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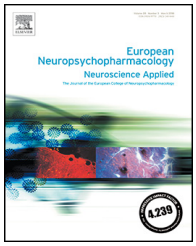

Cortical surface morphology in long-term cannabis users: A multi-site MRI study

Yann Chye[a], Chao Suo[a], Valentina Lorenzetti[a,b,c], Albert Batalla[d,e], Janna Cousijn[f], Anna E Goudriaan[g,h], Rocio Martin-Santos[e], Sarah Whittle[b], Nadia Solowij[i,j,1], Murat Yücel[a,1,*]

[a] *Brain and Mental Health Research Hub, Monash Institute of Cognitive and Clinical Neurosciences, School of Psychological Sciences, Monash University, Melbourne, Australia*
[b] *Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne and Melbourne Health, Melbourne, Australia*
[c] *School of Psychology, Faculty of Health Sciences, Australian Catholic University*
[d] *Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Centre Utrecht, Utrecht, The Netherlands*
[e] *Department of Psychiatry and Psychology, Hospital Clinic, IDIBAPS, CIBERSAM, Institute of Neuroscience, University of Barcelona, Barcelona, Spain*
[f] *Department of Developmental Psychology, University of Amsterdam, Amsterdam, The Netherlands*
[g] *Amsterdam UMC, Department of Psychiatry, Amsterdam Institute for Addiction Research, University of Amsterdam, Amsterdam, The Netherlands*
[h] *Arkin Mental Health Care, Amsterdam, The Netherlands*
[i] *School of Psychology and Illawarra Health and Medical Research Institute, University of Wollongong, Wollongong, Australia*
[j] *The Australian Centre for Cannabinoid Clinical and Research Excellence (ACRE), New Lambton Heights, Australia*

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Abstract
Cannabis exerts its psychoactive effect through cannabinoid receptors that are widely distributed across the cortical surface of the human brain. It is suggested that cannabis use may contribute to structural alterations across the cortical surface. In a large, multisite dataset of

* Corresponding author.
E-mail address: murat.yucel@monash.edu (M. Yücel).
[1] Shared senior authors.

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Dependence;
Substance use

120 controls and 141 cannabis users, we examined whether differences in key characteristics of the cortical surface – including cortical thickness, surface area, and gyrification index were related to cannabis use characteristics, including (i) cannabis use vs. non-use, (ii) cannabis dependence vs. non-dependence vs. non-use, and (iii) early adolescent vs. late adolescent onset of cannabis use vs. non-use. Our results revealed that cortical morphology was not associated with cannabis use, dependence, or onset age. The lack of effect of regular cannabis use, including problematic use, on cortical structure in our study is contrary to previous evidence of cortical morphological alterations (particularly in relation to cannabis dependence and cannabis onset age) in cannabis users. Careful reevaluation of the evidence on cannabis-related harm will be necessary to address concerns surrounding the long-term effects of cannabis use and inform policies in a changing cannabis regulation climate.

1. Introduction

Cannabis is a widely used recreational substance, valued for both its pharmacological and psychoactive properties (Atakan, 2012). While cannabis remains illegal in most countries, a number of countries have begun to decriminalise or permit its use for personal or medical purposes. This general shift in attitude has raised concerns about the potential harm of long-term cannabis use, particularly for users who begun using at an early age (Hall and Lynskey, 2016; Levine et al., 2016). The majority of cannabis initiates are adolescents under the age of 18 (Center for Behavioral Health Statistics and Quality, 2011). Early adolescent initiates may be at a greater risk of worse functional outcomes including, poorer academic performance and delinquency (Brook et al., 1999; Fergusson and Horwood, 1997; Lynskey et al., 2015; Meier et al., 2015). Additionally, initiation of use during adolescence is associated with a greater likelihood of persistent use and dependence later in life (Center for Behavioral Health Statistics and Quality, 2011; DeWit et al., 1997; Perkonigg et al., 2008). Not only do dependent cannabis users experience a range of physiological and psychological problems (e.g., social, interpersonal, and mental health issues including mood, anxiety and behavioural disorders) related to use (American Psychiatric Association, 2013; Hasin et al., 2013; van der Pol et al., 2013), cannabis dependence may also be associated with distinct brain alterations relative to non-dependent use (Chye et al., 2017b, c; Filbey and Dunlop, 2014). With the increasingly liberal cannabis policies globally likely to increase the number of new users (Hall and Weier, 2015), it is even more pertinent to verify how different aspects of cannabis use, including regular use, early initiation of use, and dependence may be associated with structural brain alterations.

