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Abstract

Orbitofrontal cortex (OFC) sulcogyral patterns are stable morphological variations established early in life. They consist of three distinct pattern types, with Type III in particular being associated with poor regulatory control (e.g., high sensation seeking and negative emotionality, low constraint), which may confer risk for earlier onset of cannabis (CB) use and greater use in later life. The OFC sulcogyral pattern may therefore be a stable trait marker in understanding individual differences in substance-use vulnerability and associated affective disturbances in users. In a large multisite cross-sectional study, we compared OFC pattern type distribution between 128 healthy controls (HC) and 146 CB users. Within users (n = 140), we explored the association between OFC pattern type and CB use level, and subsequently if level of CB use informed by OFC pattern type may mediate disturbances in affective tone, as indexed by depressive symptoms. While OFC pattern distribution did not distinguish between HC and CB groups, it informed greater lifetime use within users. Specifically, CB users with pattern Type III in the right OFC tended to use more CB over their lifetime, than did CB users with pattern Type I or II. Greater lifetime CB use was subsequently associated with higher depressive symptoms, such that it mediated an indirect association between right OFC pattern Type III and higher depressive symptoms. The present study provides evidence for neurobiological differences, specifically sulcogyral pattern of the OFC, to modulate level of CB use, which may subsequently influence the expression of depressive symptoms.

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Role of orbitofrontal sulcogyral pattern on lifetime cannabis use and depressive symptoms

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Abstract

Orbitofrontal cortex (OFC) sulcogyral patterns are stable morphological variations established early in life. They consist of three distinct pattern types, with Type III in particular being associated with poor regulatory control (e.g., high sensation seeking and negative emotionality, low constraint), which may confer risk for earlier onset of cannabis (CB) use and greater use in later life. The OFC sulcogyral pattern may therefore be a stable trait marker in understanding individual differences in substance-use vulnerability and associated affective disturbances in users. In a large multisite cross-sectional study, we compared OFC pattern type distribution between 128 healthy controls (HC) and 146 CB users. Within users (n = 140), we explored the association between OFC pattern type and CB use level, and subsequently if level of CB use informed by OFC pattern type may mediate disturbances in affective tone, as indexed by depressive symptoms. While OFC pattern distribution did not distinguish between HC and CB groups, it informed greater lifetime use within users. Specifically, CB users with pattern Type III in the right OFC tended to use more CB over their lifetime, than did CB users with pattern Type I or II. Greater lifetime CB use was subsequently associated with higher depressive symptoms, such that it mediated an indirect association between right OFC pattern Type III and higher depressive symptoms. The present study provides evidence for neurobiological differences, specifically sulcogyral pattern of the OFC, to modulate level of CB use, which may subsequently influence the expression of depressive symptoms.

Keywords: Dependence, cannabis, orbitofrontal cortex, sulcogyral pattern, MRI

Abbreviations:

OFC = orbitofrontal cortex; MOS = medial orbitofrontal sulcus; LOS = lateral orbitofrontal sulcus; CB = cannabis; HC = healthy controls

Introduction

Cannabis (CB) is a widely used psychoactive drug with a global estimate of 182 million users (United Nations Office on Drugs and Crime, 2015). Along with the high level of CB use across the world, there is a rising toll of treatment demand for CB use and its disorders (European Monitoring Centre for Drugs and Drug Addiction, 2016; United Nations Office on Drugs and Crime, 2015). Heavy CB use has been linked to affective disturbances such as depressive disorders (Degenhardt et al., 2003; Lev-Ran et al., 2014). Efforts to uncover the neural correlates of CB use have demonstrated morphological alterations across various brain regions including the hippocampus and the prefrontal cortex (Lorenzetti et al., 2016; Yücel et al., 2016). While neural abnormalities have often been interpreted as a consequence of CB use (Ashtari et al., 2011; Cousijn et al., 2012; Matochik et al., 2005; Yücel et al., 2008), premorbid structural differences may similarly confer vulnerability to develop heavier patterns of CB use (Jacobus et al., 2016; Pagliaccio et al., 2015) or affective disturbances (Amico et al., 2011). The understanding of such premorbid differences may inform knowledge on individual differences in substance use vulnerability, and the associated affective disturbances in users.

It remains unclear whether (and which) neurobiological alterations predate cannabis use onset. Besides from prospective studies, this issue can be addressed via assessing neuroanatomy that is defined early in life and relatively stable to postnatal environmental factors such as substance use. One such medium is the specific pattern of gyrification of the brain (White et al., 2010). Gyrification is the pattern of surface folding of the brain (White et al., 2010) that develops as early as 11 to 16 weeks gestation, and remains relatively stable from birth (Armstrong et al., 1995; Zilles et al., 1997). Importantly, early cortical folding forming particular sulcogyral patterns may reflect underlying connectivity or disrupted connectivity of the brain (Toro and Burnod, 2005; White et al., 2010). This provides a means for structure to inform function and behaviour, particularly in regions strongly implicated in substance use, such as the orbitofrontal cortex (OFC). Various studies have demonstrated reduced OFC volume (Battistella et al., 2014; Churchwell et al., 2010) and altered OFC function (functional connectivity in reward and inhibitory circuitry including the OFC) (Filbey and Dunlop, 2014; Filbey and Yezhuvath, 2013) in CB users. Pre-existing OFC morphological differences may also inform risk for later substance (i.e. alcohol, CB) use (Cheetham et al., 2011; Kühn et al., 2015). These studies suggest OFC morphology may reflect vulnerabilities that inform future substance use behaviour.

