativa on ultrastructure of the synapse in monkey brain. J Neurosci Res 3:87–93.

24. Schiavon A, Soares L, Bonato J, Milani H, Guimarães F, Weffort de Oliveira R (2014): Protective effects of cannabidiol against hippocampal cell death and cognitive impairment induced by bilateral common carotid artery occlusion in mice. Neurotox Res 26:307–316.

25. Hermann D, Schneider M (2012): Potential protective effects of cannabidiol on neuroanatomical alterations in cannabis users and psychosis: A critical review. Curr Pharm Des 18:4897–4905.

26. Schubart CD, Sommer IEC, Fusar-Poli P, de Witte L, Kahn RS, Boks MPM (2014): Cannabidiol as a potential treatment for psychosis. Eur Neuropsychopharmacol 24:51–64.

27. Bhattacharyya S (2014): Neurobiological and neurocognitive basis of the effects of cannabinoids in animals and man: Therapeutic potential of cannabinoids in psychiatry. Curr Pharm Des 20:2069–2071.

28. Morgan CJ, Gardener C, Schafer G, Swan S, Demarchi C, Freeman TP, et al. (2012): Sub-chronic impact of cannabinoids in street cannabis on cognition, psychotic-like symptoms and psychological well-being. Psychol Med 42:391–400.

29. Morgan CJ, Curran HV (2008): Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. Br J Psychiatry 192:306–307.

30. Demirakca T, Sartorius A, Ende G, Meyer N, Welzel H, Skopp G, et al. (2011): Diminished gray matter in the hippocampus of cannabis users: Possible protective effects of cannabidiol. Drug Alcohol Depend 114:242–245.

31. Glass M, Faull RLM, Dragunow M (1997): Cannabinoid receptors in the human brain: A detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. Neuroscience 77:299.

32. Bhattacharyya S (2009): Opposite effects of Δ-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology 35:764.

33. Bhattacharyya S, Atakan Z, Martin-Santos R, Crippa JA, Kambeitz J, Prata D, et al. (2012): Preliminary report of biological basis of sensitivity to the effects of cannabis on psychosis: AKT1 and DAT1 genotype modulates the effects of delta-9-tetrahydrocannabinol on midbrain and striatal function. Mol Psychiatry 17:1152–1155.

34. Bhattacharyya S, Falkenberg I, Martin-Santos R, Atakan Z, Crippa JA, Giampietro V, et al. (2015): Cannabinoid modulation of functional connectivity within regions processing attentional salience. Neuropsychopharmacology 40:1343–1352.

35. Morrison PD, Nottage J, Stone JM, Bhattacharyya S, Tunstall N, Brenneisen R, et al. (2011): Disruption of frontal theta coherence by delta9-tetrahydrocannabinol is associated with positive psychotic symptoms. Neuropsychopharmacology 36:827–836.

36. Bhattacharyya S, Fusar-Poli P, Borgwardt S, Martin-Santos R, Nosarti C, O'Carroll C, et al. (2009): Modulation of mediotemporal and ventrostriatal function in humans by Δ9-tetrahydrocannabinol: A neural basis for the effects of Cannabis sativa on learning and psychosis. Arch Gen Psychiatry 66:442–451.

37. Bhattacharyya S, Crippa J, Martin-Santos R, Winton-Brown T, Fusar-Poli P (2009): Imaging the neural effects of cannabinoids: Current status and future opportunities for psychopharmacology. Curr Pharm Des 15:2603–2614.

38. Lorenzetti V, Solowij N, Whittle S, Fornito A, Lubman DI, Pantelis C, et al. (2015): Gross morphological brain changes with chronic, heavy cannabis use. Br J Psychiatry 206:77–78.

39. Weiland BJ, Thayer RE, Depue BE, Sabbineni A, Bryan AD, Hutchison KE (2015): Daily marijuana use is not associated with brain morphometric measures in adolescents or adults. J Neurosci 35:1505–1512.

40. Battistella G, Fornari E, Annoni J-M, Chtioui H, Dao K, Fabritius M, et al. (2014): Long-term effects of cannabis on brain structure. Neuropsychopharmacology 39:2041–2048.

41. Gilman JM, Kuster JK, Lee S, Lee MJ, Kim BW, Makris N, et al. (2014): Cannabis use is quantitatively associated with nucleus accumbens and amygdala abnormalities in young adult recreational users. J Neurosci 34:5529–5538.

