



# Brain Anatomical Alterations in Young Cannabis Users: Is it All Hype? A Meta-Analysis of Structural Neuroimaging Studies

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## Abstract

**Introduction:** Cannabis use has a high prevalence in young youth and is associated with poor psychosocial outcomes. Such outcomes have been ascribed to the impact of cannabis exposure on the developing brain. However, findings from individual studies of volumetry in youth cannabis users are equivocal.

**Objectives:** Our primary objective was to systematically review the evidence on brain volume differences between young cannabis users and nonusers aged 12–26 where profound neuromaturation occurs, accounting for the role of global brain volumes (GBVs). Our secondary objective was to systematically integrate the findings on the association between youth age and volumetry in youth cannabis users. Finally, we aimed to evaluate the quality of the evidence.

**Materials and Methods:** A systematic search was run in three databases (PubMed, Scopus, and PsycINFO) and was reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We run meta-analyses (with and without controlling for GBV) of brain volume differences between young cannabis users and nonusers. We conducted metaregressions to explore the role of age on volumetric differences.

**Results:** Sixteen studies were included. The reviewed samples included 830 people with mean age 22.5 years (range 14–26 years). Of these, 386 were cannabis users (with cannabis use onset at 15–19 years) and 444 were controls. We found no detectable group differences in any of the GBVs (intracranium, total brain, total white matter, and total gray matter) and regional brain volumes (i.e., hippocampus, amygdala, orbitofrontal cortex, and total cerebellum). Age and cannabis use level did not predict (standardized mean) volume group differences in metaregression. We found little evidence of publication bias (Egger's test  $p > 0.1$ ).

**Conclusions:** Contrary to evidence in adult samples (or in samples mixing adults and youth), previous single studies in young cannabis users, and meta-analyses of brain function in young cannabis users, this early evidence suggests nonsignificant volume differences between young cannabis users and nonusers. While prolonged and long-term exposure to heavy cannabis use may be required to detect gross volume alterations, more studies in young cannabis users are needed to map in detail cannabis-related neuroanatomical changes.

**Keywords:** cannabis; adolescence; magnetic resonance imaging; volumes; meta-analysis; metaregression

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## Introduction

Youth is primarily when cannabis use is first initiated and is a period of rapid brain maturation.<sup>1</sup> Between 15% and 33% of youths report using cannabis in the past year in Europe and North America.<sup>2,3</sup> Of these, one in six youth cannabis users go on to develop a cannabis use disorder,<sup>4</sup> which is one of the most common drug disorders among people treated in specialist drug treatment services globally.<sup>5</sup>

It is therefore not surprising that the burden of disease from youth cannabis use is substantial. For instance, regular cannabis use has been associated with lower school attainment, early school dropout, depression, anxiety, psychosis, impulse-control disorders, suicidal ideation, addiction, and diminished life satisfaction.<sup>6</sup> Also, youth cannabis use onset predicts worse mental health in adulthood (e.g., depression, psychoses).<sup>6</sup>

These trends are alarming, as the proportion of youths who believe that cannabis use poses a risk of harm has decreased over the past decade, with cannabis being considered the least harmful illicit drug and the easiest to obtain.<sup>5,7</sup> Therefore, developing evidence to inform prevention and intervention strategies that target vulnerable youth is urgently required. From a neurobiological perspective, we have a preliminary appreciation of the fundamental processes and brain regions that are associated with cannabis use. The advancement of magnetic resonance imaging (MRI) has supported increasingly sophisticated endeavors to identify the core neurobiology of cannabis use in young people.

The adverse psychosocial outcomes associated with youth cannabis use have been ascribed (partly) to the impact of cannabis use on the developing brain. Cannabis exerts its psychoactive effects via the endocannabinoid system—which comprises cannabinoid receptors (CB1), endogenous cannabinoids (endocannabinoids), and enzymes responsible for the synthesis and degradation of endocannabinoids.<sup>8</sup>

Specifically, delta-9-tetrahydrocannabinol (THC) binds to brain cannabinoid receptors type 1 [CB1]<sup>9,10</sup> and its repeated administration can have long-lasting effects on cannabinoid-mediated plasticity<sup>11,12</sup> and atrophy.<sup>13</sup> Also, the endocannabinoid system serves an integral role in determining brain maturation.<sup>14</sup> Therefore, brain maturation during youth may be directly perturbed by exposure to exogenous cannabinoids encapsulated in cannabis—particularly to THC, which is the primary psychoactive ingredient that confers its addiction liability and psychotogenic/anxiogenic properties.<sup>15,16</sup>

A growing body of MRI research in cannabis users has now been published and has identified neuroanatomical differences between cannabis users and nonusers in distinct brain regions. Nonetheless, the literature to date provides inconsistent findings, with both presence and absence of differences between youth cannabis users and nonusers. Given the heterogeneity in samples of cannabis users, a key area worth investigating is the impact of neurodevelopmental stage (i.e., age) and cannabis use levels on neuroanatomy (e.g., age, age of cannabis use onset, dosage, and duration of use).

Most MRI studies to date have limited power to detect the neurobiological impact of using cannabis at different stages of neurodevelopment. Therefore, the concurrent use of systematic reviews, meta-analyses, and meta-regressions can be useful in measuring the strength of these effects across the totality of the available data.

To date, several reviews of cannabis and structural brain alterations have already been published.<sup>17–20</sup> However, they have not systematically quantified the effects specific to youth cannabis users, because they included samples with mean ages and age ranges across youth and adulthood (e.g., from age 12 to 55+). The heterogeneity of the ages of the reviewed samples prevents the unpacking of whether structural brain alterations in cannabis users are observable during adolescent brain maturation specifically.

Furthermore, reviews in youth cannabis use have not included complimentary meta-analyses and/or meta-regression analyses.<sup>17,18</sup> Finally, while existing meta-analyses include youth samples, older adults are typically included such that conclusions are not specific to youth. As such, detailed analyses of brain volumetric changes in youth cannabis use are currently unavailable.