The sulcogyral pattern of the OFC in particular, is a viable trait marker to glean stable prenatal differences that may inform substance use behaviour. The OFC sulcogyral pattern has been categorised by Chiavaras and Petrides (2000), based on the continuity/discontinuity of the medial orbitofrontal sulcus (MOS) and the lateral orbitofrontal sulcus (LOS), into three basic types (Type I – discontinuity of the MOS; Type II – continuity of both the MOS and the

LOS; Type III – discontinuity of the LOS; Fig. 1). In a normative population, the distribution of the OFC sulcogyral pattern is skewed, with a predominance of Type I and an underrepresentation of Type III (Chiavaras and Petrides, 2000).

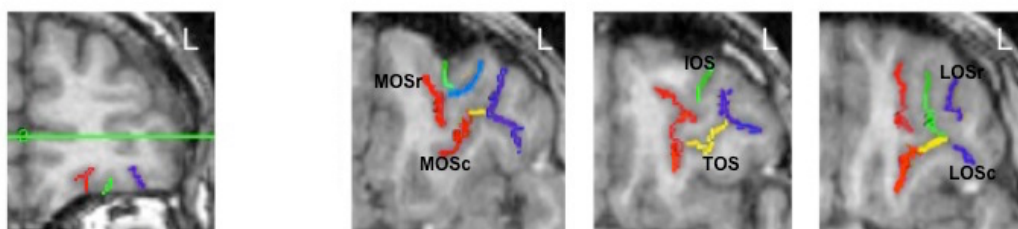


Fig. 1 Examples of the three different orbitofrontal (OFC) sulcogyral pattern types, as traced on the coronal plane, and viewed on the transverse plane. Type I: rostral and caudal regions of the medial orbitofrontal sulci (MOSr and MOSc, red) are discontinuous, while the lateral orbitofrontal sulcus (LOS, purple) is continuous; Type II: both the MOS and LOS are continuous; Type III: the rostral and caudal regions of the MOSr and MOSc, as well as LOSr and LOSc are discontinuous. Also depicted are the intermediate orbital sulci (green and blue), and the transvers orbital sulci (TOS, yellow). Reproduced with permission from Bartholomeusz et al. (2013).

However, altered pattern distribution has been associated with specific personality traits and presence of psychopathologies. In adolescents, a Type III pattern has been linked to greater ‘surgency’ (representing sensation-seeking and extraversion traits, and low levels of fear or shyness) (Whittle et al., 2014). Similarly in patients with schizophrenia, Type III pattern has been associated with temperaments (low ‘constraint’ and high ‘negative emotionality’) indicative of impulsivity, stress reaction, and proneness to anxiety and aggression (Nakamura et al., 2007), as well as poorer functioning (i.e. greater positive symptoms and lower socioeconomic status (Nakamura et al., 2007; Uehara-Aoyama et al., 2011)). Patients with schizophrenia also show an altered proportion of sulcogyral pattern relative to controls (decreased proportion of Type I, and increased proportion of Type II and III) (Bartholomeusz et al., 2013; Chakirova et al., 2010; Cropley et al., 2015; Isomura et al., 2017; Nakamura et al., 2008, 2007; Nishikawa et al., 2015; Takahashi et al., 2015; Uehara-Aoyama et al., 2011). Overall, in both healthy and schizophrenia patient populations, Type III pattern is linked to personality traits reflecting poor regulatory control. Such traits may in turn confer risk for substance use, having been demonstrated to predict an earlier onset of substance use disorder, greater dependence, and greater lifetime CB use (Creemers et al., 2010; Elkins et al., 2006; Krueger, 1999). Thus pre-existing OFC neuroanatomy, by reflecting underlying behavioural regulatory function, may be able to inform risk for later substance use. While the OFC volume has been demonstrated to predict CB use initiation in adolescents (Cheetham et al., 2011), no study has yet explored the OFC sulcogyral pattern in relation to CB use.

Regulatory deficits associated with altered OFC function may not only contribute to greater substance use, but also confer risk for affective disturbances (Diekhof et al., 2008; Drevets, 2007; Klimes-Dougan and Garber, 2016; Wagner et al., 2013a). Consistently, reduced OFC volume (Bremner et al., 2002; Lacerda et al., 2004) and altered functional connectivity between the OFC, dorsolateral prefrontal and anterior cingulate cortices (Frodl et al., 2010) have been observed in patients with depression. Importantly, regular CB use has also been associated with the emergence of affective disturbances including higher depressive symptoms (Crane et al., 2015) and an increased risk of developing depression (Lev-Ran et al., 2014). It is proposed that impaired OFC regulatory function and neuroanatomy underlies the concurrent development of CB use and depressive symptoms (Otten et al., 2010; Volkow and Fowler, 2000), via intensifying the strength of impulse and emotions (Beer et al., 2006; Wagner et al., 2013b). If specific OFC sulcogyral pattern types reflects distinct regulatory functions (Whittle et al., 2014), then these pattern type may inform later level of CB use and affective disturbances in CB users.

In this study, we (i) compared the distribution of OFC pattern type between healthy controls (HC) and CB users to discern neural differences that may inform CB use; (ii) explored the association between OFC pattern type and CB use levels (i.e. three distinct measures including age of onset of regular use, current monthly use, and cumulative lifetime use) in CB users, to understand if potentially pre-existing OFC pattern type may inform later levels of CB use. We additionally (iii) explored whether higher levels of CB use will mediate a possible link between OFC pattern type and greater depressive symptoms, as guided by any significant association between OFC pattern type and specific CB use variables from analysis (ii). We hypothesised (i) OFC pattern distribution to be altered in CB users compared to HC; (ii) Type III pattern – linked to traits indicative of poor regulatory control – will be associated with higher CB use levels; and that (iii) CB users with Type III pattern would have greater current depressive symptoms, and that this relationship would be mediated by greater CB use level.