The psychoactive component of cannabis, delta9-tetrahydrocannabinol (THC), exerts its effect through cannabinoid receptors (CB1R) that are widely distributed in the human brain, particularly across the cortical surface (Gaoni and Mechoulam, 1964; Westlake et al., 1994). The cortical surface undergoes extensive developmental changes (e.g., in thickness, volume, and gyrification) across adolescence (Cao et al., 2017; Coupé et al., 2017; Jacobus and Tapert, 2014; Toga et al., 2006). Importantly, such neurodevelopmental changes are in part driven by CB1Rs, as part of an endogenous cannabinoid system (ECS) involved in fundamental processes such as neuronal cell proliferation, differentiation, morphogenesis and synaptogenesis (Harkany et al., 2008; Svíženská et al., 2008). Notably, THC exposure, especially during adolescence relative to adulthood, has been shown to demonstrably alter CB1R expression and neuronal growth in rats, potentially contributing to neurostructural alterations across the cortical surface (Burston et al., 2010; Dalton and Zavitsanou, 2010; Dean et al., 2001; Grigorenko et al., 2002; Molina-Holgado et al., 2002; Rubino et al., 2015; Villares, 2007). Furthermore, rodent research shows that CB1R density increases during normal development, peaking in adolescence, before decreasing to adult values (de Fonseca et al., 1993). Thus, the evidence not only points toward a dynamic ECS heavily involved in modulating neuromaturational events during adolescence, but also implies a potential for the ECS to be more sensitive to cannabinoid insult during adolescence, that may contribute to observable neurostructural alterations along the cortical surface.

Previous human neuroimaging studies have demonstrated differences in cortical thickness in cannabis users relative to non-using controls. However, these studies have not been consistent in the direction of reported results, nor the affected brain regions. For example, one study found that cannabis users had a thinner cortex in the right fusiform gyrus relative to non-using controls (Mashhoon et al., 2015a), while another reported thicker cortices in cannabis users in a number of regions across the frontal, parietal, temporal, and occipital lobes (Jacobus et al., 2015). Yet another found no significant difference in cortical thickness between cannabis users and controls (Mata et al., 2010). Adolescent onset of cannabis use may also moderate cortical thickness differences between cannabis users and controls, with one study finding that cannabis dosage was positively associated with cortical thickness across the frontal and temporal lobes in early onset ($<$16 years of age) users, but negatively associated with cortical thickness in late onset users (Filbey et al., 2015). However, other studies have instead demonstrated thinner cortices in the frontal and inferior and middle temporal brain regions; and thicker cortices in lingual, parietal, and paracentral regions, of early adolescent cannabis users relative to non-users (Jacobus et al., 2014; Lopez-Larson et al., 2011), making it difficult to infer a consistent effect of adolescent onset of cannabis use on cortical morphology. Finally, emerging evidence suggests that cannabis-associated effects on subcortical neuroanatomy and cortico-subcortical connectivity may be

more reflective of problematic cannabis use (i.e., cannabis dependence) rather than recreational use (Chye et al., 2017b, c; Filbey and Dunlop, 2014). These studies particularly implicated frontal and limbic areas, thought to be involved in aberrant reward and decision-making processes in dependence (Volkow et al., 2003). The effect of cannabis dependence vs. non-dependent use, however, has yet to be explored in relation to cortical thickness. In sum, the lack of consistency of study findings to date makes it difficult to infer specific cortical morphological changes that may be associated with cannabis use, onset age, or dependence.