This evidence gap prevents the understanding of whether brain maturation renders the adolescent brain more vulnerable or more resilient to the impact of regular cannabis exposure, compared to adult samples where neurodevelopment has concluded. We are yet to know if the evidence is consistent in showing that the adolescent brain shows volumetric alterations comparable to those observed in adult samples.

We hereby aim to address a knowledge gap on the evidence for brain structural changes in cannabis users, by reporting for the first time (to our knowledge), a series of meta-analyses on the neuroanatomical correlates specific to youth cannabis use. We defined youth as age ranging from 12 to 26 years, in line with rigorous neuroscientific evidence that significant adolescent neurodevelopment occurs through this time.<sup>1</sup>

Data from studies that used T1-weighted structural MRI are included in our analyses, as this provides a relatively stable brain measure that minimizes state-related processes associated with the effects of acute intoxication, residual effects from recent cannabis use, and withdrawal. We selected all studies conducted thus far that examined youth samples of cannabis users with an age range of 12–26 years.<sup>1</sup>

We are the first to explore the influence of age and cannabis use levels (i.e., age of cannabis use onset, cumulative dosage, duration) on brain volumetry in youth cannabis users using metaregression analyses. We also are the first to systematically account for the influence of global brain volume (GBV, which is known to change during neurodevelopment) on regional brain volumes, to better assess the specificity of any regional differences.<sup>21,22</sup> In sum, this work adds new knowledge by reporting meta-analyses on cannabis users versus nonusers samples during adolescent neurodevelopment specifically, metaregressions exploring the impact of age and cannabis use levels on volumetry in adolescence, and by parceling out the confounding effect of GBVs.

## Materials and Methods

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>23</sup> See Supplementary Table S1 for PRISMA checklist.

### Eligibility criteria

We selected studies based on the following inclusion criteria: (1) peer-reviewed; (2) human samples; (3) youth age defined as 12 to 26 years;<sup>1</sup> (4) published in English; (5) neuroanatomical assessment via T1-weighted MRI scans; (6) compared regular cannabis users (as defined by each study protocol) and nonusers; (7) current cannabis use in the cannabis-using sample, which included ongoing use and up to 28-day abstinence; and (8) upper age limit of the sample  $\leq 26$  years, as the main focus was to examine the neurobiology of cannabis exposure on youth brain structure. In cannabis using samples, cannabis was the current primary substance of regular use.

Exclusion criteria were the following: (1) regular use of substances other than cannabis, nicotine, or alcohol; (2) diagnosis of a mental health disorder, including substance use disorders or dependence on substances (other than cannabis and nicotine use disorders/dependence); and (3) cannabis-user group abstinent for  $> 28$  days.

### Searches and study selection

Our search followed PRISMA guidelines. One author (M.K.) searched three online databases; PubMed, Scopus, and PsycINFO on the 17th of May 2021, using the terms “Marijuana OR Cannabis” and “MRI OR Neuroimaging.” Two authors (L.D. and M.K.) removed duplicates and completed eligibility screening. The eligible studies were compared, and disagreements about inclusion/exclusion criteria were then discussed and resolved by consensus. If consensus could not be reached, the third author (V.L.) made an independent decision.

Electronic database searches of PubMed, Scopus, and PsycINFO identified 2911 articles (Fig. 1). Removal of duplicates across databases resulted in 2375 articles. Of these, 2300 articles were discarded for not meeting the main eligibility criteria based on title and abstract screening. The full text of the remaining 75 articles were further assessed, resulting in the identification of 13 empirical studies. Further cross-referencing (e.g., on reference lists of included studies) identified an additional three studies. For two studies, data request did not yield information necessary to run the meta-analysis; they were therefore excluded.<sup>24,25</sup>