42. Filbey FM, Aslan S, Calhoun VD, Spence JS, Damaraju E, Caprihan A, et al. (2014): Long-term effects of marijuana use on the brain. Proc Natl Acad Sci 111:16913–16918.

43. Yip SW, DeVito EE, Kober H, Worhunsky PD, Carroll KM, Potenza MN (2014): Pretreatment measures of brain structure and reward-processing brain function in cannabis dependence: An exploratory study of relationships with abstinence during behavioral treatment. Drug Alcohol Depend 140:33–41.

44. Batalla A, Soriano-Mas C, Lopez-Sola M, Torrens M, Crippa JA, Bhattacharyya S, et al. (2014): Modulation of brain structure by catechol-O-methyltransferase Val(158) Met polymorphism in chronic cannabis users. Addict Biol 19:722–732.

45. Solowij N, Walterfang M, Lubman DI, Whittle S, Lorenzetti V, Styner M, et al. (2013): Alteration to hippocampal shape in cannabis users with and without schizophrenia. Schizophr Res 143:179–184.

46. Schacht JP, Hutchison KE, Filbey FM (2012): Associations between cannabinoid receptor-1 (CNR1) variation and hippocampus and amygdala volumes in heavy cannabis users. Neuropsychopharmacology 37:2368–2376.

47. Lorenzetti V, Solowij N, Fornito A, Lubman DI, Yucel M (2014): The association between regular cannabis exposure and alterations of human brain morphology: An updated review of the literature. Curr Pharm Des 20:2138–2167.

48. Lorenzetti V, Lubman DI, Whittle S, Solowij N, Yücel M (2010): Structural MRI findings in long-term cannabis users: What do we know? Subst Use Misuse 45:1787–1808.

49. Lopez-Larson MP, Bogorodzki P, Rogowska J, McGlade E, King JB, Terry J, et al. (2011): Altered prefrontal and insular cortical thickness in adolescent marijuana users. Behav Brain Res 220:164–172.

50. Solowij N, Yücel M, Respondek C, Whittle S, Lindsay E, Pantelis C, et al. (2011): Cerebellar white-matter changes in cannabis users with and without schizophrenia. Psychol Med 41:2349–2359.

51. Ashtari M, Avants B, Cyckowski L, Cervellione KL, Roofeh D, Cook P, et al. (2011): Medial temporal structures and memory functions in adolescents with heavy cannabis use. J Psychiatr Res 45:1055–1066.

52. McQueeny T, Padula CB, Price J, Medina KL, Logan P, Tapert SF (2011): Gender effects on amygdala morphometry in adolescent marijuana users. Behav Brain Res 224:128–134.

53. Cousijn J, Wiers RW, Ridderinkhof KR, van den Brink W, Veltman DJ, Goudriaan AE (2012): Grey matter alterations associated with cannabis use: Results of a VBM study in heavy cannabis users and healthy controls. Neuroimage 59:3845–3851.

54. Churchwell JC, Lopez-Larson M, Yurgelun-Todd DA (2010): Altered frontal cortical volume and decision making in adolescent cannabis users. Front Psychol 1:225.

55. Mata I, Perez-Iglesias R, Roiz-Santianez R, Tordesillas-Gutierrez D, Pazos A, Gutierrez A, et al. (2010): Gyrification brain abnormalities associated with adolescence and early-adulthood cannabis use. Brain Res. 1317:297–304.

56. Medina KL, Nagel BJ, Tapert SF (2010): Abnormal cerebellar morphometry in abstinent adolescent marijuana users. Psychiatry Res 182:152–159.

57. Medina KL, McQueeny T, Nagel BJ, Hanson KL, Yang TT, Tapert SF (2009): Prefrontal cortex morphometry in abstinent adolescent marijuana users: Subtle gender effects. Addict Biol 14:457–468.

58. Yücel M, Solowij N, Respondek C, Whittle S, Fornito A, Pantelis C, et al. (2008): Regional brain abnormalities associated with heavy long-term cannabis use. Arch Gen Psychiatry 65:1–8.

59. Medina KL, Nagel BJ, Park A, McQueeny T, Tapert SF (2007): Depressive symptoms in adolescents: Associations with white matter volume and marijuana use. J Child Psychol Psychiatry 48:592–600.

