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ORIGINAL PAPER

Does regular cannabis use affect neuroanatomy? An updated systematic review and meta-analysis of structural neuroimaging studies

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Abstract

Regular cannabis use is associated with adverse cognitive and mental health outcomes that have been ascribed to aberrant neuroanatomy in brain regions densely innervated with cannabinoid receptors. Neuroanatomical differences between cannabis users and controls have been assessed in multiple structural magnetic resonance imaging (sMRI) studies. However, there is heterogeneity in the results leading to cautious interpretation of the data so far. We examined the sMRI evidence to date in human cannabis users, to establish more definitely whether neuroanatomical alterations are associated with regular cannabis use. The regional specificity and association with cannabis use indices (i.e. cumulative dosage, duration) were also explored. We systematically reviewed and meta-analysed published sMRI studies investigating regional brain volumes (cortical, subcortical and global) in cannabis users and non-user controls. Three electronic databases were searched (PubMed, Scopus, and PsycINFO). A total of 17 meta-analyses were conducted (one for each cortical, subcortical and global volume) using the generic inverse variance method, whereby standardised mean difference in volume was calculated between users and non-users. Exploratory meta-regressions were conducted to investigate the association between cannabis use indices and regional brain volumes. A total of 30 articles were eligible for inclusion, contributing 106 effect sizes across 17 meta-analyses. Regular cannabis users had significantly smaller volumes of the hippocampus (SMD = 0.14, 95% CIs [0.02, 0.27]; $Z = 2.29$, $p = 0.02$, $I^2 = 74\%$) and orbitofrontal cortex {medial (SMD = 0.30, 95% CIs [0.15, 0.45]; $Z = 3.89$, $p = 0.0001$, $I^2 = 51\%$), lateral (SMD = 0.19, 95% CIs [0.07, 0.32]; $Z = 3.10$, $p = 0.002$, $I^2 = 26\%$)} relative to controls. The volumes of the hippocampus and orbitofrontal cortex were not significantly associated with cannabis duration and dosage. Our findings are consistent with evidence of aberrance in brain regions involved in reward, learning and memory, and motivation circuits in the regular use of substances other than cannabis, pointing to commonality in neurobiological abnormalities between regular users of cannabis and of other substances.

Introduction

Cannabis is the most widely used illicit substance globally, with upwards of ~ 180 million users [11]. Regular cannabis use has been perceived as relatively harmless by the general and scientific community [15, 11]. Yet, regular cannabis use has been associated with comorbid psychopathologies

Valentina Lorenzetti and Yann Chye have contributed equally to the manuscript.

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or elevated symptoms of depression, anxiety and psychosis [1, 15, 11, 1, 15] and deficits in performance in selected areas of cognition, including reward processing, learning and memory [1, 1, 15]. Adverse mental health outcomes and cognitive deficits in cannabis users have been ascribed to alteration in the neuroanatomy of pathways that underlie emotion, stress, cognitive control and addiction [15]. As such, attempts have been made to assess the neuroanatomical integrity of regular cannabis users with structural magnetic resonance imaging (sMRI) techniques that allow imaging the brain in vivo at a high resolution (i.e. mm), with somewhat heterogeneous findings.

The most consistent findings suggest neuroanatomical differences between regular cannabis users and non-cannabis using controls, in the hippocampus, amygdala, prefrontal cortex (PFC) and cerebellum [37]. Notably, these brain regions are high in cannabinoid receptors type 1 (CB1) [11], to which delta-9-tetrahydrocannabinol (THC), the psychoactive compound of cannabis, binds [43]. Recent sMRI evidence indicates that these alterations are correlated with heavier cannabis use or are observed more consistently in samples of heavier cannabis users (e.g. longer duration, higher dosage, more severe problem use) [17–11, 15]. On the other hand, several sMRI studies report a lack of neuroanatomical differences between cannabis users and controls, and no associations between level of cannabis use and neuroanatomical measures [43, 37, 37]. The heterogeneity of reported findings across studies can, to some extent, be overcome by a meta-analysis, allowing for greater confidence in interpreting the evidence on neuroanatomical changes in cannabis users. This evidence is required to inform debates on the extent of the potential neurobiological harms associated with regular cannabis exposure.

To our knowledge, only one previous meta-analysis and meta-regression of sMRI studies in cannabis users versus controls exists [11]. This work focused on whole brain, intracerebroventricular, hippocampal, and amygdala volumes as regions of interest (ROIs), finding significant reduction in hippocampal and amygdala volumes in cannabis users. However, they did not examine other cortical and subcortical regions, many of which are densely innervated with CB1 receptors that may mediate the effect of cannabis on the brain. Moreover, since 2013, > 10 additional studies have been published which examined additional brain regions. As such, an updated meta-analysis on the data published to date is warranted.

In this study, we aimed to quantitatively examine the extent of neuroanatomical differences between regular cannabis users and controls, by synthesising the sMRI findings to date in a meta-analysis. To this end, we meta-analysed volumetric data available for cortical (i.e. anterior cingulate (ACC), orbitofrontal (OFC), prefrontal (PFC) and parietal cortices), subcortical (i.e. hippocampus, amygdala, striatum, nucleus accumbens (NAc), caudate, putamen), cerebellum, and global brain areas (i.e. total brain, intracranium, total white matter and total grey matter). Secondly, we explored the association between patterns of cannabis use and the volumetry of regions that differed between cannabis users and controls, informed by our first analysis. This included a series of eight exploratory meta-regressions using either duration or cumulative dosage as predictors, and the volume of select brain regions that differed between groups as dependent variables if > 2 studies assessed either duration or dosage (i.e. the hippocampus and the total, medial and lateral portions of the OFC, but not the nucleus accumbens).