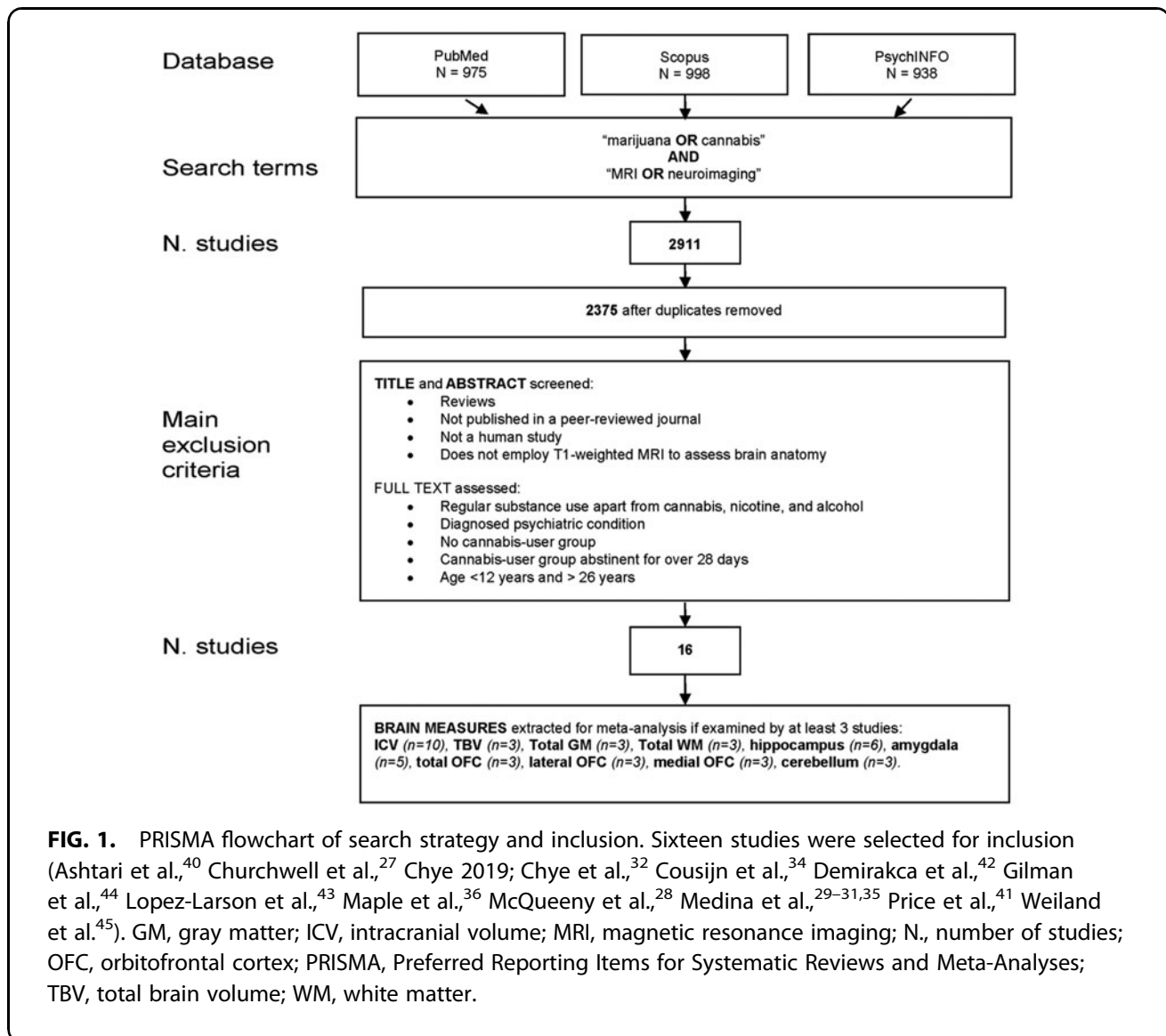
### Data extraction

Outcome measures were included when examined by  $\geq 3$  studies. Outcome measures were GBV (i.e., intracranial volume [ICV], total brain volume [TBV]), total white matter (TWM), total gray matter (TGM), regional brain volumes—hippocampus, amygdala, orbitofrontal cortex (total, medial, and lateral portions; OFC), and cerebellum.

Data on the following variables were extracted from the included studies: sample size (number), sex composition (number of males and females), mean age (years), and cannabis use indices, including age of cannabis use onset (years), cannabis use duration (years), and lifetime cannabis dosage (cones, episodes). All data were extracted by M.K. and cross-checked by V.L. In cases where studies met all of the inclusion criteria but did not report data necessary for computing effect sizes for our analyses, data were requested from the corresponding author.

### Additional handling of data

We standardized measures of cannabis dosage that were heterogeneous between studies to cones, to enable inter-study comparison (one joint = 3 cones, 1 g = 12 cones).<sup>26</sup> This conversion could not be applied to studies that only measured cannabis dosage in episodes.<sup>27–31</sup>



Where the same brain measures from overlapping study samples were reported by multiple studies, we removed duplicates and only extracted the most recently reported values.

Duplicate volumes were from the following areas: ICV,<sup>29,32–35</sup> hippocampus,<sup>33,34</sup> and OFC.<sup>32,34</sup>

In a study where female and male cannabis users and nonusers were reported separately,<sup>36</sup> a weighted pooled mean and standard deviation (SD) for key variables were calculated with the available information. In the same study, where duration of cannabis use was not directly reported,<sup>36</sup> duration was derived from age and age of onset of use information.

In one study,<sup>33</sup> both manual and automated brain region segmentation were reported; we have extracted only manually calculated volumes as manual tracing is considered the gold standard for volumetry.<sup>37</sup>

#### Meta-analyses of regional brain volume

For all meta-analyses, regional brain volumes were collapsed across left and right hemispheres. For each region, we computed standardized mean difference (SMD) and the standard error of the SMD between cannabis users and nonusers.

Individual SMDs were synthesized using meta-analysis and the method of generic inverse variance

(random effects assumed) using Review Manager 5.4.1 (the Nordice Cochrane centre, Copenhagen). The effect size of the SMD was computed to allow for variation in outcome measures, by estimating differences between cannabis users and nonusers on the volume of each selected brain region (i.e.,  $SMD = \text{mean1} - \text{mean2}/\text{pooled SD}$ ). The magnitude of the SMD was interpreted as the following: 0.2=small effect, 0.5=medium effect, and 0.8=large effect.<sup>38</sup> A positive SMD indicates smaller volumes in youth cannabis users relative to nonusers. A negative SMD reflects a larger volume in youth users than nonusers. Random-effects models were used to account for high heterogeneity across studies.

Meta-analyses compared groups by GBVs, which included ICV ( $n=10$ ), TBV ( $n=3$ ), and brain volumes adjusted for GBVs: TGM ( $n=3$ ), TWM ( $n=3$ ), hippocampus ( $n=6$ ), amygdala ( $n=5$ ), total, medial, and lateral OFC ( $n=3$ ), and cerebellum ( $n=3$ ).

We ran sensitivity meta-analysis using raw volumes (without accounting for the influence of GBV) for the following regions: TGM ( $n=3$ ), TWM ( $n=3$ ), hippocampus ( $n=6$ ), amygdala ( $n=5$ ), and cerebellum ( $n=3$ ). The methods to adjust regional volumes for GBV and to compute raw volumes are described in Supplementary Data S1.

**Exploratory metaregressions: age and cannabis use levels in young cannabis users as predictors of differences in volumes (SMDs) between groups**

We conducted 10 methods of moments (random-effect model) exploratory metaregressions, to examine whether the age of young cannabis users predicted differences in volumes (SMDs) between groups. We ran an additional 15 exploratory metaregressions using cannabis use levels as predictors of (standardized mean) volume group differences. Cannabis use levels included duration and lifetime dosage in cones (ICV, hippocampus, and amygdala), lifetime exposure in episodes (ICV), and past month dosage in cones (ICV, hippocampus).

**Publication bias and quality assessment**

Examination of publication bias was conducted on all meta-analyses included in the study and included (1) conducting Egger's test of publication bias<sup>39</sup> on the data from all brain regions and (2) the quality assessment of all studies using the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment for Case-Control Studies (<https://www.nhlbi.nih.gov/>). For Egger's test, 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.

## Results

**Overview of samples' characteristics**

Supplementary Figure S1 overviews the samples' demographic and cannabis use characteristics. The samples comprised 830 youth (264 female) aged between 14 and 26 years from 16 studies.<sup>27–36,40–45</sup> Of these, 386 were cannabis users and 444 were nonusers and all groups were matched by age (Supplementary Table S2). Youth started using cannabis between the age of 15 and 19 and used cannabis for a mean duration of 1.6 to 6.2 years. The range of cannabis cumulative dosage was 4739 to 30,114 cones and 402 to 1352 episodes.