Method

Participants

We examined an aggregated sample of 128 HC and 146 regular CB users aged 17 to 55 years, the data of which have been previously collected across four research sites including the University of Amsterdam (Amsterdam, N=76) (Cousijn et al., 2012), University of Barcelona (Barcelona, N=60) (Batalla et al., 2013), University of Wollongong (Wollongong, N=34) (Solowij et al., 2013), and Monash University (Melbourne, N=104) (Yücel et al., 2016). Informed written consent was obtained from all participants. All regular CB users had used CB at least two smoking days per month for a minimum of two months, and the majority of users smoked almost daily for a substantial period of time (duration of regular use, *Mdn* = 6

years, range = 0.5 – 38 years). Meanwhile, all HCs had minimal CB exposure (used less than 50 times in their life, and did not use in last month). Exclusion criteria were: any history of chronic medical illness or neurological condition; use of psychoactive medications; any lifetime Axis I disorder according to the Diagnostic and Statistical Manual for Mental Disorders-Fourth Edition (other than nicotine use disorder, or cannabis use disorder for cannabis users); general MRI contraindications; regular use of other drugs (>50 times in the past 10 years) apart from cannabis, alcohol, and nicotine; and IQ<80.

Measures

Participants' demographic, IQ level, depressive symptoms, and substance use levels (alcohol, tobacco, CB) were separately collected from each site using differing measures. We standardized these measures across sites. CB use levels measured include age of onset of regular use (defined as at least twice/month for at least two months), current monthly use, and cumulative lifetime use. CB users self-reported use in units familiar to them (e.g., joints, bong, grams smoked), and use was then converted to cones, a standardised unit for comparison (e.g., 1 gram = 12 cones, and 1 paper joint = 3 cones; see standardised guidelines provided at <https://cannabissupport.com.au/media/1593/timeline-followback.pdf>).

IQ was estimated using 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) (Barcelona) (Wechsler, 1997); the National Adult Reading Test (NART) (Wollongong) (Nelson, 1982); and the Wechsler Abbreviated Scale of Intelligence (WASI) (Melbourne) (Wechsler, 1999). The vocabulary subscale score from the Barcelona site was converted to an estimated full scale IQ by standardising to the mean and standard deviation of the average IQ of CB and HC respectively of the three other sites. Depressive symptoms were obtained using the Beck Depression Inventory (BDI) (Amsterdam, Barcelona, Melbourne) (Beck et al., 1961) and Hamilton Depression Rating Scale (HAMD) (Wollongong) (Hamilton, 1960). Depressive symptom scores from each site were standardised, using previously reported population norms for each scale as the mean by which obtained depressive symptom scores were converted to a z-score (Crawford et al., 2011; Zimmerman et al., 2004).

Structural Image Processing

T1-weighted structural MR images were independently acquired at each imaging site. Scanner details are documented in the Supplementary Table 1, and by the original research groups (Batalla et al., 2013; Cousijn et al., 2012; Yücel et al., 2016, 2008). MR images were preprocessed using FreeSurfer image analysis (<http://surfer.nmr.mgh.harvard.edu/>) version 5.3.0 to correct for intensity non-uniformity artifacts (Sled et al., 1998; Zheng et al., 2009). The intensity of the subsequent MR images was then standardised between sites - based on the average grey matter, white matter, and cerebrospinal fluid intensity from each site, using

the FMRIB Software Library (FSL; <http://www.fmrib.ox.ac.uk/fsl/>), to ensure consistency across sites for subsequent manual tracing. Finally, MR images were visually inspected and reoriented along the anterior commissure-posterior commissure (AC-PC) plane only if they deviated from the plane by more than 0.1 radian.

OFC sulcogyral pattern classification

The OFC sulcogyral pattern types were classified for each MR image using the visualisation and analysis software Analyze 12.0 (AnalyzeDirect, Overland Park, KS), based on the continuity/discontinuity of the MOS and LOS between the rostral and caudal regions (Chiavaras and Petrides, 2000). In Type I, the MOS was disconnected while the LOS was intact. In Type II, both the MOS and LOS were intact. For Type III, both the MOS and LOS were disconnected. In rare cases where LOS was disconnected but MOS was intact ($n = 27$; classified as Type IV in some papers (Chakirova et al., 2010)), we classified the OFC pattern as Type III, in accordance with the method used by (Bartholomeusz et al., 2013).

All sulci appearing on the orbital surface were traced in the coronal plane slice-by-slice, and identified on the transverse plane. A fissure was considered a sulcus if it was visible in at least four coronal and four transverse slices. A sulcus was considered continuous with another sulcus if they were clearly connected in at least three slices. OFC pattern classification was performed by Y.C. while blinded to gender, group, and imaging site. Intra- and inter-rater reliability (interclass correlation coefficient, ICC) performed by Y.C., C.F.B., and E.P.G., on 20 randomly selected brains from the Melbourne Neuropsychiatry Centre (University of Melbourne, Department of Psychiatry) database, were 0.90 and 0.75 respectively. All ambiguous classifications identified in the current sample (i.e. 14% of the total sample) were reviewed by C.F.B. and consensus reached. To further ensure Y.C.'s classification validity, a subset of 20 randomly selected brains (5 from each imaging site) that were not reviewed by C.B., from the current sample, were also reviewed by E.P.G. Consensus between Y.C. and E.P.G. was high at a level of 92.5%.