Methods

Eligibility criteria

We selected studies based on the following inclusion criteria: (1) peer-reviewed; (2) human samples; (3) published in English; (4) neuroanatomical assessment via T1-weighted MRI scans; (5) compared regular cannabis users (as defined by each study protocol) and non-users; (6) regular exposure to cannabis in the cannabis-using sample, which included ongoing use and up to 28-day abstinence [64–37] as the main focus was to examine effects of prolonged exposure. In the cannabis using samples, cannabis was defined as the current primary substance of regular use. Exclusion criteria were: (1) regular use of substances other than cannabis, nicotine, or alcohol; (2) a diagnosis of a mental health disorder including substance (but not cannabis and nicotine) use disorders and alcohol dependence; and (3) cannabis-user group abstinent for > 28 days.

Information sources and study selection

As shown in Fig. 1, electronic database searches of PubMed, Scopus, and PsycINFO were performed in line with PRISMA guidelines on the 28 February 2018 (Y.C.) using the search terms “Marijuana OR Cannabis” and “MRI OR Neuroimaging”. Eligibility screening was performed after removal of duplicates, supplementary cross-referencing and manual searches (Y.C. and V.L.).

Data extraction

Outcome measures were MRI volumetric outputs. These included global brain measures (i.e. total brain, intra-cranium, total white matter, total grey matter), subcortical regions (i.e. hippocampus, NAc, amygdala, striatum, putamen, caudate), the cerebellum and cortical regions (total, medial and lateral portions of the OFC, parietal lobe, PFC, ACC). Where the same brain measures from overlapping

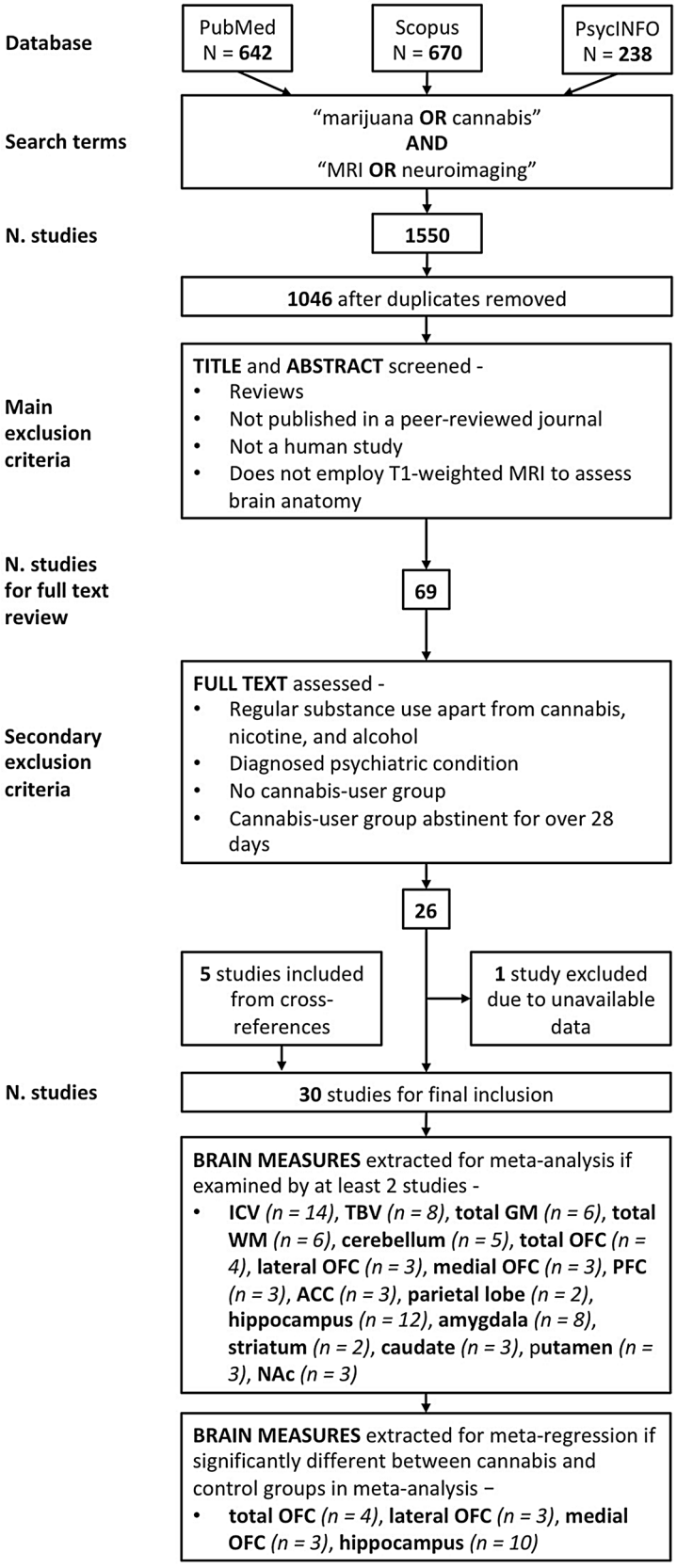

Fig. 1 Flow diagram of search strategy and inclusion. *N* number of studies, *MRI* magnetic resonance imaging, *ICV* intracranial volume, *TBV* total brain volume, *GM* grey matter, *WM* white matter, *OFC* orbitofrontal cortex, *PFC* prefrontal cortex, *ACC* anterior cingulate cortex, *NAc* nucleus accumbens