The MRI data acquisition and processing varied between studies (Supplementary Data S2 and Supplementary Table S3).

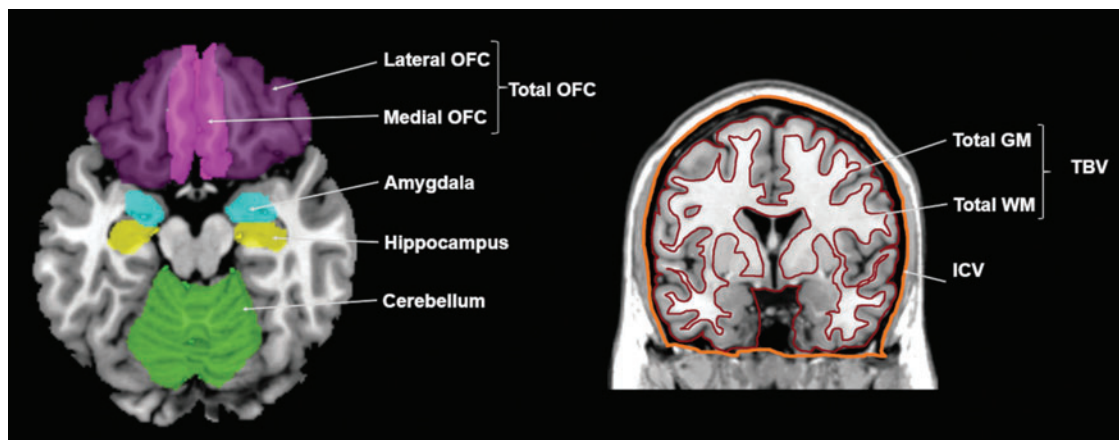
**Meta-analyses of brain volume differences between cannabis users and nonusers**

The meta-analyzed regions are shown in Figure 2. Our meta-analytic results overviewed in Table 1 show that groups were nonsignificantly different for GBVs (ICV, TBV) and GBV-corrected regional brain volumes (TGM, TWM, hippocampus, amygdala, total, medial, and lateral OFC, and cerebellum). These results are reported in detail in forest plots (Figs. 3 and 4) and funnel plots (Supplementary Figs. S2 and S3).

Nonsignificant group differences emerged for raw regional volumes (TGM, TWM, hippocampus, amygdala, and cerebellum; Supplementary Table S4).

**Metaregressions: age and cannabis use level as a predictors of group differences in volumes (SMDs)**

Table 2 shows that the age of young cannabis users did not significantly predict group differences (SMDs) in the volumes of the ICV, TBV, TGM, TWM, hippocampus, amygdala, total, medial, and lateral OFC, and cerebellum. Further, there was no significant effect of cannabis use level (onset, duration, lifetime cones, and monthly cones) on SMD group differences for ICV, hippocampus, and amygdala, and of lifetime episodes on SMD group differences in ICV.



**FIG. 2.** Overview of the meta-analyzed samples' sample size, age, and cannabis use levels. Each data point represents a different study sample. Color images are available online.

#### Publication bias

Funnel plots for all regions suggest reasonable symmetry (Supplementary Figs. S2). Egger's test was not significant ( $p > 0.1$ ), suggesting that there was little evidence of publication bias in the reviewed studies.

#### Overview of studies' quality assessment

Supplementary Table S5 summarizes the quality assessment using NHLBI Quality Assessment for Case-Control Studies. Overall, the quality of the studies was good. All studies were assessed as providing clear research objectives, including appropriate populations, and providing information about their data analyses. In all but two studies, cannabis users and nonusers were recruited from the same population. In one study,<sup>40</sup> cannabis users were recruited from a therapeutic

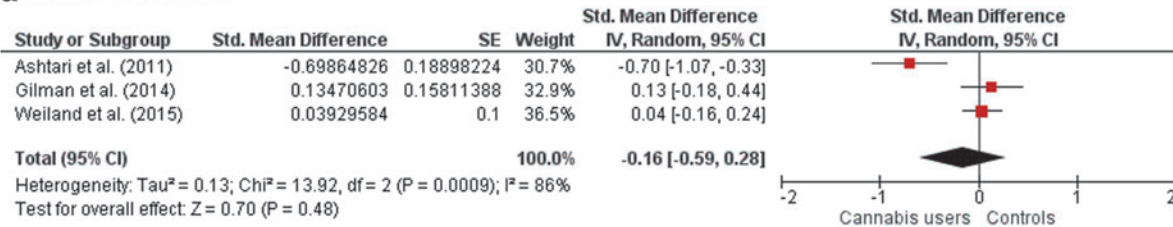
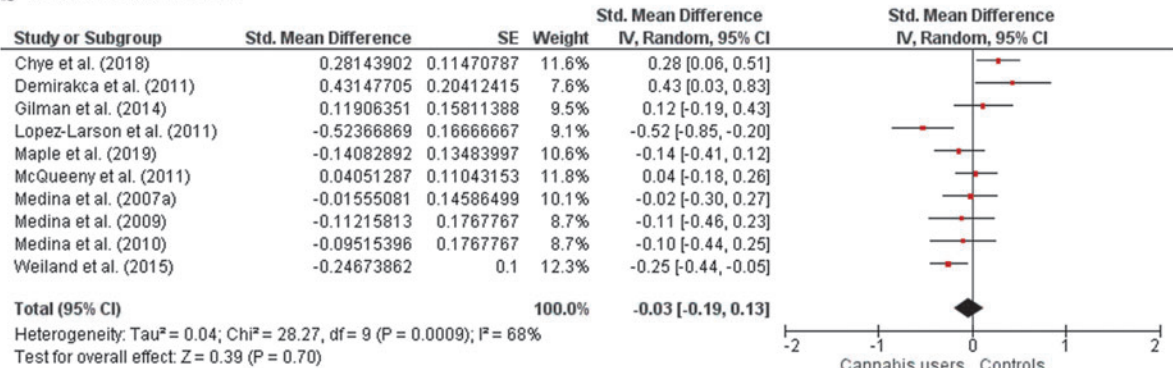
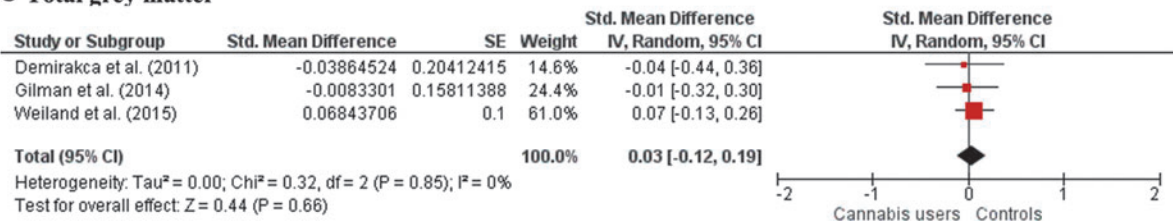
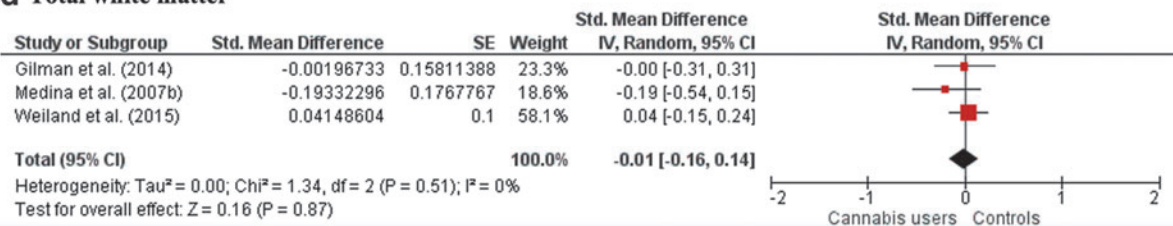
community, while nonusers were recruited via flyers in the community and by word of mouth. In another study,<sup>44</sup> the information on whether groups were recruited from the same population was missing.