Statistical Analyses

Group differences between HC and CB users for variables including age, IQ, depressive symptoms, alcohol, and tobacco use were assessed using independent-samples t-test; while group differences for gender were assessed via Pearson's χ^2 statistics. To ensure that OFC pattern distribution was not related to imaging site, countries, or continents, we ran separate Pearson's χ^2 statistics for HC and CB users, comparing left and right OFC pattern across sites, and across continents. We also compared left and right OFC pattern distribution by age, gender, IQ, depressive symptoms, alcohol and tobacco use to assess and rule out any demographic confounder.

To discern putative pre-existing neural differences in CB users relative to HC in OFC sulcogyral pattern distribution (separately for right and left hemisphere) we ran χ^2 statistics. Subsequently to understand the link between OFC sulcogyral pattern and CB use levels in CB users only, we performed a series of three separate ANCOVAs to explore whether OFC pattern affected three distinct measures of CB use levels (i.e., age of onset of regular use, current monthly use, and cumulative lifetime use). Fixed factors included left and right OFC patterns, dependent variables included one of the three measures of CB use level, and the remaining two measures of CB use levels were used as covariates. We corrected for multiple comparisons (i.e. three comparisons corresponding to three CB use measures) using Benjamini and Yekutieli's modified false discovery rate (FDR) method (Benjamini and Yekutieli, 2001).

Finally, to explore the role of higher CB use level as a mediator between specific OFC pattern type and greater depressive symptoms, we ran post-hoc analyses with the significant CB use variable emerging from the ANCOVA results, in a mediation model. CB use level is adopted as a mediator between OFC pattern types (categorical factor) and depressive symptoms. The mediation model was tested using the Hayes PROCESS macro (2.16.2), instead of the causal step approach (wherein each path of the model is ascertained separately), due to criticisms of the latter approach (Hayes, 2016, 2013, 2009). Indirect effect was calculated using bias-corrected bootstrap confidence interval (CI) method, with 5,000 resamples.

Results

Demographics

Sample data and OFC pattern distribution of HC and CB users are presented in Table 1. HC and CB users were matched by age, gender, and alcohol use level. CB users had a significantly lower IQ ($p < .001$), greater depressive symptoms ($p < .001$), and used more cigarettes per month ($p < .001$) than HC. Further sample characteristics by imaging site are provided in Supplementary Table 2.

Table 1 Overview of Demographic, IQ, Substance Use Levels (Mean (SD)), and Orbitofrontal Cortex (OFC) Pattern Distribution (n (%)) of Healthy Controls (HC) and Cannabis (CB) Users

	HC ^c	CB ^c	N	t/ χ^2	p
	N = 128	N = 146			
Age	26.25 (8.86)	28.41 (10.51)	274	1.84	.07
Gender (% M / F)	71.09/28.91	67.12/32.88	274	0.50	.51
IQ ^a	109.26 (10.43)	103.58 (10.67)	270	-4.41	<.001**
Depressive Symptoms ^b	-0.41 (0.65)	0.26 (1.19)	267	5.56	<.001**
Alcohol (StDr/mth) ^c	19.71 (23.63)	24.55 (25.13)	264	1.61	.11
Tobacco (Cig/mth) ^c	29.89 (96.49)	258.01 (236.04)	267	10.56	<.001**

Cannabis Use

Onset Regular Use (years)	-	17.85 (3.37)	141		
Current Use (cones/month)	-	339.59 (322.90)	143		
Lifetime Use (cones)	-	58,164.51	144		
		(99,182.44)			
Right OFC ^c sulcogyral pattern, n (%)				1.06	.59
Type I	63 (49)	69 (47)			
Type II	21 (16)	31 (21)			
Type III	44 (34)	46 (32)			
Left OFC sulcogyral pattern, n (%)				0.30	.86
Type I	64 (50)	70 (48)			
Type II	25 (20)	27 (18)			
Type III	39 (30)	49 (34)			

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

^b Depressive symptoms measured with the Beck Depression Inventory (BDI; Amsterdam, Barcelona, Melbourne) (Beck et al., 1961) and Hamilton Depression Rating Scale (HAMD; Wollongong) (Hamilton, 1960); and subsequently standardized to a z-score based on reported population means (Crawford et al., 2011; Zimmerman et al., 2004).

^c StDr/mth = standard drinks per month; Cig/mth = cigarettes smoked per month; OFC = orbitofrontal cortex; HC = healthy controls; CB = cannabis users

** $p < .001$

Prior to the main analysis, χ^2 tests within each of HC and CB groups, examined across imaging sites, within and across continents, suggested no significant differences in OFC pattern distribution associated with imaging site, and within or across continents (Supplementary Table 3). Nor did OFC pattern distribution differ significantly by gender, IQ, and demographic variables in the right and left hemispheres (Table 2). Therefore we did not include any of these variables as factors in any further analyses.