study samples were reported by multiple studies, we removed duplicates and only analysed the most recently-reported values. Duplicates included: total brain volume [15, 43, 1, 15, 37]; intra-cranial volume [1, 1, 1, 11, 15, 11, 15, 1, 37, 43, 1, 15, 37]; hippocampal volume [1, 1, 1, 15, 11, 15, 43, 15, 37]; amygdala volume [15, 37] and OFC volume [11, 11].

We also extracted data on sample size, sex, and mean age; cannabis use levels including age of onset of cannabis use, duration of use, estimated lifetime and monthly dosage, and lifetime episodes. All data were extracted by Y.C. and P.D.S. and data extraction was cross-checked by V.L. Where studies met inclusion criteria, but did not report sufficient information to compute the required effect size(s) for the meta-analysis, data were requested from the corresponding author of the paper. Data requests were not met for one study, which was excluded from the meta-analysis.

Additional handling of data

As different studies utilise a variety of measures for cannabis use, we homogenised these measures into a standard cannabis unit to enable inter-study comparison (cones; one joint = 3 cones, 1 g = 12 cones; for other conversions see guidelines from the National Cannabis Prevention and Information Centre at https://cannabissupport.com.au/media/1593/timeline-followback.pdf). This conversion could not be applied to studies that only reported episodes of cannabis use.

In studies where cannabis users or controls were divided into subgroups specific to the focus of each study's investigation [e.g. cannabis users exposed to THC but not cannabidiol (CBD), cannabis users exposed to both THC and CBD, and cannabis users whose exposure status cannot be ascertained [15]], weighted mean and SD were calculated with the available information. Regional brain volumes were also collapsed across left and right hemispheres for the main analysis.

Filbey et al. [11] report on a cannabis + tobacco user group, and a cannabis only user group; in this instance we included the cannabis + tobacco user group in our analysis, as this is more in line with other studies included in the analysis. Yip et al. [43] report on current cannabis users and abstinent cannabis users; only current users were included in our analysis, as per our inclusion criteria.

Meta-analyses of regional brain volume

We completed a series of 17 separate meta-analyses for distinct brain regions that were examined by at least two studies (i.e. total intracranial, total brain, total grey matter, total white matter, ACC, parietal cortex, PFC, total OFC, medial OFC, lateral OFC, hippocampus, amygdala, caudate, NAc, putamen, striatum, and cerebellum volumes). Two areas were examined by two studies (i.e. whole striatum and parietal cortex) and these were meta-analysed to explore the strength of the emerging effects. For each region, we calculated the standardised mean difference (SMD) and the standard error (SE) of the SMD between cannabis users and controls.

Individual SMDs were synthesised using meta-analysis and the method of generic inverse variance (random effects assumed) in Review Manager 5.3 (the Nordice Cochrane Centre, Copenhagen). The SMD effect size was computed to allow for variation in outcome measures, by estimating differences between cannabis users and controls on the volume of each selected brain region (i.e., SMD = ($mean_{control} - mean_{cannabis}$)/pooled SD). SMD magnitude can be interpreted as: 0.2 = small effect, 0.5 = medium effect, and 0.8 = large effect. We entered the control group means and SDs first in our calculations of SMDs, thus (1) a positive SMD reflects a larger brain volume in controls relative to cannabis users, (2) a negative SMD reflects a larger brain volume in cannabis users versus controls. Random-effects models were used to account for high heterogeneity across studies. Study bias was explored using funnel plots and Egger's test of publication bias [1].

Exploratory meta-regressions with cannabis use indices

We conducted eight method of moments (random-effect model) exploratory meta-regressions. These measured the impact of lifetime dose (cones) of cannabis and duration of use, on the volumes of select brain regions that differed between cannabis users and controls in the meta-analysis, i.e. the hippocampus, total, lateral, and medial OFC.

All human and animal studies have been approved by the appropriate ethics committee and have, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Results

Study selection

Electronic database searches of PubMed, Scopus, and PsycINFO identified 1550 papers (Fig. 1). Removal of duplicates across databases resulted in 1046 papers. Of these, screening of title and abstracts resulted in 977 papers being discarded for not meeting the main eligibility criteria. The full text of the remaining 69 papers was further assessed, resulting in the identification of 26 empirical studies. Further cross-referencing identified an additional 5 studies [15, 11, 43, 15, 37]. For one study, data request

did not yield information necessary to run the meta-analysis; it was therefore excluded.

Overall, the studies' selection led to the identification of 30 studies that were used in the meta-analysis [1, 1, 1, 11, 1, 11, 11, 1, 11, 11, 1, 15, 1, 37, 15, 1, 11, 64–43, 43, 1, 1, 37, 37, 43, 15, 37].