60. Medina KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ, Tapert SF (2007): Effects of alcohol and combined marijuana and alcohol use hippocampal volume and asymmetry. Neurotoxicol Teratol 29:141–152.

61. Jager G, Van Hell HH, De Win MML, Kahn RS, Van Den Brink W, Van Ree JM, et al. (2007): Effects of frequent cannabis use on hippocampal activity during an associative learning memory task. Eur Psychopharmacol 17:289–297.

62. Tzilos GK, Cintron CB, Wood JB, Simpson NS, Young AD, Pope HG Jr, et al. (2005): Lack of hippocampal volume change in long-term heavy cannabis users. Am J Addict 14:64–72.

63. Matochik JA, Eldeth DA, Cadet DA, Bolla KI (2005): Altered brain tissue composition in heavy marijuana users. Drug Alcohol Depend 77:23–30.

64. Block RI, O'Leary DS, Ehrhardt JC, Augustinack JC, Ghoneim MM, Arndt S, et al. (2000): Effects of frequent marijuana use on brain tissue volume and composition. Neuroreport 11:491–496.

65. Wilson W, Mathew R, Turkington T, Hawk T, Coleman RE, Provenzale J (2000): Brain morphological changes and early marijuana use. A MRI and PET study. J Addict Dis 19:1–22.

66. Hannerz J, Hindmarsh T (1983): Neurological and neuroradiological examination of chronic cannabis smokers. Ann Neurol 13:207–210.

67. Kuehnle J, Mendelson JH, Davis KR, New PF (1977): Computed tomographic examination of heavy marijuana smokers. JAMA 237:1231–1232.

68. Co BT, Goodwin DW, Gado M, Mickhael M, Hill SY (1977): Absence of cerebral atrophy in chronic cannabis users. Evaluation by computerized transaxial tomography. JAMA 237:1229–1230.

69. Stefanis C (1976): Biological aspects of cannabis use. In: Petersen R, editor. The International Challenge of Drug Abuse. Rockville, MD: National Institute on Drug Abuse, 149–178.

70. Campbell AMG, Evans M, Thomson JLG, Williams MJ (1971): Cerebral atrophy in young cannabis smokers. Lancet 2:1219–1224.

71. Cousijn J, Goudriaan AE, Ridderinkhof KR, van den Brink W, Veltman DJ, Wiers RW (2013): Neural responses associated with cue-reactivity in frequent cannabis users. Addict Biol 18:570–580.

72. Yücel M, Lorenzetti V, Suo V, Zalesky A, Fornito A, Fernandez F, et al. (2015): Marijuana and brain health: Hippocampal injury, protection and recovery. Presented at Organization of the Human Brain Mapping, June 14–18, 2015, Honolulu, Hawaii.

73. Adams IB, Martin BR (1996): Cannabis: Pharmacology and toxicology in animals and humans. Addiction 91:1585–1614.

74. Monnet-Tschudi F, Hazekamp A, Perret N, Zurich M-G, Mangin P, Giroud C, et al. (2008): Delta-9-tetrahydrocannabinol accumulation, metabolism and cell-type-specific adverse effects in aggregating brain cell cultures. Toxicol Appl Pharmacol 228:8–16.

75. Rocchetti M, Crescini A, Borgwardt S, Caverzasi E, Politi P, Atakan Z, et al. (2013): Is cannabis neurotoxic for the healthy brain? A meta-analytical review of structural brain alterations in non-psychotic users. Psychiatry Clin Neurosci 67:483–492.

76. Scallet AC (1991): Neurotoxicology of cannabis and THC: A review of chronic exposure studies in animals. Pharmacol Biochem Behav 40:671–676.

77. Tonini R, Ciardo S, Cerovic M, Rubino T, Parolaro D, Mazzanti M, et al. (2006): ERK-dependent modulation of cerebellar synaptic plasticity after chronic Δ9-tetrahydrocannabinol exposure. J Neurosci 26:5810–5818.

78. Martin BR, Sim-Selley LJ, Selley DE (2004): Signaling pathways involved in the development of cannabinoid tolerance. Trends Pharmacol Sci 25:325–330.