Table 2 Comparison of Differences in Orbitofrontal Cortex (OFC) Pattern Distribution in All Participants by Demographic, IQ, and Cannabis Use Levels

Right Hemisphere	<i>Type I</i> <i>N = 132</i>	<i>Type II</i> <i>N = 52</i>	<i>Type III</i> <i>N = 90</i>	<i>N</i>	<i>F/χ²</i>	<i>p</i>
Age	26.90 (9.86)	26.34 (8.48)	28.75 (10.40)	274	1.41	.25
Gender (% M / F)	69.70/30.30	69.20/30.80	67.80/32.20	274	0.09	.95
IQ ^a	106.58 (11.74)	104.91 (8.85)	106.52 (10.75)	270	0.54	.58
Depressive Symptoms ^b	-0.04 (1.07)	-0.11 (0.84)	-0.02 (1.09)	267	0.16	.85
Alcohol (StDr/mth) ^c	22.88 (26.32)	22.72 (25.26)	21.14 (21.22)	264	0.29	.87
Tobacco (Cig/mth) ^c	161.53 (221.55)	127.19 (207.63)	172.48 (236.13)	267	0.47	.63
Cannabis Use ^a	<i>Type I</i> <i>N = 67</i>	<i>Type II</i> <i>N = 28</i>	<i>Type III</i> <i>N = 45</i>	<i>N</i>	<i>F</i>	<i>p</i>
Onset Regular Use (years)	17.73 (3.09)	18.16 (4.05)	17.84 (3.41)	140	0.15	.86
Current Use (cones/month)	371.73 (402.87)	280.48 (216.76)	327.46 (243.54)	140	2.31	.10
Lifetime Use (cones)	49,392.85 (70,590.47)	38,737.82 (45,936.98)	73,538.91 (89,776.01)	140	3.91	.02*
Left Hemisphere	<i>Type I</i> <i>N = 134</i>	<i>Type II</i> <i>N = 52</i>	<i>Type III</i> <i>N = 88</i>	<i>N</i>	<i>F/χ²</i>	<i>p</i>
Age	27.05 (9.59)	25.97 (8.71)	28.78 (10.66)	274	1.61	.20
Gender (% M / F)	64.90/35.10	73.10/26.90	72.70/27.30	274	2.02	.37
IQ ^a	105.62 (11.81)	105.94 (10.32)	107.39 (9.82)	270	0.79	.45
Depressive Symptoms ^b	-0.08 (0.97)	-0.05 (1.08)	-0.01 (1.11)	267	0.16	.86
Alcohol (StDr/mth) ^c	22.23 (23.38)	24.44 (27.41)	21.14 (24.61)	264	0.29	.75
Tobacco (Cig/mth) ^c	149.63 (207.43)	138.73 (208.58)	160.74 (235.55)	267	0.18	.83
Cannabis Use ^a	<i>Type I</i>	<i>Type II</i>	<i>Type III</i>	<i>N</i>	<i>F</i>	<i>p</i>

	<i>N</i> = 67	<i>N</i> = 26	<i>N</i> = 47			
Onset Regular Use (years)	17.78 (3.50)	18.14 (2.84)	17.80 (3.55)	140	0.11	.90
Current Use (cones/month)	323.48 (244.38)	319.04 (345.98)	372.92 (410.44)	140	0.09	.92
Lifetime Use (cones)	53,420.97 (74,265.86)	40,971.54 (54,277.86)	65,080.13 (83,109.55)	140	0.67	.51

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

^b Depressive symptoms measured with the Beck Depression Inventory (BDI; Amsterdam, Barcelona, Melbourne) (Beck et al., 1961) and Hamilton Depression Rating Scale (HAMD; Wollongong) (Hamilton, 1960); and subsequently standardized to a z-score based on reported population means (Crawford et al., 2011; Zimmerman et al., 2004).

^c StDr/mth = standard drinks per month; Cig/mth = cigarettes smoked per month

^d ANCOVA on cannabis use level in cannabis users only, with right and left hemisphere OFC pattern as fixed factors, and the other two CB use levels as covariates.

Cumulative lifetime CB use of two users has been winsorised to reduce their influence (864,000 and 459,000 respectively replaced with 355,712 and 356,704, i.e., 3.00 and 3.01 standard deviations above the mean).

**p*<.05

OFC pattern type distribution across groups – HC vs. CB

χ^2 tests of OFC pattern distribution between HC and CB users, indicated that both groups did not differ significantly in right ($\chi^2(2) = 1.06, p = .59$) or left ($\chi^2(2) = 0.30, p = .86$) OFC pattern distribution.

OFC pattern association with level of CB use

To discern the association between OFC pattern type and level of CB use, three separate ANCOVAs were performed (i.e. one each for CB use levels – age of onset of regular use, current monthly use, and cumulative lifetime use). As CB use levels were strongly correlated (range of $r = -.301 - .622, p < .001$), the remaining two CB use levels were used as covariates in all three ANCOVA analyses. For this analysis, six CB users (all males) were excluded from the original sample due to missing CB use levels, resulting in a final sample of 140 CB users¹. Cumulative lifetime CB use of two users was winsorised to reduce their influence (864,000 and 459,000 respectively replaced with 355,712 and 356,704, i.e., 3.00 and 3.01 standard deviations above the mean). IQ and tobacco use, while differing between HC and CB users, were not adopted as covariates, as they were not significantly related to OFC pattern type (Table 2), nor did they affect the association between OFC pattern type and level of CB use as covariates in the subsequent analysis.

ANCOVA with right and left OFC pattern as fixed factor show that the right OFC pattern was significantly associated with cumulative lifetime use (Table 2; $F_{2,133} = 3.91, p = .022, \eta_p^2 = .055$)². After false discovery rate (FDR) correction (B-Y method (Benjamini and Yekutieli, 2001), critical value = .02) the strength of this association was reduced to trend-level. We observed that those CB users with right OFC Type III pattern had higher cumulative lifetime use ($M = 73,539, SD = 89,776$) than those with Type I ($M = 49,393, SD = 70,590, p = .010, 95\% CI [7314, 52249]$) or Type II ($M = 38,738, SD = 45,937, p = .039, 95\% CI [1499, 57799]$), controlling for age of onset of regular use and current monthly use (Fig. 2). We therefore adopted cumulative lifetime CB use as a mediator in the subsequent mediation model between OFC pattern type and depressive symptoms. No other significant association was found.