Of these, 18 study samples were selected for meta-regressions using either duration of use and dosage as predictors of brain volumes that differed between cannabis users and controls. These included the lateral and medial portions of the OFC (3 studies/6 samples [11, 11, 43], where [11] consisted of samples from four sites—Amsterdam, Barcelona, Wollongong, and Melbourne); the total OFC (4 studies/7 samples [11, 11, 11, 43]) and the hippocampus (12 studies/15 samples [1, 1, 1, 15, 15, 1, 15, 11, 43, 1, 37, 37] where [1] consisted of samples from four sites).

Study characteristics

The included studies along with participant characteristics are presented in Table 1. Most samples comprised adult participants, and after exclusion of overlapping samples, this meta-analysis included 717 cannabis users (aged 17–40 years, 30.13% female) and 778 non-cannabis using controls (aged 16–36 years, 38.43% female). All cannabis using samples consumed cannabis on a regular basis. Cumulative cannabis exposure was highly variable, cannabis use onset commenced at an age range between 15 and 20 years and duration of cannabis use varied between 2 and 21 years.

Meta-analyses of regional brain volume

Table 2 overviews the meta-analysis results for the 17 examined regions. For regional brain measures, cannabis users relative to controls had a significantly smaller volume of the hippocampus and OFC (i.e. overall, medial and lateral portions) (see forest plots in Fig. 2, and funnel plots in Supplementary Fig. 1).

There were no group differences in the volumes of other subcortical regions (i.e. amygdala, NAc, striatum, caudate, putamen), the cerebellum (see forest plots in Supplementary Fig. 2, and funnel plots in Supplementary Fig. 3), and cortical areas (i.e. PFC, ACC, parietal, with forest plots and funnel plots shown in Supplementary Figs. 4, 5, respectively).

Global brain measures encompassed intracranial volume, total brain volume, total grey matter and total white matter, none of which differed between cannabis users and controls (see forest plots and funnel plots in Supplementary Figs. 6, 7, respectively).

Exploratory meta-regression with cannabis use indices

The hippocampus meta-regression was non-significant for lifetime cones (regression coefficient 0.0000, 95% CI 0.0000–0.0000, $Z = 0.2736$, $p > 0.05$) and duration of use (regression coefficient 0.0028, 95% CI − 0.0688 to 0.0745, $Z = 0.774$, $p > 0.05$), indicating that lifetime dose/duration did not predict hippocampal volumes. Further meta-regressions on lateral, medial, and total OFC were run, all which were non-significant, probably due to a lack of power.

Publication bias

Examination of publication bias was conducted on the meta-analyses that showed significant between-group differences. Hippocampus, NAc, total OFC, lateral OFC and medial OFC funnel plots all suggest reasonable symmetry (Supplementary Fig. 1). Moreover, Egger's test of publication bias [1] was conducted on the data from these five brain regions. We based evidence of asymmetry on $p < 0.1$ and present intercepts with 90% confidence intervals. This is the same significance level used in previous analyses of heterogeneity in meta-analysis. Egger's test was not significant in any case ($p > 0.1$), suggesting little evidence of publication bias in our sample.

Discussion

We conducted a series of meta-analyses and meta-regressions of up-to-date findings on the neuroanatomical correlates of regular cannabis use. Our findings corroborate those from a previous meta-analysis and suggest that cannabis users have reduced hippocampal volumes relative to controls. Additionally, we identified smaller orbitofrontal cortex in cannabis users relative to controls. These results are in line with the notion that regular cannabis use is associated with neuroanatomical alterations in selected brain regions—hippocampus, orbitofrontal cortex—which underscore memory and reward processes thought to be relevant in the aetiology of substance dependence [11]. Exploratory meta-regressions revealed that cannabis dosage and duration of use were not associated with hippocampal and OFC volumes, suggesting that these cannabis use parameters did not drive their volumetric reduction in cannabis users versus controls.

The OFC and hippocampus have putative roles in directing motivation, memory, and reward function, which are crucial in the aetiology and development of substance dependence. Significantly, our findings corroborate reports from individual studies that posit regular cannabis use is associated with alteration of a cluster of brain regions, which

Table 1 Structural magnetic resonance imaging studies of regular cannabis users and non-using controls