79. Rubino T, Vigano D, Realini N, Guidali C, Braida D, Capurro V, et al. (2008): Chronic delta 9-tetrahydrocannabinol during adolescence provokes sex-dependent changes in the emotional profile in adult rats: Behavioral and biochemical correlates. Neuropsychopharmacology 33:2760–2771.

80. Breivogel CS, Childers SR, Deadwyler SA, Hampson RE, Vogt LJ, Sim-Selley LJ (1999): Chronic Δ9-tetrahydrocannabinol treatment produces a time-dependent loss of cannabinoid receptors and cannabinoid receptor-activated G proteins in rat brain. J Neurochem 73:2447–2459.

81. Burston JJ, Wiley JL, Craig AA, Selley DE, Sim-Selley LJ (2010): Regional enhancement of cannabinoid CB1 receptor desensitization in female adolescent rats following repeated delta-tetrahydrocannabinol exposure. Br J Pharmacol 161:103–112.

82. Sim-Selley LJ (2003): Regulation of cannabinoid CB1 receptors in the central nervous system by chronic cannabinoids. Crit Rev Neurobiol 15:91–119.

83. Hill SY, Muddasani S, Prasad K, Nutche J, Steinhauer SR, Scanlon J, et al. (2007): Cerebellar volume in offspring from multiplex alcohol dependence families. Biol Psychiatry 61:41–47.

84. Paus T (2005): Mapping brain maturation and cognitive development during adolescence. Trends Cogn Sci 9:60–68.

85. Herning RI, Better WE, Tate K, Cadet JL (2005): Cerebrovascular perfusion in marijuana users during a month of monitored abstinence. Neurology 64:488–493.

86. Robbe D, Montgomery SM, Thome A, Rueda-Orozco PE, McNaughton BL, Buzsaki G (2006): Cannabinoids reveal importance of spike timing coordination in hippocampal function. Nat Neurosci 9:1526–1533.

87. Skosnik PD, D'Souza DC, Steinmetz AB, Edwards CR, Vollmer JM, Hetrick WP, et al. (2012): The effect of chronic cannabinoids on broadband EEG neural oscillations in humans. Neuropsychopharmacology 37:2184–2193.

88. Heath RG (1976): Marihuana and Δ9-THC: Acute and chronic effects on brain function of monkeys. In: Brande MC, Szara S, editors. Pharmacology of Marihuana. New York: Raven Press, 345–356.

89. Heath RG (1976): Cannabis sativa derivates: Effects on brain function of monkeys. In: Nahas GG, editor. Marihuana: Chemistry, Biochemistry and Cellular Effects. New York: Springer-Verlag, 507–519.

90. Rogers BP, Morgan VL, Newton AT, Gore JC (2007): Assessing functional connectivity in the human brain by fMRI. Magn Reson Imaging 25:1347–1357.

91. Rockland KS, Van Hoesen GW (1999): Some temporal and parietal cortical connections converge in CA1 of the primate hippocampus. Cerebral Cortex 9:232–237.

92. Whitlock JR, Sutherland RJ, Witter MP, Moser M-B, Moser EI (2008): Navigating from hippocampus to parietal cortex. Proc Natl Acad Sci U S A 105:14755–14762.

93. Vincent JL, Kahn I, Snyder AZ, Raichle ME, Buckner RL (2008): Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. J Neurophysiol 100:3328–3342.

94. Catenoix H, Magnin M, Guenot M, Isnard J, Mauguiere F, Ryvlin P (2005): Hippocampal-orbitofrontal connectivity in human: An electrical stimulation study. Clin Neurophysiol 116:1779–1784.

95. Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD (2009): Neurodegenerative diseases target large-scale human brain networks. Neuron 62:42–52.

96. Harding IH, Solowij N, Harrison BJ, Takagi M, Lorenzetti V, Lubman DI, et al. (2012): Functional connectivity in brain networks underlying cognitive control in chronic cannabis users. Neuropsychopharmacology 37:1923–1933.

97. Zalesky A, Solowij N, Yucel M, Lubman DI, Takagi M, Harding IH, et al. (2012): Effect of long-term cannabis use on axonal fibre connectivity. Brain 135:2245–2255.

98. Hyman SE, Malenka RC, Nestler EJ (2006): Neural mechanisms of addiction: The role of reward-related learning and memory. Annu Rev Neurosci 29:565–598.