¹ The six excluded CB users did not differ in age ($M = 26.33, SD = 11.91, n = 6; t(144) = -0.49, p = .62$), IQ ($M = 103.58, SD = 9.20, n = 5; t(141) = 0.00, p = 1.00$), alcohol use ($M = 22.40, SD = 18.08, n = 5; t(139) = 0.20, p = .85$), and tobacco use ($M = 92.00, SD = 141.19, n = 4; t(140) = 1.43, p = .15$) from non-excluded CB users. Nor did they differ significantly in OFC sulcogyral pattern type distribution (n of Type I:II:III = 2:3:1, $\chi^2(2) = 3.13, p = .21$; and n of Type I:II:III = 3:1:2, $\chi^2(2) = 0.02, p = .99$ for the right and left hemispheres respectively) from the non-excluded CB users. However they did report lower depressive symptoms ($M = -.80, SD = 0.15, n = 6; t(142) = 2.27, p = .03$) than non-excluded CB users.

² ANCOVA with unwinsorised data suggest however that results no longer hold ($F_{2,133} = 2.22, p = 0.11, \eta_p^2 = .032$).

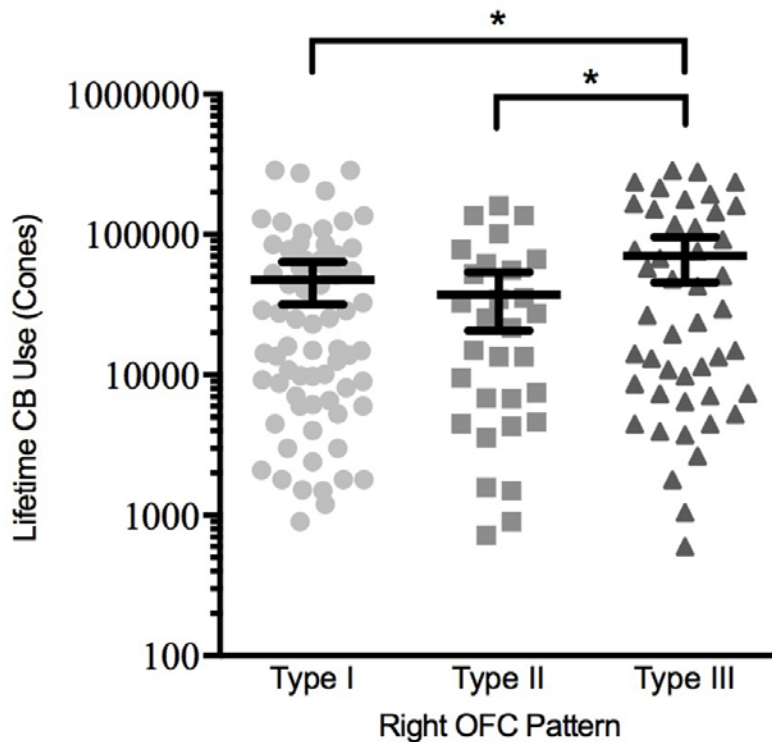


Fig. 2 Cumulative lifetime use in cannabis (CB) users by right orbitofrontal cortex (OFC) pattern type, * $p < .05$. Error bars represent 95% confidence interval.

Lifetime CB use as mediator between OFC pattern and depressive symptoms

Given the higher incidence of depressive symptoms in our sample of CB users compared to HC, and the OFC’s role in the manifestation of affective dysregulation in substance dependence (Diekhof et al., 2008), we explored cumulative lifetime CB use as a mediator between right OFC Type III pattern and depressive symptoms. The right OFC Type III pattern was modeled as a categorical variable (i.e. presence versus absence of Type III). Covariates included current monthly CB use and age of onset of regular use, which did and did not significantly affect the model, respectively.

Within CB users, having a right OFC Type III pattern was not directly associated with depressive symptoms. However, as shown in Fig. 3, right OFC Type III pattern was indirectly associated with higher depressive symptoms, through greater amount of lifetime CB use ($b = 0.14$, 95% CI [0.04, 0.30])³. Given the significant difference between HC and CB users in IQ and tobacco use level, we further conducted a second mediation analysis with lifetime CB use, IQ, and tobacco use as joint mediators to rule out the influence of these confounders on the model (Supplementary Figure 1). Both IQ and tobacco use were not significant mediators of the model, and they did not significantly influence the association between right OFC Type III, lifetime CB use, and depressive symptoms.

³ Mediation model remains valid and significant when re-analysed with unwinsorised data.