In addition to cortical thickness, the surface morphology of the brain can also be examined via surface area and gyrification, both of which have been found to change with age, particularly during childhood and adolescence (Raznahan et al., 2011). The gyrification index is a quantitative approach to measuring the degree of cortical folding (Zilles et al., 1988). Only three studies, to our knowledge, have examined surface area and gyrification in relation to cannabis use, finding reduced gyrification and trend level reduction in surface area in frontal brain regions (Filbey et al., 2015; Mata et al., 2010; Shollenbarger et al., 2015). In this study we explored the cortical surface morphology – i.e., cortical thickness, surface area and gyrification index, in a multisite sample of regular cannabis users and controls aggregated from pre-collected data across four independent research sites (Batalla et al., 2013; Cousijn et al., 2014; Solowij et al., 2013; Yücel et al., 2016). We attempted to delineate the relation between cortical morphology, and (i) cannabis use, (ii) cannabis dependence, and (iii) cannabis onset age. While we are not able to formulate a directional hypothesis given the inconsistencies in the literature to date, we expect indices of surface morphology to be altered in cannabis users relative to controls, and that these differences will be more pronounced in dependent, as well as early-onset cannabis users.

2. Experimental procedures

2.1. Participants

Data from 140 cannabis users (CB) and 121 non-using controls (CON) were compiled from four independent imaging sites in Amsterdam ($N = 76$) (Cousijn et al., 2014), Barcelona ($N = 55$) (Batalla et al., 2013), Wollongong ($N = 30$) (Solowij et al., 2013), and Melbourne ($N = 100$) (Yücel et al., 2016). All CB had used cannabis at least two days per month for at least two months, with most CB having almost daily use for a considerable time period (duration of regular use, Mdn = 6 years, range = 0.5–38 years). Meanwhile, CON had used cannabis less than 50 times and did not use in the past month. Further inclusion and exclusion criteria have been reported previously (Chye et al., 2017a, b).

Measures related to participants' demographic and substance use characteristics (i.e., age, gender, IQ, monthly standard alcoholic drinks, monthly cigarettes use, and cannabis use measures) were separately collected and standardised across sites. Estimated IQ was measured with the Dutch version of the National Adult Reading Test (DART; Schmand et al., 1991) in Amsterdam, the vocabulary subscale of the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Wechsler, 1997) in Barcelona, the National Adult Reading Test (NART; Nelson, 1982) in Wollongong, and the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) in Melbourne. Cannabis use measures included monthly and lifetime cannabis consumption (measured in cones, https://cannabissupport.com.au/media/1593/ timeline-followback.pdf), age of initiation of regular cannabis use, and cannabis dependence.

Information on cannabis dependence was collected from three of the four imaging sites – the Mini International Neuropsychiatric Interview's (MINI) 'non-alcohol psychoactive substance use disorders' module, with a cut-off of 3 and above indicating dependence, in Amsterdam (Lecrubier et al., 1997); and the Severity of Dependence Scale (SDS), with a cut-off of 4 and above as dependent, in Barcelona and Melbourne (Gossop et al., 1995). This was used to separate the aggregated sample into 70 dependent users (CB-dep), 50 non-dependent users (CB-nondep), and 106 CON, after excluding subjects with missing dependence information.

Within cannabis users, age of initiation of regular cannabis use was also used to separate early to mid- adolescent-onset (EA-CB, initiation of regular cannabis use at 16 years or younger) and late adolescent-onset (LA-CB, initiation at 17 years or older) users, across all four sites. This resulted in 50 EA-CB, 86 LA-CB, and 121 CON.