In one study,<sup>40</sup> the case representation was classified as "poor": this study included only males. Two studies did not control for all significant potential confounders in their statistical analyses and were classified as "fair." This includes one study<sup>42</sup> where the total ICV, alcohol, and nicotine consumption were used as covariates and another study<sup>27</sup> where only total segmented brain volume was used as a covariate. None of the studies justified their sample sizes. Two criteria of NHLBI scale were not applicable (i.e., random selection of study participants and blinding of exposure assessors).

**Table 1. Overview of Results from Meta-Analyses of Regional and Global Brain Volume Comparison Between Youth Cannabis Users and Nonusers: Main Analyses**

Brain area	No. of studies	Sample size		Meta-analytic results				
		Cannabis	Controls	SMD	95% CI	Z	p	I <sup>2</sup>
TBV	3	84	84	-0.16	-0.59 to 0.28	0.70	0.48	86%
ICV	10	245	279	-0.03	-0.19 to 0.13	0.39	0.70	68%
TGM	3	81	83	0.03	-0.12 to 0.19	0.44	0.66	0%
TWM	3	86	86	-0.01	-0.16 to 0.14	0.16	0.87	0%
Hippocampus	6	159	164	-0.03	-0.14 to 0.08	0.57	0.57	0%
Amygdala	5	152	173	0.01	-0.10 to 0.11	0.11	0.92	0%
Total OFC	3	78	93	0.17	0.07 to 0.40	1.38	0.17	58%
Lateral OFC	3	78	93	0.08	-0.10 to 0.26	0.90	0.37	28%
Medial OFC	3	78	93	0.29	0.05 to 0.64	1.66	0.10	80%
Cerebellum	3	99	108	0.03	-0.10 to 0.17	0.45	0.65	0%

ICV, intracranial volume; OFC, orbitofrontal cortex; SMD, standardized mean difference; TBV, total brain volume; TGM, total gray matter; TWM, total white matter.

**a Total brain volume****b Intracranial volume****c Total grey matter****d Total white matter**

**FIG. 3.** Overview of meta-analyzed global brain volumes and regional brain volumes. TGM, total gray matter; TWM, total white matter. Color images are available online.

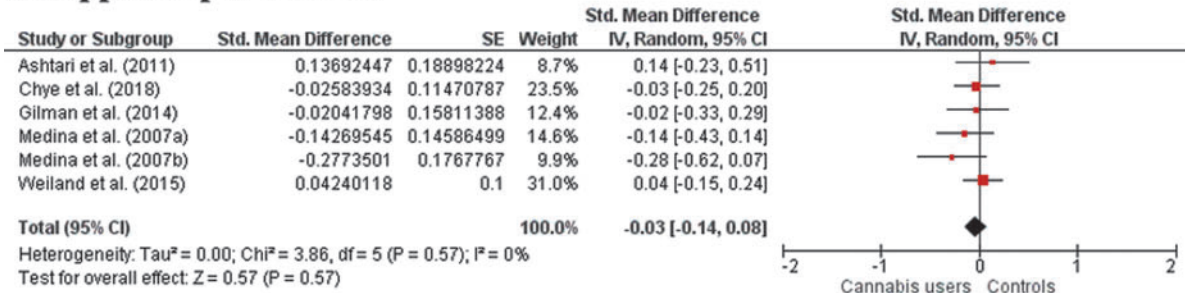
**Discussion**

The current meta-analysis shows nonsignificant differences between youth cannabis users and controls in global and regional brain volumes. In addition, age was not a significant predictor of regional brain volume differences between groups. Therefore, the impact of cannabis use on brain volumetry in youth appears to be different from that reported in samples comprising

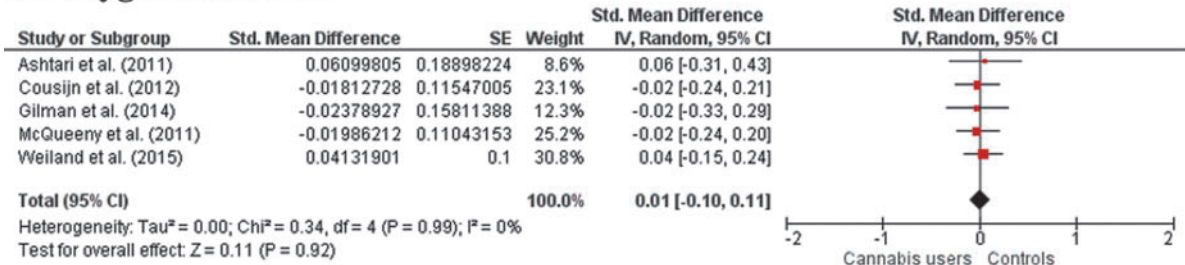
adults—or both adults and adolescents—where gross volumetric reductions were reported within the hippocampus and the OFC.