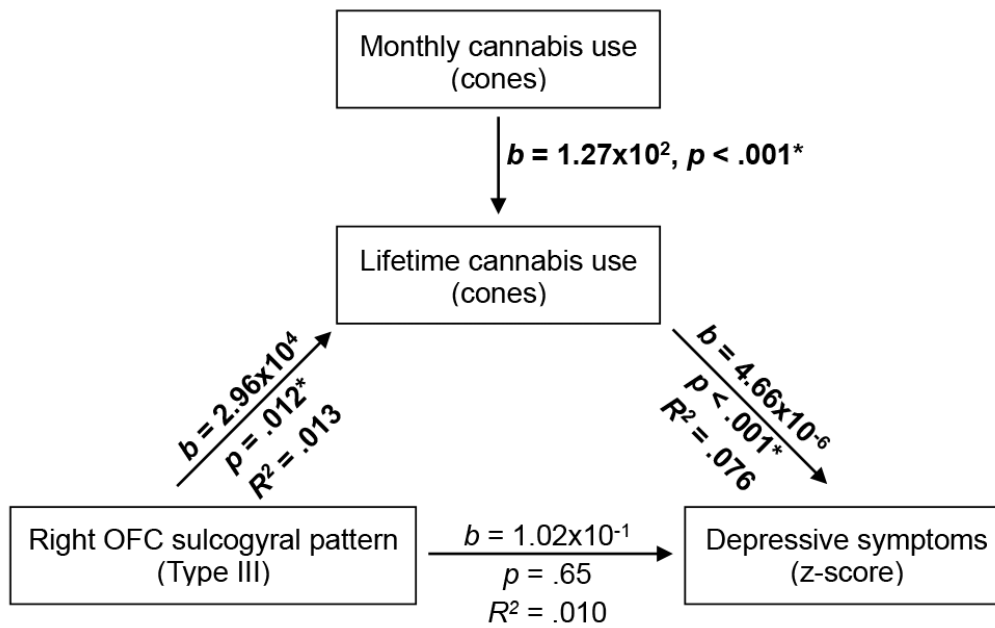


Fig. 3 Cumulative lifetime cannabis (CB) use as mediator between right orbitofrontal cortex (OFC) pattern type (categorical, Type III vs. non-Type III) and depressive symptoms in CB users; indirect effect, $b = 0.14$, 95% CI = [0.04, 0.30].

Discussion

Our study was the first to investigate OFC sulcogyral pattern – largely determined by birth (Chi et al., 1977) and measured via a validated classification method (Bartholomeusz et al., 2013; Chiavaras and Petrides, 2000) – in relation to CB use, CB use levels and associated depressive symptoms. We found no significant differences between the CB and HC groups, in contrast with our first hypothesis. However, those CB users with right OFC Type III pattern (relative to Type I and II) had higher cumulative lifetime CB use; and cumulative use in turn mediated an indirect association between right OFC Type III pattern and higher depressive symptoms. Our findings support the hypothesis that specific OFC gyrification patterns (i.e. Type III pattern) are associated with greater lifetime cannabis use, and are furthermore consistent with previous studies demonstrating greater CB use to be associated with higher depressive symptoms (Crane et al., 2015). In sum, OFC pattern type did not contribute to the risk of becoming a CB user, but had an impact on individuals who became CB users, by predisposing them to greater levels of use throughout their lifetime. These users with greater levels of lifetime CB use may subsequently experience greater depressive symptoms.

Our findings suggest that Type III pattern in the right hemisphere may predispose individuals to greater levels of CB use. This may occur via the altered emotional and cognitive features associated with Type III pattern – such as poor regulatory control, including higher negative emotionality, impulsivity, and stress reactivity (Nakamura et al., 2007; Whittle et al., 2014). The OFC function is relevant to regulatory control as it is involved in monitoring and

processing motivational information, therefore supporting context-appropriate behaviour (Diekhof et al., 2008; Kringelbach and Rolls, 2004; Tremblay and Schultz, 1999). Impaired regulatory function of the OFC could thus manifest as a maladaptively intense drive to procure substances, facilitating greater and more compulsive substance-seeking (Volkow and Fowler, 2000). Indeed, the temperamental variables linked to Type III pattern (e.g. higher negative emotionality, impulsivity, stress reactivity, and sensation-seeking (Nakamura et al., 2007; Whittle et al., 2014)) have been associated with CB use – increased use frequency and risk of lifetime use (Creemers et al., 2010, 2009). Nevertheless, future studies will be necessary to substantiate the link between OFC neuroanatomy, temperamental variables of behaviour regulation, and substance use.

In our exploratory analyses, we further showed that higher lifetime CB use is associated with higher depressive symptoms, thus mediating an indirect association between Type III pattern and greater depressive symptoms. This is consistent with previous evidence linking heavy CB use and depressive symptoms (Crane et al., 2015) or risk of developing depressive disorders (Lev-Ran et al., 2014). We suggest that the Type III pattern may reflect poor regulatory control, which underlies the greater level of CB use, and in turn higher CB-use-related depressive symptoms in users. In substantiation of our claim, CB use and greater depressive symptoms have been demonstrated to co-occur in adolescents with low levels of self-control (Otten et al., 2010). Additionally in a study of abstinent substance-dependent users, measures of self-regulation and emotional functioning were directly correlated (Verdejo-García et al., 2007), suggesting regulatory control to be relevant to the manifestation of emotional disturbances such as depressive symptoms. Unfortunately, as we do not have a direct measure of 'regulatory control', we are unable to examine the contribution of this trait behaviour in both OFC pattern and related psychopathologies. Our findings contrast previously reported association between right OFC Type I pattern (not Type III) and higher depressive symptoms in a community sample of non-CB-using adolescents (Whittle et al., 2014). This may reflect the specific interaction between CB use and pattern type on emerging depressive symptoms, with higher depressive symptoms in CB users with OFC Type III pattern manifesting as a result of prolonged high levels of use. However in our sample of HCs, we did not find any association between OFC pattern type and depressive symptoms either (analysis not shown, $p = .67$ and $p = .77$ for left and right hemisphere respectively). We speculate our lack of finding to be due to the age difference between our adult sample and Whittle and colleague's (2014) adolescent sample, as emotional regulation may develop with age (McRae et al., 2012).