	First author	Year	CON		CB		Cannabis use[b]					Brain regions
			N (males)	Age M ± SD	*N* (males)	Age M ± SD	Onset age M ± SD	Duration M ± SD	Lifetime cones M ± SD	Lifetime episodes M ± SD	Montly cones M ± SD	
1	Block	2000	13 (6)	22.3 ± 1.8	18 (9)	22.6 ± 2.1	18.7	3.9 ± 0.4	–	3660 ± 407	–	ICV, GM, WM, cerebellum, parietal, hippocampus
2	Tzilos	2005	26 (19)	29.5 ± 8.5	22 (16)	38.1 ± 6.2	16.0 ± 4.1	22.6 ± 5.7	–	20,140 ± 13,866	–	ICV, TBV, GM, WM, hippocampus
3	Delisi	2006	10 (9)	23.0 ± 4.4	10 (9)	21.1 ± 2.9	–	–	–	–	–	TBV
4	Medina	2007a	21 (14)	17.5 ± 1.1	26 (16)	17.6 ± 0.9	15.0	2.0	–	402 ± 260	–	ICV, hippocampus
5	Medina	2007b	16 (11)	18.0 ± 0.9	16 (12)	18.0 ± 0.7	15.0	3.4 ± 1.7	–	476 ± 269	–	Hippocampus
6	Yücel	2008	16 (16)	36.4 ± 9.8	15 (15)	39.8 ± 8.9	20.1 ± 6.9	19.7 ± 7.3	186,184 ± 210,022	62,000	636 ± 565	Amygdala
7	Medina	2009	16 (10)	18.0 ± 0.7	16(12)	18.0 ± 0.9	15.0	3.0 ± 2.0	–	476 ± 269	–	WM, PFC
8	Churchwell	2010	18 (12)	17.2 ± 3.5	18 (16)	17.7 ± 4.0	15.7 ± 0.2	1.98	–	1352 ± 323	–	OFC, lateral OFC, medial OFC
9	Mata	2010	44 (25)	25.8 ± 5.8	30 (23)	25.7 ± 5.0	17.3 ± 3.9	8.4 ± 9.4	11,619 ± 9387	–	83 ± 67	ICV
10	Medina	2010	16 (10)	18.0 ± 0.7	16 (12)	18.0 ± 0.9	15.0	3.4 ± 1.7	–	476 ± 269	–	ICV, cerebellum
11	Ashtari	2011	14 (14)	18.5 ± 1.4	14 (14)	19.3 ± 0.1	15.0	5.3 ± 2.1	30,114 ± 13,500	–	529 ± 237	ICV, TBV, hippocampus, amygdala
12	Demirakca	2011	13 (13)	23.0 ± 2.0	11 (11)	22.0 ± 2.0	16.0 ± 2.0	5.4	5322	–	99	ICV, GM
13	Lopez-Larson	2011	18 (12)	17.3 ± 0.8	18 (17)	17.8 ± 1.0	15.7 ± 0.9	1.55 ± 1.2	–	1346 ± 1372	–	ICV
14	McQueeny	2011	47 (36)	17.7 ± 0.9	35 (27)	18.0 ± 0.9	15.0	3.0	–	446 ± 365	–	ICV, amygdala
15	Solowij	2011	16 (16)	36.4 ± 9.8	15 (15)	39.8 ± 8.9	20.1 ± 5.4	19.7 ± 7.3	150,350 ± 133,566	–	636 ± 565	TBV, cerebellum, cerebellar WM
16	Cousijn	2012	42 (26)	21.9 ± 2.4	33 (21)	21.3 ± 2.4	18.8 ± 2.3	2.5 ± 1.9	4739 ± 4275	–	156 ± 115	Cerebellum, cerebellar WM, ACC, amygdala, striatum
17	Schacht	2012	37 (14)	27.3 ± 7.9	94 (69)	24.2 ± 7.4	17.8 ± 3.2	10.1 ± 8.6	–	–	–	ICV, hippocampus, amygdala
18	Kumra	2012	51 (25)	16.2 ± 2.3	16 (8)	16.6 ± 1.7	13.0 ± 2.0	3.6	–	1032 ± 634	–	Hippocampus
19	Batalla	2013	28 (28)	22.1 ± 3.0	29 (29)	20.8 ± 2.1	18.1 ± 2.1	2.8 ± 2.2	15,609 ± 12,576	–	–	GM, WM, PFC, ACC, striatum
20	Filbey	2014	62 (39)	30.0 ± 7.4	48 (33)	28.3 ± 8.3	18.1 ± 3.4	9.8 ± 8.0	–	5672 ± 715	–	OFC
21	Gilman	2014	20 (9)	20.7 ± 1.9	20 (9)	21.3 ± 1.9	16.6 ± 2.1	6.2 ± 3.4	10,880 ± 9335	–	146 ± 126	ICV, TBV, GM, WM, hippocampus, amygdala, NAc, caudate, putamen
22	Yip	2014	20 (20)	29.2 ± 10.1	7 (7)	23.6 ± 15.3	14.1 ± 0.6	8.7 ± 1.9	–	–	–	Putamen
23	Filbey	2015	16 (5)	26.9 ± 6.9	55 (32)	24.4 ± 8.3	–	–	–	5959 ± 8876	–	TBV, hippocampus
24	Lorenzetti	2015	16 (16)	36.0 ± 10.0	15 (15)	40.0 ± 9.0	19.0	21.0	–	62,000	–	ACC

Table 1 (continued)