2.2. Structural image processing

T1-weighted structural MR images were acquired from the individual sites (Batalla et al., 2013; Chye et al., 2017a, b; Cousijn et al., 2014; Solowij et al., 2013; Yücel et al., 2016), with two sites (Amsterdam and Wollongong) using a Phillips Intera 3T scanner with an 8-channel head coil, one site (Barcelona) using a GE Signa Excite 1.5T scanner with an 8-channel head coil, and one site (Melbourne) using a Siemens-Trio 3T scanner with a 32-channel head coil.

All MR images underwent a noise removal step, using the prefiltered rotationally invariant nonlocal means filter (PRINLM) (https://sites.google.com/site/pierrickcoupe/softwares/denoising-for-medical-imaging/mridenoising), to remove systematic variations due to noise (Fellhauer et al., 2015; Gaser and Coupé, 2010; Manjón et al., 2012). Subsequently, preprocessing for surface-based analysis was performed using FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) version 5.3.0, which included motion correction (Reuter et al., 2010), non-uniform intensity normalisation (N3) at 500 iterations (Sled et al., 1998), automated Talairach transformation, removal of non-brain tissue (Ségonne et al., 2004), and tessellation of outer grey matter and white matter boundaries (Fischl et al., 2002). All reconstructions were visually inspected and manually edited as necessary by a blinded rater (Y.C.). The reconstructed surfaces were inflated and registered to a common spherical surface space, with a smoothing level – full width half maximum (FWHM) of 10 mm, to allow for accurate matching of cortical locations across subjects (Fischl et al., 1999).

Whole-brain vertex-wise measures of surface morphology – cortical thickness, surface area, and gyrification index were obtained. Cortical thickness reflects the distance between grey/white boundary and pial mesh at each vertex (Fischl and Dale, 2000). The surface area is computed at the grey/white boundary, as the average area of all triangles surrounding each vertex. Finally, the 3D gyrification index represents the area ratio of the outer hull of the brain, and its actual convoluted pial surface (Schaer et al., 2012, 2008) (Fig. 1).

2.3. Statistical analysis

Three sets of linear models were run, to test for the main effect of (i) cannabis use – CB vs. CON, (ii) cannabis dependence – CB-dep vs. CB-nondep vs. CON, and (iii) cannabis onset – EA-CB vs. LA-CB vs. CON, respectively. All models were controlled for intracranial volume, imaging site, gender, age, IQ, alcohol use, and cigarette use.