It is noteworthy that the association we found between lifetime CB use and OFC pattern was confined to the right hemisphere. The right hemisphere is suggested to be specialised for socioemotional functioning and emotion management (Borod 1992; Schore 2001; Tranel *et al.* 2002). Greater right over left frontal activation has also been linked to

greater negative affective response and difficulties with affective regulation, that may be related to both internalising (e.g. anxious behavior) and externalising (e.g. aggressive behaviour) problems (Wheeler *et al.* 1993; Fox *et al.* 1996). An overwhelming percentage of studies investigating OFC pattern type have found evidence linking pattern Type III and psychopathology in the right hemisphere (Chakirova *et al.* 2010; Takayanagi *et al.* 2010; Bartholomeusz *et al.* 2013). Overall, our study along with the examples above contribute to evidence of the lateralisation of OFC function (Happaney *et al.* 2004), possibly related to asymmetry in the timeline and functional specialization of cortical development (Toga & Thompson 2003).

The OFC classification method used in this study is both valid and reliable, and minimally affected by confounders including gender differences and imaging sites. In support of the reliability of our OFC classification, the percentage distribution of OFC pattern found in our sample (Type I:II:III = 49:19:32%) was similar to that of previously examined samples of healthy controls (aggregated means of Type I:II:III = 60:19:20%; $\chi^2(2) = 4.32$, $p = .12$) (Bartholomeusz *et al.*, 2013; Chakirova *et al.*, 2010; Chiavaras and Petrides, 2000; Cropley *et al.*, 2015; Ganella *et al.*, 2015; Isomura *et al.*, 2017; Lavoie *et al.*, 2014; Nakamura *et al.*, 2007; Nishikawa *et al.*, 2015; Takahashi *et al.*, 2014, 2015; Takayanagi *et al.*, 2010; Uehara-Aoyama *et al.*, 2011; Watanabe *et al.*, 2014; Whittle *et al.*, 2014). We also did not find any gender-related differences in OFC pattern distribution, consistent with most previous studies (Uehara-Aoyama *et al.*, 2011; Whittle *et al.*, 2014). Finally, we did not observe any imaging site related differences, which points to the reliability of OFC pattern classification across different scanners in our sample. While there is no single conclusive study on the stability of the OFC pattern across countries and population, it nevertheless appears to be a potentially stable morphological trait marker, useful for understanding temperament, behaviour, and psychopathology.

We acknowledge some limitations of our study. Firstly, while we propose self-regulatory deficits related to OFC Type III pattern to predispose CB users to greater levels of use, we did not have measures of behavioural self-regulation. As such, we were unable to examine the relationship between behavioural regulation and OFC pattern type. This may represent a possible future avenue for investigation. Second, depressive symptoms were only assessed cross-sectionally at the time of assessment. Therefore we cannot discern to what extent depressive symptoms precipitated CB use, and whether OFC pattern may have informed depressive symptoms prior to CB initiation. We also did not examine other measures of affective disturbances such as anxiety, in relation to CB use. We adopted depressive (rather than anxiety) symptoms as an index of affective disturbance due to the link between CB use and subsequent depressive symptoms (Degenhardt *et al.*, 2003), and on grounds of anxiety symptoms possibly precipitating rather than being a consequence of CB use (Stapinski *et al.*, 2016). Furthermore, not all imaging sites collected information on

anxiety symptoms. Future longitudinal studies will be necessary to fully explore whether OFC pattern is associated with differences in depressive and anxiety symptoms prior to CB use, or whether such outcomes arose as a result of continual CB exposure. Additionally, as genetic factors may affect cortical folding patterns (Atkinson et al., 2015), genetic or epigenetic factors guiding early neurodevelopment may present as more robust biomarkers of CB use level (Agrawal and Lynskey, 2006; Ystrom et al., 2014), as compared to OFC sulcogyral pattern. Multifactorial models integrating genetic, neurobiological, and behavioural factors will be necessary to provide a more complete account of the causal influences on CB use. Finally, we did not find any association between OFC pattern and alcohol or tobacco use. The specificity of the association between OFC pattern and greater lifetime CB use, rather than other substance (alcohol and tobacco) use may be due to the fact that alcohol and tobacco use were quantified as 'monthly use' in our study, rather than 'cumulative use'. Indeed, we also found no association with current monthly CB use. Given that short-term measures of use (i.e. monthly, compared to lifetime use) may fluctuate with situational changes, these may be less reliably associated with stable trait markers such as OFC pattern. However, further clarification in users of other substances (e.g. alcohol, tobacco) will be necessary.

Conclusion

In conclusion, while there was no particular OFC pattern Type that conferred risk for CB use versus non-use, OFC Type III pattern in the right hemisphere was associated with greater lifetime use in CB users. Greater lifetime CB use was in turn associated with greater depressive symptoms in CB users. Future longitudinal work is needed to ascertain the extent to which OFC pattern informs pre-existing temperamental features that may contribute towards substance use. Meanwhile, comprehensive examination and integration of various factors including genetic, ethnic, and prenatal factors might provide insight regarding the moderators of OFC pattern distribution across populations. This may in turn support the use of OFC pattern type as a stable trait marker to further understand pre-existing vulnerabilities that influence substance use level among CB and/or other substance users, and mental health problems, in general or specifically associated with substance use.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Conflict of interest

None.

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Author contribution

VL and MY designed the study; NS, MY, AB, JC, AEG, RMS, SW, and VL collected the data; YC, AEG, and CB contributed to the data analysis and interpretation; YC wrote the manuscript, while CB, VL, NS, and CS provided critical revision to the manuscript. All authors have approved the final article.

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