First author	Year	CON		CB		Cannabis use[b]					Brain regions
		N (males)	Age M ± SD	*N* (males)	Age M ± SD	Onset age M ± SD	Duration M ± SD	Lifetime cones M ± SD	Lifetime episodes M ± SD	Montly cones M ± SD	
25 Price	2015	32 (14)	21.1 ± 2.3	27 (15)	21.4 ± 2.2	–	–	5833 ± 10,955	–	98 ± 105	OFC, lateral OFC, medial OFC, PFC, parietal
26 Weiland[a]	2015(i)	29 (16)	27.5 ± 6.8	29 (16)	27.4 ± 7.1	–	–	–	–	–	ICV, TBV, GM, WM, cerebellum, hippocampus, amygdala, NAc
	2015(ii)	50 (36)	16.8 ± 1.0	50 (41)	16.7 ± 1.1	–	–	–	–	–	
27 Yücel	2016	37 (18)	30.0 ± 11.3	61 (29)	32.7 ± 10.9	16.7 ± 3.4	15.4 ± 9.6	74,528 ± 46,690	–	–	TBV
28 Chye[a]	2017(i)	43 (27)	22.0 ± 2.5	33 (22)	21.3 ± 2.4	18.9 ± 2.3	2.5 ± 1.9	4739 ± 4275	–	159 ± 115	OFC, lateral OFC, medial OFC, caudate
	2017(ii)	26 (26)	22.0 ± 2.9	29 (29)	20.8 ± 2.1	18.1 ± 2.1	2.8 ± 2.2	15,611 ± 12,577	–	224 ± 138	
	2017(iii)	15 (14)	35.7 ± 10.9	15 (14)	39.3 ± 9.5	19.9 ± 5.4	18.8 ± 7.8	186,744 ± 209,625	–	656 ± 557	
	2017(iv)	37 (18)	30.0 ± 11.3	63 (29)	32.2 ± 10.7	16.7 ± 3.4	15.3 ± 10.0	72,774 ± 76,353	–	396 ± 309	
29 Chye[a]	2018(i)	43 (27)	22.0 ± 2.5	33 (22)	21.3 ± 2.4	18.9 ± 2.3	2.5 ± 1.9	4739 ± 4275	–	159 ± 115	ICV, hippocampus
	2018(ii)	26 (26)	22.0 ± 2.9	29 (29)	20.8 ± 2.1	18.1 ± 2.1	2.8 ± 2.2	15,611 ± 12,577	–	224 ± 138	
	2018(iii)	15 (14)	35.7 ± 10.9	15 (14)	39.3 ± 9.5	19.9 ± 5.4	18.8 ± 7.8	186,744 ± 209,625	–	656 ± 557	
	2018(iv)	37 (18)	30.0 ± 11.3	63 (29)	32.2 ± 10.7	16.7 ± 3.4	15.3 ± 10.0	72,774 ± 76,353	–	396 ± 309	
30 Moreno-Alcazar	2018	100 (40)	31.3 ± 6.9	14 (4)	30.1 ± 5.2	17.1 ± 2.9	14.4 ± 6.7	–	–	–	Hippocampus, amygdala, caudate, putamen, NAc

CB cannabis users, *CON* non-cannabis-using controls, *ROI* region of interest, which includes, *ICV* intracranial volume, *TBV* total brain volume, *GM* total grey matter, *WM* total white matter, *OFC* orbitofrontal cortex, *PFC* prefrontal cortex, *NAc* nucleus accumbens

[a]Weiland et al. [37] reported on two separate samples—(1) adult, and (2) adolescent; and Chye et al. [1, 15] reported four samples from separate sites (i = Amsterdam, ii = Barcelona, iii = Wollongong, and iv = Melbourne)

[b]Where mean and/or SD values are not reported or unable to be estimated from the original studies, these values are not presented

Table 2 Overview of brain areas examined across studies and meta-analytic results

Brain area	*N* studies	Sample size		Meta-analytic results				
		CAN	HC	SMD	95% CI	*Z*	*p*	I^2 (%)
ICV	13	523	469	− 0.02	− 0.15, 0.12	0.25	0.80	76
TBV	8	276	218	− 0.05	− 0.26, 0.17	0.42	0.68	82
TGM	6	179	179	0.02	− 0.09, 0.13	0.36	0.72	11
TWM	6	184	182	0.02	− 0.08, 0.12	0.41	0.68	0
Hippocampus*	12	514	514	0.14	0.02, 0.27	2.29	**0.02**	74
Amygdala	8	304	355	0.02	− 0.14, 0.17	0.21	0.84	75
Striatum	2	62	70	− 0.79	− 1.71, 0.14	1.66	0.10	97
NAc	3	113	199	− 0.15	− 0.45, 0.15	1.00	**0.32**	85
Caudate	3	174	241	0.09	− 0.16, 0.35	0.71	0.48	85
Putamen	3	41	140	− 0.08	− 0.72, 0.56	0.24	0.81	94
Cerebellum	5	161	166	0.67	− 0.52, 1.87	1.10	0.27	99
Total OFC***	4	233	233	0.27	0.27, 0.37	5.20	**0.00001**	17
Lateral OFC***	3	185	171	0.19	0.07, 0.32	3.10	**0.002**	26
Medial OFC***	3	185	171	0.30	0.15, 0.45	3.89	**0.0001**	51
PFC	3	72	76	0.05	− 0.11, 0.21	0.60	0.55	0
ACC	3	77	86	− 0.03	− 0.32, 0.27	0.18	0.85	71
Parietal	2	45	45	0.03	− 0.33, 0.39	0.14	0.89	64

*$p < .05$, **$p < .01$, ***$p < .001$

ICV intracranial volume, *TBV* total brain volume, *TGM* total grey matter, *TWM* total white matter, *NAC* nucleus accumbens, *OFC* orbitofrontal cortex, *PFC* prefrontal cortex, *ACC* anterior cingulate cortex, *B* regression coefficient, unstandardized beta

are key components of reward neurocircuitry. Specifically, alteration in the neuroanatomy, activity and connectivity between the hippocampus and OFC has been consistently demonstrated in the regular use of substances other than cannabis [15, 15, 15] and future studies should examine whether connectivity between these brain regions is aberrant in regular cannabis users, particularly in those cannabis users with higher dependence levels. The observed alterations in these regions across cannabis and other substance use disorders suggest that they share a common neurobiological signature [11, 11, 1]. This notion is in line with neuroscientific theories of addiction [15, 11], whereby repeated exposure to/dependence on substances is characterised by neuroadaptations across the brain's reward, learning, and motivation circuits.