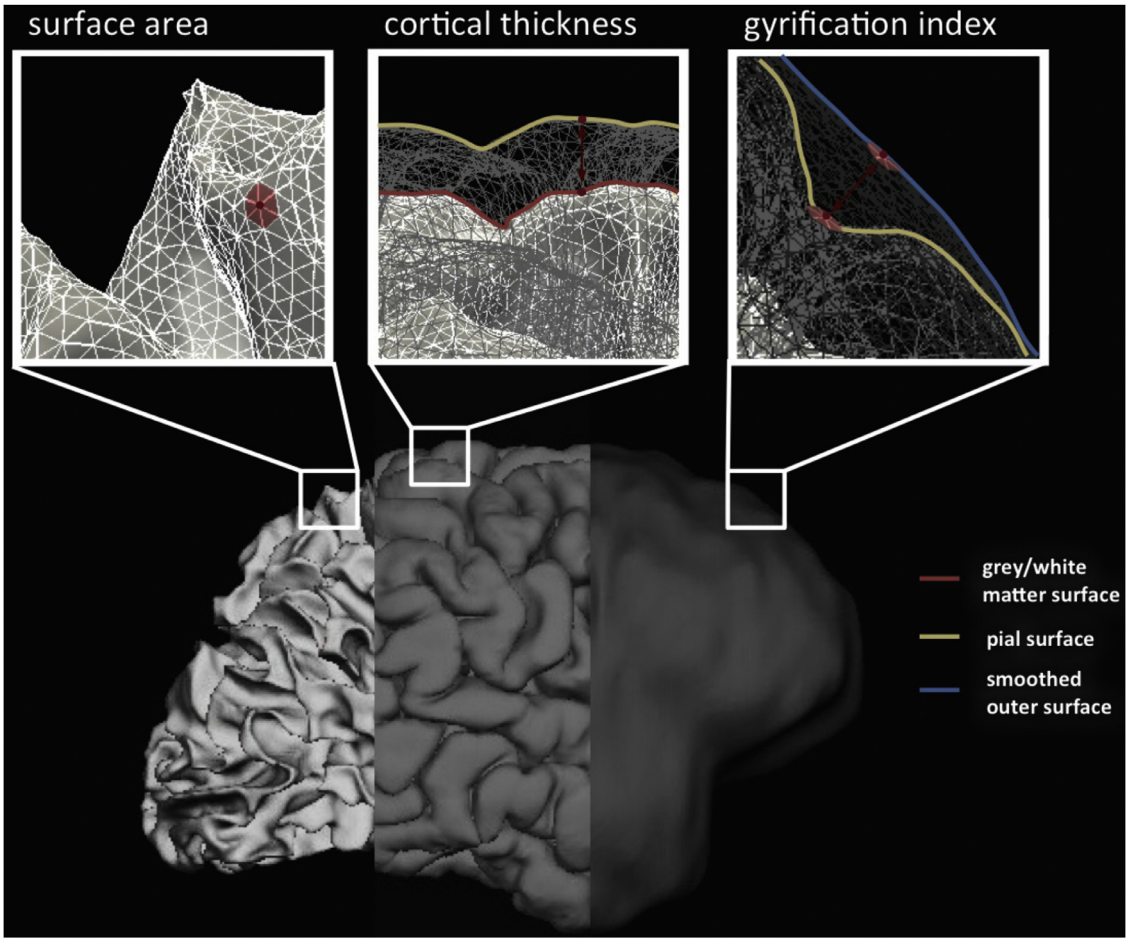

Fig. 1 Surface model of the brain, where vertex-wise (i) surface area represents the average area of all triangles surrounding each vertex on the grey/white matter surface; (ii) cortical thickness represents the distance between the grey/white matter boundary and the pial surface; and (iii) gyrification index represents the area ratio between the smoothed outer surface of the brain and its convoluted pial surface.

Statistical analysis was performed with a permutation-based approach through the Permutation Analysis of Linear Models (PALM; Winkler et al., 2014) tool. To accelerate permutation and inference, a tail-approximation approach with a lower number of permutation (i.e., 500) was adopted, as recommended by Winkler et al. (2016). Spatial statistics were computed using the threshold-free cluster enhancement (TFCE) method (height and extend parameters = 2 and 1, respectively; Smith and Nichols, 2009), which transforms vertex statistics by the vertex's neighbouring cluster-like support. Inference was based on family-wise error rate (FWER)-corrected alpha level of $p < .05$.

3. Results

3.1. Cortical surface morphology by cannabis use

Sample characteristics by cannabis use (i.e., CON and CB) are presented in Table 1. CB had a significantly lower IQ, and smoked significantly more cigarettes, than CON. When surface morphology was compared between CON and CB, controlling for age, gender, IQ, alcohol and nicotine use, imaging site, and intracranial volume, no significant differences in cortical thickness, surface area, or gyrification index were found.

3.2. Cortical surface morphology by cannabis dependence

Sample characteristics by cannabis dependence (i.e., CON, CB-nondep, CB-dep) are presented in Table 2. CB-dep consumed significantly more cannabis per month relative to CB-nondep, but had comparable cannabis onset age and lifetime use. Similarly, we did not find any significant difference in cortical thickness, surface area, and gyrification index between CON, CB-nondep, or CB-dep.

3.3. Cortical surface morphology by onset of cannabis use

Sample characteristics by onset of cannabis use (i.e., CON, EA-CB, LA-CB) are presented in Table 3. EA-CB smoked more cigarettes per month than did LA-CB, and also consumed

Table 1 Sample characteristics of controls (CON) and cannabis users (CB) across 4 sites (mean (SD)).