99. Ramus SJ, Davis JB, Donahue RJ, Discenza CB, Waite AA (2007): Interactions between the orbitofrontal cortex and the hippocampal memory system during the storage of long-term memory. Ann N Y Acad Sci 1121:216–231.

100. Rueda MR, Posner MI, Rothbart MK (2005): The development of executive attention: Contributions to the emergence of self-regulation. Dev Neuropsychol 28:573–594.

101. Mesulam MM (1990): Large-scale neurocognitive networks and distributed processing for attention, language, and memory. Ann Neurol 28:597–613.

102. Solowij N, Jones KA, Rozman ME, Davis SM, Ciarrochi J, Heaven PC, et al. (2011): Verbal learning and memory in adolescent cannabis users, alcohol users and non-users. Psychopharmacology 216:131–144.

103. Takagi M, Yücel M, Cotton SM, Baliz Y, Tucker A, Elkins K, et al. (2011): Verbal memory, learning, and executive functioning among adolescent inhalant and cannabis users. J Stud Alcohol Drugs 72:96–105.

104. Takagi M, Lubman DI, Cotton S, Fornito A, Baliz Y, Tucker A, et al. (2011): Executive control among adolescent inhalant and cannabis users. Drug Alcohol Rev 30:629–637.

105. McPartland JM, Duncan M, Di Marzo V, Pertwee RG (2015): Are cannabidiol and Δ9-tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review. Br J Pharmacol, 172, 737–753.

106. Thomas A, Baillie G, Phillips A, Razdan R, Ross R, Pertwee R (2007): Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. Br J Pharmacol 150:613–623.

107. Pertwee RG, Ross RA (2002): Cannabinoid receptors and their ligands. Prostaglandins Leukot Essent Fatty Acids 66:101–121.

108. Batalla A, Bhattacharyya S, Yucel M, Fusar-Poli P, Crippa JA, Nogue S, et al. (2013): Structural and functional imaging studies in chronic cannabis users: A systematic review of adolescent and adult findings. PloS One 8:e55821.

109. Skopp G, Strohbeck-Kuehner P, Mann K, Hermann D (2007): Deposition of cannabinoids in hair after long-term use of cannabis. Forensic Sci Int 170:46–50.

110. Khajuria H, Nayak BP (2014): Detection of Δ9-tetrahydrocannabinol (THC) in hair using GC-MS. Egypt J Forensic Sci 4:17–20.

111. Buchan BJ, Dennis ML, Tims FM, Diamond GS (2002): Cannabis use: Consistency and validity of self-report, on-site urine testing and laboratory testing. Addiction 97:98–108.

112. Clarke RC, Watson DP (2007): Cannabis and the natural cannabis medicine. In: ElSohly MA, editor. Marijuana and the Cannabinoids. New York: Humana Press, 1–15.

113. Van der Kooy F, Pomahacova B, Verpoorte R (2009): Cannabis smoke condensate II: Influence of tobacco on tetrahydrocannabinol levels. Inhal Toxicol 21:87–90.

114. Lorenzetti V, Cousijn J (2015): Cannabis use disorders and brain morphology. In: Preedy VR, editor. Neuropathology of Drug Addictions and Substance Misuse: Common Substances of Abuse—Tobacco, Alcohol, Cannabinoids and Opioids. London: Elsevier.

115. Solowij N, Stephens RS, Roffman RA, Babor T, Kadden R, Miller M, et al. (2002): Cognitive functioning of long-term heavy cannabis users seeking treatment. JAMA 287:1123–1131.

116. Yücel M, Lubman DI, Solowij N, Brewer WJ (2007): Understanding drug addiction: A neuropsychological perspective. Aust N Z J Psychiatry 41:957–968.

117. Solowij N, Battisti R (2008): The chronic effects of cannabis on memory in humans: A review. Curr Drug Abuse Rev 1:81–98.

118. Verstraete AG (2004): Detection times of drugs of abuse in blood, urine, and oral fluid. Ther Drug Monit 26:200–205.

119. Goodwin RS, Darwin WD, Chiang CN, Shih M, Li S-H, Huestis MA (2008): Urinary elimination of 11-nor-9-carboxy-Δ9-tetrahydrocannabinol in cannabis users during continuously monitored abstinence. J Anal Toxicol 32:562–569.