The lack of significant group differences across our analyses could indicate that youth brain structure is highly resilient to environmental insults (such as repeated cannabis use). This is supported by a recent large cohort study<sup>24</sup> that shows no volume differences

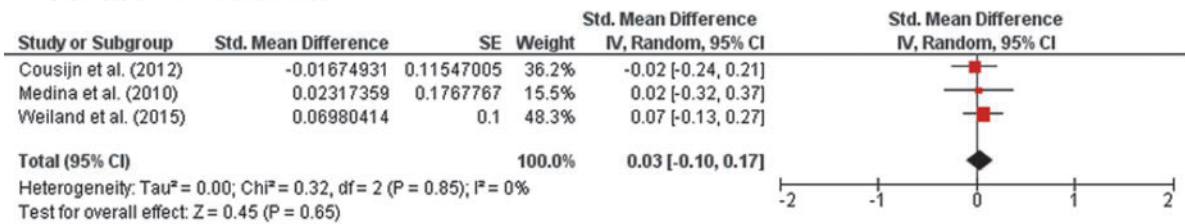
### a Hippocampal volumes



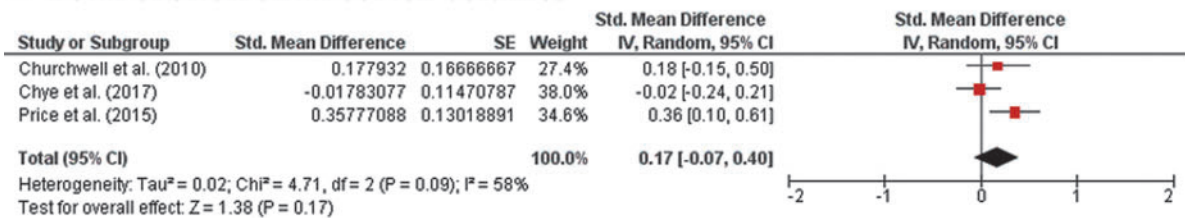
### b Amygdala volumes



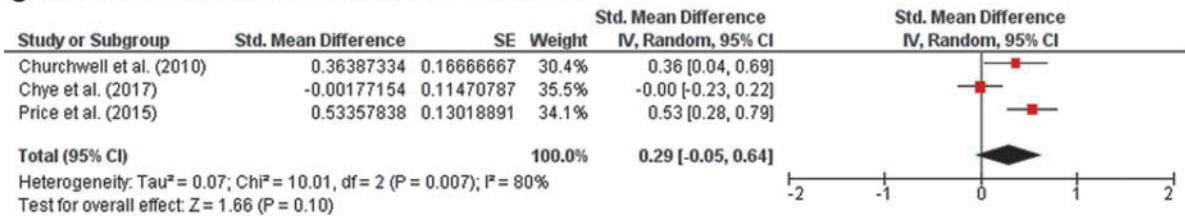
### c Cerebellar volumes



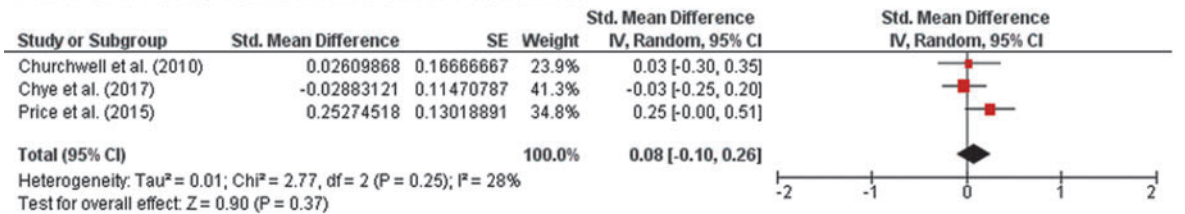
### d Total orbitofrontal cortex volumes



### e Medial orbitofrontal cortex volumes



### f Lateral orbitofrontal cortex volumes



**Fig. 4.** Overview of forest plots showing non-significant meta-analytic differences between adolescent cannabis users and non-using controls in the volume of global brain regions, hippocampus, amygdala, cerebellum and orbitofrontal cortex (total, medial, lateral). Color images are available online.



**Table 2. Results from Exploratory Metaregressions Measuring How Age Predicts Regional and Global Volumetry in Youth Cannabis Users (Based on Main Analysis)**

Cannabis users			Metaregression results					
	No. of studies	Sample size	<i>B</i>	SE	95% CI	<i>Z</i>	<i>p</i>	Beta
TBV	3	84	0.0157	0.1647	−0.3071 to 0.3385	0.0951	0.9242	0.3058
ICV	10	245	0.0362	0.1435	−0.2451 to 0.3174	0.2521	0.8010	0.4379
TGM	3	81	−0.0187	0.1188	−0.2515 to 0.2142	−0.1570	0.8752	−0.9791
TWM	3	86	−0.0057	0.1023	−0.2061 to 0.1948	−0.0554	0.9558	−0.2169
Hippocampus	6	159	−0.0036	0.0933	−0.1865 to 0.1794	−0.0383	0.9695	−0.0807
Amygdala	5	152	−0.0081	0.0757	−0.1565 to 0.1402	−0.2073	0.9145	−0.4883
Total OFC	3	78	−0.0520	0.2397	−0.5219 to 0.4178	−0.2171	0.8281	−0.7481
Lateral OFC	3	78	−0.0118	0.1256	−0.2579 to 0.2344	−0.0936	0.9254	−0.4273
Medial OFC	3	78	−0.0994	0.4432	−0.9681 to 0.7694	−0.2242	0.8226	−0.7682
Cerebellum	3	99	−0.0157	0.1038	−0.2190 to 0.1877	−0.1511	0.8799	−0.9642

SE, standard error.

between young cannabis users and controls in a range of GBV (TBV, TWM volume, TGM volume), lobar (frontal, temporal, occipital, parietal, insular, and limbic), and regional (such as putamen, caudate, nucleus accumbens, amygdala, hippocampus, and thalamus).