	CON $N = 121$	CB $N = 140$	t_{259}/X^2
Age (years)	26.12 (9.03)	28.03 (10.25)	1.58
Gender (% M/F)	70.25 / 29.75	67.14 / 32.86	0.29
IQ[a]	109.31 (10.54)	103.45 (10.74)	−4.44*
Alcohol (StDr/mth)[b]	19.87 (23.77)	24.43 (25.18)	1.50
Nicotine (Cig/mth)[b]	30.88 (97.92)	254.96 (233.77)	9.82*
Intracranial volume, mm^3 (10^6)	1.55 (0.20)	1.52 (0.17)	−1.22
Cannabis use			
Age of regular Use	-	17.84 (3.38)	-
Current use (cones/month)	-	334.08 (322.32)	-
Lifetime use (cones)	-	57,107 (99,987)	-

[a] Estimated IQ measured with the Dutch version of the National Adult Reading Test (DART; Schmand et al., 1991) (Amsterdam), the vocabulary subscale of the Wechsler Adult Intelligence Scale - Third Edition (WAIS-III; Wechsler, 1997) (Barcelona); the National Adult Reading Test (NART; Nelson, 1982) (Wollongong); and the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) (Melbourne).
[b] StDr/mth = standard drinks per month; Cig/mth = cigarettes smoked per month
* $p < .001$.

Table 2 Sample characteristics of controls (CON), non-dependent (CB-nondep) and dependent (CB-dep) cannabis users across 3 sites (mean (SD)).

	CON $N = 106$	CB-nondep $N = 50$	CB-dep $N = 70$	$F_{2,223}/X^2$
Age (years)	24.77 (7.91)	27.07 (10.33)	26.74 (9.18)	1.61
Gender (% M/F)	66.98 / 33.02	60.00 / 40.00	64.29 / 35.71	0.73
IQ[a]	108.65 (10.71)	103.03 (11.13)	102.13 (10.86)	9.15**,[c]
Alcohol (StDr/mth)[b]	18.70 (23.90)	21.54 (25.03)	21.88 (22.78)	0.46
Nicotine (Cig/mth)[b]	30.94 (96.72)	236.90 (249.97)	219.72 (197.66)	35.89**,[d]
Intracranial volume, mm^3 (10^6)	1.53 (0.19)	1.46 (0.19)	1.53 (0.15)	2.72
Cannabis use				
Age of regular use	-	17.79 (2.66)	17.44 (3.23)	0.61
Current use (cones/month)	-	229.81 (202.25)	351.64 (290.95)	−2.54*
Lifetime use (cones)	-	32,375 (47,641)	50,431 (72,812)	−1.54

[a] Estimated IQ measured with the Dutch version of the National Adult Reading Test (DART; Schmand et al., 1991) (Amsterdam), the vocabulary subscale of the Wechsler Adult Intelligence Scale - Third Edition (WAIS-III; Wechsler, 1997) (Barcelona); and the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) (Melbourne).
[b] StDr/mth = standard drinks per month; Cig/mth = cigarettes smoked per month.
[c] CON > CB-nondep, $p = .003$; CON > CB-dep, $p < .001$.
[d] CON < CB-nondep, $p < .001$; CON < CB-dep, $p < .001$.
* $p < .05$.
** $p < .001$.

more cannabis than LA-CB. However, no significant differences in cortical thickness, surface area, and gyrification index were found between CON, EA-CB, and LA-CB.