120. Drummer OH (2005): Review: Pharmacokinetics of illicit drugs in oral fluid. Forensic Sci Int 150:133–142.

121. Beck O, Stephanson N, Sandqvist S, Franck J (2013): Detection of drugs of abuse in exhaled breath using a device for rapid collection: Comparison with plasma, urine and self-reporting in 47 drug users. J Breath Res 7:026006.

122. American Psychiatric Association (1996): Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC: American Psychiatric Press.

123. American Psychiatric Association (2013): Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC: American Psychiatric Press.

124. Adamson SJ, Sellman JD (2003): A prototype screening instrument for cannabis use disorder: The Cannabis Use Disorders Identification Test (CUDIT) in an alcohol-dependent clinical sample. Drug Alcohol Rev 22:309–315.

125. Buchan BJ, Dennis ML, Tims FM, Diamond GS (2002): Cannabis use: Consistency and validity of self-report, on-site urine testing and laboratory testing. Addiction 97:98.

126. Brown SA, Myers MG, Lippke L, Tapert SF, Stewart DG, Vik PW (1998): Psychometric evaluation of the Customary Drinking and Drug Use Record (CDDR): A measure of adolescent alcohol and drug involvement. J Stud Alcohol Drugs 59:427.

127. Fureman B, Parikh G, Bragg A, McLellan A (1990): Addiction Severity Index. A Guide to Training and Supervising ASI Interviews. Philadelphia: University of Pennsylvania/Philadelphia VAMC, Center for Studies of Addiction.

128. Lecrubier Y, Sheehan D, Weiller E, Amorim P, Bonora I, Sheehan KH, et al. (1997): The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: Reliability and validity according to the CIDI. Eur Psychiatry 12:224–231.

129. Budney AJ, Novy PL, Hughes JR (1999): Marijuana withdrawal among adults seeking treatment for marijuana dependence. Addiction 94:1311–1322.

130. Koob GF (2009): Neurobiological substrates for the dark side of compulsivity in addiction. Neuropharmacology 56(suppl 1):18–31.

131. Everitt BJ, Parkinson JA, Olmstead MC, Arroyo M, Robledo P, Robbins TW (1999): Associative processes in addiction and reward: The role of amygdala-ventral striatal subsystems. Ann N Y Acad Sci 877:412–438.

132. Ongur D, Price JL (2000): The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb Cortex 10:206–219.

133. Hamilton CM, Strader LC, Pratt JG, Maiese D, Hendershot T, Kwok RK, et al. (2011): The PhenX Toolkit: Get the most from your measures. Am J Epidemiol 174:253–260.

134. Sobell LC, Sobell MB (1992): Timeline Follow-Back: A Technique for Assessing Self-Reported Alcohol Consumption. Totowa, NJ: Humana Press.

135. Morgan CJ, Schafer G, Freeman TP, Curran HV (2010): Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: Naturalistic study [corrected]. Br J Psychiatry 197:285–290.

136. Di Forti M, Morgan C, Dazzan P, Pariante C, Mondelli V, Marques TR, et al. (2009): High-potency cannabis and the risk of psychosis. Br J Psychiatry 195:488–491.

137. Bohn MJ, Babor TF, Kranzler HR (1995): The Alcohol Use Disorders Identification Test (AUDIT): Validation of a screening instrument for use in medical settings. J Stud Alcohol 56:423–432.

138. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO (1991): The Fagerström test for nicotine dependence: A revision of the Fagerström Tolerance Questionnaire. Br J Addict 86:1119–1127.

139. Rosenbaum CD, Carreiro SP, Babu KM (2012): Here today, gone tomorrow … and back again? A review of herbal marijuana alternatives (K2, Spice), synthetic cathinones (bath salts), kratom, Salvia divinorum, methoxetamine, and piperazines. J Med Toxicol 8:15–32.

140. Gunderson EW, Haughey HM, Ait-Daoud N, Joshi AS, Hart CL (2012): "Spice" and "K2" herbal highs: A case series and systematic review of the clinical effects and biopsychosocial implications of synthetic cannabinoid use in humans. Am J Addict 21:320–326.

141. Musshoff F, Madea B, Kernbach-Wighton G, Bicker W, Kneisel S, Hutter M, et al. (2014): Driving under the influence of synthetic cannabinoids ("Spice"): A case series. Int J Legal Med 128:59–64.