Our results contrast with findings of volume reductions reported in previous meta-analyses of adults<sup>20,46</sup> or of adults and youth,<sup>19</sup> which have found lower hippocampus and OFC volumes in cannabis users. Thus, age may moderate how regular cannabis exposure affects volumetry.<sup>47</sup> It is possible that mechanisms underlying neurodevelopment protect from cannabinoid-related volumetric alterations of the hippocampus/OFC.<sup>48,49</sup>

For example, brain maturation is characterized by high production and level of brain-derived neurotrophic factor within the hippocampus, which can promote neurogenesis<sup>50</sup> and may protect against cognitive deficits elicited by THC exposure within this region.<sup>51</sup> In addition, levels of cannabidiol (CBD) in cannabis may protect against THC-related adverse effects on volumetry.<sup>52</sup>

Finally, changes in the endocannabinoid system, which drive significant and rapid changes during brain maturation in brain areas, including the OFC and the hippocampus, might protect the developing brain from cannabinoid exposure through complex, yet, uncharted mechanisms, as previously suggested.<sup>53–56</sup> Thus, findings of reduced volumes in cannabis using adults or in samples comprising both adults and youth—but not in those comprising only youth as examined herein—suggest that regular canna-

bis exposure may exert detrimental effects on the brain after neuromaturational processes have taken place.

One important consideration is that the lack of meta-analytic differences in volumetry between youth cannabis users and nonusers coexist with strong evidence of adverse psychological, educational, and cognitive outcomes in youth cannabis users.<sup>6</sup> Thus, it is plausible that changes in volumetry do not underpin these psychological, educational, and cognitive outcomes in young cannabis users, or that the psychosocial differences manifest before neurobiological differences.

The lack of differences between youth cannabis users and nonusers, may be due to the heterogeneity of cannabis use levels and cannabis use-related problems (e.g., severity of dependence and driving while intoxicated) in the examined samples. Indeed, previous evidence<sup>32,33,57</sup> and neuroscientific theories of addiction<sup>58,59</sup> show that neural alterations occur in samples with more chronic levels of cannabis use and with greater severity of cannabis dependence. Thus, volume alterations related to chronic use might be conflated by the fact that such alterations did not occur in samples of youth with lighter patterns of use and who do not experience significant problems in relationship to use.

Alternatively, it is possible that because the examined samples are young, they may not have been exposed for long enough to detect differences using MRI.

Indeed, there is evidence that volume reductions in cannabis users can be dose-dependent (e.g.<sup>60</sup>). Yet, some studies in young people detect group differences in volumetry<sup>61</sup> and cognition<sup>62</sup> in samples with extremely low levels of cannabis use. Thus, low levels of

use may be sufficient to observe volume alterations in selected samples, and key variables may moderate the influence of cannabis on neurodevelopment (e.g., heavier use, cannabis type and potency used, and psychosocial characteristics of the samples). Cannabis use levels were also poorly and inconsistently measured, and future work is required to use standardized tools to measure cannabis use to enable the integration of the findings.<sup>63,64</sup>

#### Cannabis or GBV effects?

The results from our meta-analysis may reflect a true nonsignificant difference in volumetry between cannabis users and controls in youth. Indeed, we accounted for the impact of GBVs on regions for TGM, TWM, hippocampus, amygdala, and cerebellum. Specifically, for these regions, we ran analyses with raw volumes and with corrected volumes, and group differences remained nonsignificant, suggesting that GBVs may not change how cannabis affect these brain regions in youth. These findings need to be examined for OFC volumes as we could not run such analyses (i.e., with raw volumes vs. with GBV' correction) for the OFC (total, medial, and lateral) as only one study provided raw OFC volumes.

The lack of findings for an effect of GBV on regional volumetry may be specific to the youth cannabis users. GBVs have previously shown to robustly predict regional brain volumes through the lifespan, including at different rates through brain maturation.<sup>65</sup> Indeed, MRI studies routinely account for and show a significant effect of GBVs (e.g., as covariates) when examining volumetric differences between groups or associations between volumetry and behavioral data.

We cannot exclude that this finding replicates to adult samples beyond the period of neurodevelopment. As (to our knowledge) previous meta-analyses did not parcel out the impact of GBVs on the meta-analyzed volumes, including a mix of raw and corrected volumes, the differences between cannabis users and controls reported in previous meta-analyses might have been partly confounded by GBVs.

#### Tools may lack sensitivity to detect subtle neuroanatomical alterations

The methods used in the studies included in our meta-analyses may not be sensitive enough to detect existing brain alterations in youth cannabis users. First, volumetry may not be adequate to detect existing subtle neuroanatomical alterations, for example, of the micro-

structure, compared to other tools that examine brain images at the voxel level such as voxel-based morphometry and diffusion-weighted imaging, for example, fixel-based analysis. Indeed, other meta-analyses using proton magnetic resonance spectroscopy to measure hippocampal metabolite concentrations<sup>17,52</sup> and morphometric analysis on the FreeSurfer-segmented subcortical regions<sup>66</sup> have found differences in brain function in youth cannabis users.

As the imaging tools varied significantly between studies, the application of replicable (acquisition and analysis) protocols and advanced in MR tools will prove useful to explore neuroanatomical correlates of youth cannabis users in a reliable manner, so the study results can be readily integrated.