4. Discussion

While regular cannabis use has been associated with altered cortical morphology, previous findings have not been consistent in terms of the direction or region of alteration, which included increase, decrease, and lack of change in cortical morphology, across all four cortical lobes (Filbey et al., 2015; Jacobus et al., 2015, 2014; Lopez-Larson et al., 2011; Mashhoon et al., 2015b; Shollenbarger et al., 2015). Furthermore, no study on cannabis use has yet comprehensively explored the three different indices of cortical surface morphology in tandem, with most studies examining cortical thickness, and only three to date further exploring surface area or gyrification (Filbey et al., 2015; Mata et al., 2010; Shollenbarger et al., 2015). Here, we comprehensively examined cortical thickness, surface area, and gyrification index in relation to cannabis use, dependence, and onset age, across the whole cortex, and demonstrated no significant effects on cortical surface morphology.

While our findings are inconsistent with some previous findings of altered cortical thickness in cannabis users relative to non-users, and furthermore did not support our hypotheses, they nevertheless reflect the lack of consistency in the evidence to date. Studies have alternately suggested cannabis use to be associated with thinner cortex in regions of the temporal and occipital lobe (Mashhoon et al., 2015a) and in the frontal lobe (Lopez-Larson et al., 2011), thicker cortex in the temporal and parietal lobe (Lopez-Larson et al., 2011), or thicker cortex in a number of regions across all frontal, parietal, temporal, and occipital lobe (Jacobus et al., 2015). Meanwhile, one further study also found no group difference in cortical thickness in cannabis users (Mata et al., 2010). While such discrepancy in findings

Table 3 Sample characteristics of controls (CON), early to mid adolescent-onset (EA-CB) and late adolescent-onset (LA-CB)[a] cannabis users across 4 sites (mean (SD)).

	CON $N = 121$	EA-CB $N = 50$	LA-CB $N = 86$	$F_{2,254}/X^2$
Age (years)	26.12 (9.03)	29.23 (10.06)	27.69 (10.47)	1.93
Gender (% M/F)	70.25 / 29.75	60.00 / 40.00	69.77 / 30.23	1.88
IQ[b]	109.31 (10.54)	101.97 (11.65)	104.40 (10.25)	10.30***,[d]
Alcohol (StDr/mth)[c]	19.87 (23.77)	27.16 (28.74)	23.17 (23.29)	1.61
Nicotine (Cig/mth)[c]	30.88 (97.92)	320.95 (229.02)	224.18 (231.64)	55.98***,[e]
Intracranial volume, mm^3 (10^6)	1.55 (0.20)	1.55 (0.16)	1.50 (0.18)	1.72
Cannabis use				
Age of regular use	-	14.80 (1.25)	19.62 (2.93)	122.12***
Current use (cones/month)	-	439.70 (316.09)	274.10 (317.17)	8.64**
Lifetime use (cones)	-	83,182 (86,874)	43,879 (106,474)	4.91*

[a] Early adolescent-onset cannabis use (EA-CB) is defined as regular use by 16 years or younger, while late adolescent-onset cannabis use is defined as regular use commencing at 17 years or older.

[b] Estimated IQ measured with the Dutch version of the National Adult Reading Test (DART; Schmand et al., 1991) (Amsterdam), the vocabulary subscale of the Wechsler Adult Intelligence Scale - Third Edition (WAIS-III; Wechsler, 1997) (Barcelona); the National Adult Reading Test (NART; Nelson, 1982) (Wollongong); and the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) (Melbourne).

[c] StDr/mth = standard drinks per month; Cig/mth = cigarettes smoked per month.

[d] CON > EA-CB, $p < .001$; CON > LA-CB, $p = .001$.

[e] CON < EA-CB, $p < .001$; CON < LA-CB, $p < .001$; EA-CB > LA-CB, $p = .003$.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

may be due to other moderators such as onset age of regular cannabis use, as evidenced by the opposing association between cannabis dosage and cortical thickness found by one study in early vs. late onset users (Filbey et al., 2015), we did not find any effect of cortical morphology between early and late cannabis users. Our study has the benefit of being a large multisite study with a sample size of up to $N = 261$ (in comparison to previous studies, $N = 30$ - 74), affording us greater statistical power to examine and verify previous findings.