In contrast, we did not find any alterations in other key regions of the reward circuit such as the NAc and dorsal striatum, which purportedly relates to 'habitual' and 'compulsive' substance use; and the amygdala, which is ascribed to the experience of stress, craving and withdrawal experienced at the severe stages of addiction [15]. The negative findings may be due to the lower number of studies available for such regions (i.e. n = 3 for NAc, n = 6 for caudate, n = 3 putamen and n = 2 for total striatum) , which may have undermined the power to detect these effects. Alternatively, cannabis dependence severity across the samples was not consistently high enough to lead to observable robust alteration of neural pathways involved in habitual use, craving and withdrawal. Also, regular cannabis use may involve distinct neural pathways from those engaged in the regular use of other substances, and the dorsal striatum and amygdala may be engaged to a lesser extent.

Several putative mechanisms may drive the observed neural alterations in cannabis users. The hippocampus and OFC may direct the reinforcing effect of cannabis, with dopaminergic inputs along striato-orbitofrontal circuits heavily mediating the motivational salience of drug reward [37, 1], supported by the hippocampus' contextual and relational input [37, 11]. Reductions of the hippocampus and OFC volume may reflect neuroadaptations that occur with learning [1, 15] and anticipating/maintaining [1]—respectively—the association between cannabis and its rewarding value that emerges with regular long-term cannabis consumption. Alterations of the OFC and the hippocampus volumes may also result from the potential neurotoxic effects of chronic exposure to high level of cannabinoid compounds such as THC [43], particularly in regular long term users [1, 1].

In contrast with the notion that indices of cannabis use levels—such as duration and dosage—drive neuroanatomical alterations found in cannabis users relative to controls (i.e. hippocampus and OFC), meta-regressions failed to find any such associations. This negative finding may have been due to the lack of power to detect such associations, because a low number of studies was available for the OFC (i.e. n =

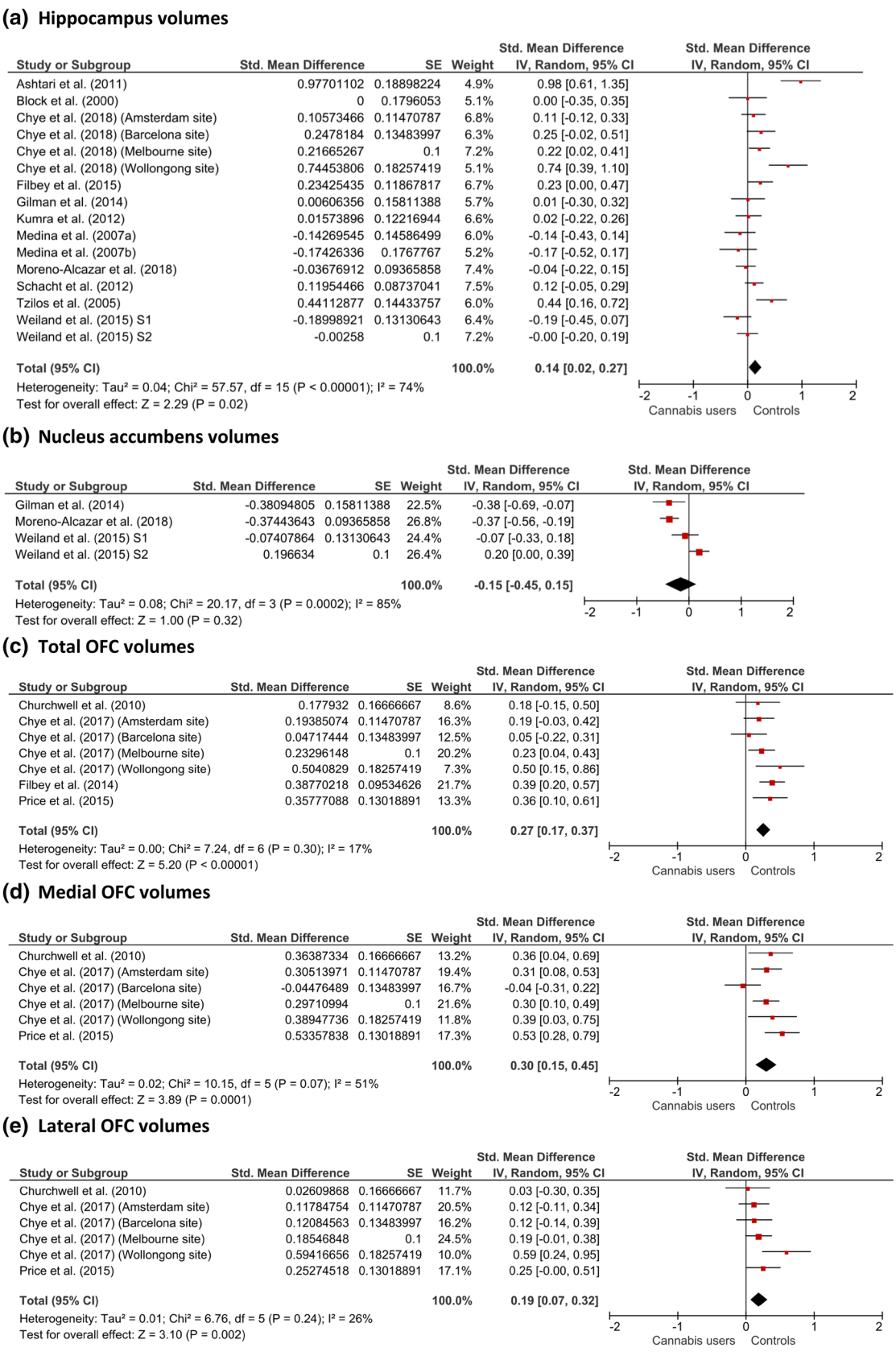

Fig. 2 Overview of forest plots showing significant meta-analytic differences between cannabis users and non-using controls in the total volumes of the hippocampus, nucleus accumbens and total, medial and lateral orbitofrontal cortex (OFC)