To this end, the concurrent use of high strength MRI scanners, standardized and state-of-the art acquisition sequences that enable acquiring high-resolution images of the youth brain *in vivo* (e.g., those developed by the Human Connectome Project, [www.humanconnectomeproject.org](http://www.humanconnectomeproject.org), magnetization-prepared rapid gradient-echo imaging [MPRAGE]) and analyses pipelines that account for the specific features of the youth brain (e.g., use of tailored templates), will be necessary to characterize neuroanatomical alterations in youth cannabis users.

Second, the statistical approaches used in this work did not take account of nonlinear trajectories of brain development that might have affected the data differently across different sample ages<sup>67</sup> and to the noneven effect that drug exposure can have at different stages of brain maturation.<sup>68</sup> Indeed, nonlinear effects cannot adequately be modeled by meta-analyses and metaregressions as these statistical approaches rely on general linear models.

Future studies are warranted to combine multimodal tools, including pubertal stage (e.g., using Tanner stages), sex hormones (e.g., from saliva and hair analyses), and detailed cannabis exposure (e.g., timeline-follow back<sup>69</sup>) and cannabis use-related problems (e.g., Cannabis Use Disorder Identification Test<sup>70</sup>) to examine in detail how cannabis use in youth affects neurodevelopment.

#### Limitations of the literature to date and of the meta-analysis

The results from this work must be interpreted in light of key methodological limitations. First, the role of additional variables that may affect volumetry is unclear, such as sex differences (most youth were male), pubertal stage, varying levels of cannabis and other substance use

(i.e., these were measured in a minority of studies and using inconsistent metrics, and their effects could not be systematically assessed), mental health (e.g., level of stress, subclinical psychopathology symptoms, early trauma), education and socioeconomic status, parental education, and mental health.

Second, we had limited power to detect group differences and effect of age and cannabis use levels on selected brain areas that were examined by a lower number of studies (e.g., TBV, TGM, TWM, OFC, and cerebellum were examined by three studies, and cannabis use levels were measured largely by one or two studies with a few exceptions).

Meta-analyses and mega-analyses of the updated literature with new evidence are needed to confirm the results hereby reported. Third, while we accounted for GBVs, this was not done using consistent methods. Indeed, volumes accounted for GBVs in inconsistent ways: in 10 out of 16 studies as a ratio to overall ICV, in one study as a ratio to TBV, in two studies as a ratio of regional to total segmented brain volume, and multiplying the obtained quotient by 100. Therefore, while our results accounted for GBVs, the heterogeneity of the methods used to this end may have conflated the emerging effects. We mitigated against this risk with sensitivity analyses which replicated the main results.

Despite these methodological considerations, this is the first study to date to integrate the evidence on volume alterations in cannabis using youth, and the findings provide a useful synthesis of the evidence, methodologies that inform directions for future work. Specifically, our work highlights the need to conduct systematic assessment of neuroanatomy in youth cannabis users, which incorporate standardized imaging, statistical and clinical measures of brain integrity, pubertal stage, and cannabis use.

**So, how and when does the effect of cannabis on the brain start?**

Previous evidence shows volume alterations in samples comprising either adults or both adults and youth. We are yet to know how and when the effect of cannabis use on volumetry starts. Our meta-analysis of cross-sectional studies in young cannabis users did not show significant alterations. Robust longitudinal methodologies (e.g., ABCD study, <https://abcdstudy.org/>) will be required to confirm the lack of group differences at distinct neurodevelopmental stages, while embracing complex psychosocial factors associated with youth cannabis use, for example,

risk of mental health problems, negative life events, trauma, peers and parental substance use, and well-being levels.

Another important direction for future work is to examine how cannabis potency affects the integrity of the developing brain. Indeed, cannabis potency has been reported to increase in street and legally sold cannabis products,<sup>71,72</sup> and such products are increasingly accessible also to youth.<sup>73</sup> Because the endogenous cannabinoid system is directly perturbed by cannabinoid exposure, exposure to increasingly potent cannabis products might have a stronger and more detrimental impact on the developing brain.

However, this notion is largely unexamined as a few studies measured THC in participants' specimens or in their samples of cannabis plant matter. This issue needs to be urgently addressed as the potency of cannabis can have greater neurotoxic,<sup>74,75</sup> psychoactive, psychotogenic,<sup>76,77</sup> and angiogenic effects,<sup>77</sup> and has greater addiction liability.<sup>78</sup>

## Conclusion

In contrast with meta-analytic evidence on adult samples or on samples comprising both adults and youth, this meta-analysis of structural MRI findings specific to youth regular cannabis users suggests no volume alterations, and no effect of age and cannabis use level on group differences in volumetry.

Previous evidence of volume alterations in samples of adults or of adults and youth may be driven by adult cannabis users assessed after brain maturation has occurred. While methodological limitations may have hindered our ability to robustly detect volumetry alterations in youth cannabis use, multimodal longitudinal imaging work is required to confirm the lack of group differences by examining within-subject changes and other properties of neural integrity that may be affected by cannabis use during youth.

Important areas for future work include measuring and embracing the role of cannabis potency, pubertal stage, and personal (and parental) education, to identify which brain maturation stage is most vulnerable to cannabis-related brain and mental health/wellbeing. New knowledge will be necessary to provide clear recommendations for preventive interventions targeting youth at risk and update addiction theory with novel mechanistic insights into neurodevelopment.

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## Supplementary Material

Supplementary Data S1  
 Supplementary Data S2  
 Supplementary Table S1  
 Supplementary Table S2  
 Supplementary Table S3  
 Supplementary Table S4  
 Supplementary Table S5  
 Supplementary Figure S1  
 Supplementary Figure S2  
 Supplementary Figure S3

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### Abbreviations Used

CBD = cannabidiol  
 GBVs = global brain volumes  
 GM = gray matter  
 ICV = intracranial volume  
 MPRAGE = magnetization-prepared rapid gradient-echo imaging  
 MRI = magnetic resonance imaging  
 NHLBI = National Heart, Lung, and Blood Institute  
 OFC = orbitofrontal cortex  
 PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses  
 SD = standard deviation  
 SE = standard error  
 SMD = standardized mean difference  
 TBV = total brain volume  
 TGM = total gray matter  
 THC = delta-9-tetrahydrocannabinol  
 TWM = total white matter  
 WM = white matter