We additionally found no association between cortical surface area and gyrification index in relation to cannabis use. Although a number of studies have demonstrated altered cortical volume (which reflects the product of surface area and cortical thickness) in relation to both cannabis use and cannabis dependence, particularly in the orbitofrontal cortex (Chye et al., 2017b; Filbey and Dunlop, 2014; Price et al., 2015), it is unclear which component is driving these alterations. Only two previous studies have examined surface area in relation to cannabis use, and have similarly found no effect (Mata et al., 2010; Shollenbarger et al., 2015). However, these studies, when comparing cortical gyrification in adolescent and young adult cannabis users vs. controls, showed bilaterally decreased sulci concavity in the frontal, temporal, and parietal lobes and thinner sulci in the right frontal lobe of users, contrary to our finding (Mata et al., 2010; Shollenbarger et al., 2015). A further study that compared gyrification in early onset (mean age of regular use 16.5 years) vs. late onset (mean age of regular use 19 years) cannabis users further suggested that the association between cannabis use (quantity and duration) and reduced gyrification (in the PFC) is only apparent in early onset users (Filbey et al., 2015).

Our lack of findings may be due to differences in analytic approach. A number of previous studies (i.e., those that have found thicker cortices, and those that have found lower gyrification, in cannabis users relative to non-users) explored region-of-interest (ROI)-level (Jacobus et al., 2015, 2014; Mata et al., 2010; Shollenbarger et al., 2015) rather than whole-brain vertex-level differences. While an ROI-level approach is useful in identifying less extreme group-averaged differences across larger pre-defined regions, the latter is useful for identifying focal differences at a higher spatial resolution and across regional boundaries (Boulos et al., 2016; Li et al., 2014). Additionally, we adopted a permutation approach to analysing the data, an approach that is increasingly recommended as a non-parametric statistical alternative that is robust to non-random sampling (e.g., often in case-control studies), and has been demonstrated to have comparable power to parametric approaches (Ludbrook and Dudley, 1998; Winkler et al., 2016, 2014). Finally, we controlled for intracranial volume as a covariate in our cortical thickness analysis, despite cortical thickness scaling minimally with brain size (Im et al., 2008), compromising statistical power in favour of consistency across analysis of all surface morphometry. A limitation to our study however, is the cross-sectional design, which prevents us from verifying trends in surface morphology across neurodevelopment in cannabis users. Additionally, the restricted age range of our sample (range = 18-56) meant that we are not able to fully explore age-related differences in relation to cannabis use (Klein et al., 2014; Lopez-Larson et al., 2011).

Overall, this study examined cortical surface alteration related to cannabis use and onset, in a large multinational imaging cohort. We did not find any evidence of cortical surface alteration (i.e., cortical thickness, surface area, gyrification index) in relation to cannabis use, dependence, or age of initiation, despite previous evidence to the contrary. Our lack of finding in a well-powered study suggests that

cortical surface morphology may be less associated with cannabis use than previously assumed. Nevertheless, we do not exclude potential underlying changes at the network or molecular level. The lack of consensus between past study findings, as well as our current finding, inadvertently echoes the opposing sentiments surrounding the harms and safety of long-term cannabis use. Given the current trend of widespread changes in cannabis regulation, it is even more prudent to carefully reassess the evidence surrounding cannabis-related effects, to guide informed policy and decision-making.

Conflict of interest

All authors report no financial interest or potential conflict of interest.

Contributors

Y.C., V.L., N.S. and M.Y. were responsible for the study concept and design. V.L., A.B., J.C., A.E.G., R.M.S., S.W., N.S. and M.Y. contributed to data acquisition. Y.C. performed the data analysis, while C.S. assisted in analysis methodology. Y.C. drafted the manuscript, while C.S., V.L., N.S. and M.Y. provided critical intellectual input and revision. All authors reviewed and approved the final version of the manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2018.11.1110.

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