7), but may reflect a lack of association for the hippocampal meta-regression that was well powered (i.e. 15 studies). Other cannabis-related measures may drive neuroanatomical alterations in cannabis users, such as cannabis dependence (e.g. Severity of Dependence Scale [1, 11]), severity of problem cannabis use disorder (e.g. DSM-V criteria [1], Cannabis Use Disorder Identification Test [1]) and cannabis potency (e.g. THC and THC/CBD ratio from toxicology analyses [11]). These variables could be not included in the meta-regression as they were assessed by a minority of studies. Future studies should perform careful assessment of the level of cannabis use (e.g. dosage, duration, age of use onset, average smoking days/month, accounting for abstinence periods), cannabis potency and the severity of cannabis dependence/problem use, and where possible determine proportional exposure to THC and CBD [1, 11, 1, 37, 11, 11] to systematically measure which variables drive neuroanatomical differences between cannabis users and controls.

Variables unrelated to the direct effects of cannabinoids may also drive neuroanatomical alterations in cannabis users. For example, regular cannabis use and cannabis dependence (e.g. craving, withdrawal) have been associated with high stress levels [1, 1], and psychopathologies characterised by elevated stress (e.g. depression, anxiety, psychotic disorders [1, 15, 11, 1, 15]). Chronic circulating high amounts of stress hormones have also been shown to affect the neuronal ultrastructure within the OFC [1] and hippocampus [11]. However, stress levels and psychopathology symptoms have been inconsistently assessed in the literature, which precludes assessment of whether this variable played a role in our findings. Other factors that may contribute to neural alterations in cannabis users or mediate cannabis-related effect include comorbid alcohol or tobacco use [1, 11, 15], genetic polymorphism [37, 1], socioeconomic status and childhood maltreatment [15]. The relative contribution of these variables to the neuroanatomical correlates of cannabis use has been poorly examined and is unclear.

The results from this meta-analysis must be considered with caution. First, although significant, the volumetric group differences were small statistically, suggesting that there was a considerable overlap between regular cannabis users and controls. This is plausible as regular cannabis users comprise a wide variety of participants, with heterogeneous levels of dependence, entrenched sub-clinical comorbidities (i.e. participants were screened for psychopathologies) and other psychosocial variables that also affect neuroanatomy. Second, our ability to detect group differences in some of the examined brain regions (i.e. the whole striatum, caudate, putamen) may have been affected by the small number of studies that examined these areas (i.e. two-to-three studies). Future meta-analyses comprising additional studies are required to confirm the results in these under-investigated regions. Third, the cross-sectional study designs prevents drawing any conclusions on the causal nature of group differences between cannabis users and controls. These alterations may either follow or predate cannabis use onset, as preliminarily shown for the OFC [1, 15], which are ascribed to personality traits such as impulsivity and sensitivity to reward that predate substance use onset [43]. Neural differences between cannabis users and controls also may normalise with prolonged abstinence [15]. Fourth, multiple cannabinoid compounds encapsulated in commonly smoked cannabis may exert independent and interactive effects on the central nervous system (e.g. THC and CBD [15]), a notion to be elucidated in future studies. Finally, the lack of a standardised diagnostic assessment for problematic (rather than recreational) cannabis use in the meta-analysed samples precludes the understanding of whether group differences between cannabis users and controls were driven by a subgroup of more severe cannabis users, as shown in preliminary work on cannabis use neurobiology [15] and postulated by neuroscientific theories of addiction whereby the transition from recreational use to dependence is characterised by neuroadaptations in reward pathways [17–1].

In summary, this meta-analysis provides evidence that regular cannabis use is associated with neuroanatomical alterations in multiple brain regions, namely smaller OFC and hippocampal volumes, all of which are key components of the reward, learning, and motivation circuits underpinning and altered in other substance use disorders. While these findings suggest common neural alterations between those who use cannabis and other substances on a regular basis, the lack of dosage- and duration-dependent associations highlights the need to elucidate whether such alterations are driven by cannabis-related measures (e.g. dosage, dependence, potency), confounders entrenched with regular cannabis use (e.g. stress and symptoms of anxiety, depression and psychosis; impulsivity, comorbid tobacco and alcohol use, and illicit substance use) or distinct motivational factors that drive one to smoke cannabis regularly (e.g. to experience pleasure, for habit [37], to cope with/avoid difficult emotions [43], to regulate one own's homeostasis [37], among others). We warrant the conduct of detailed assessment of cannabis-related measures and confounders to enable the elucidation of mechanisms driving neuroanatomical differences between cannabis users and controls and identify subgroup of users who may be particularly vulnerable to the adverse neurobehavioural effects of cannabis. Progress in this direction will in turn be able to inform public policy and clinical treatment strategies that target and protect the most vulnerable users.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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