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ORIGINAL INVESTIGATION

Orbitofrontal and caudate volumes in cannabis users: a multi-site mega-analysis comparing dependent versus non-dependent users

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Abstract
Rationale Cannabis (CB) use and dependence are associated with regionally specific alterations to brain circuitry and substantial psychosocial impairment.
Objectives The objective of this study was to investigate the association between CB use and dependence, and the volumes of brain regions critically involved in goal-directed learning and behaviour—the orbitofrontal cortex (OFC) and caudate.
Methods In the largest multi-site structural imaging study of CB users vs healthy controls (HC), 140 CB users and 121 HC were recruited from four research sites. Group differences in OFC and caudate volumes were investigated between HC and CB users and between 70 dependent (CB-dep) and 50 non-dependent (CB-nondep) users. The relationship between quantity of CB use and age of onset of use and caudate and OFC volumes was explored.
Results CB users (consisting of CB-dep and CB-nondep) did not significantly differ from HC in OFC or caudate volume. CB-dep compared to CB-nondep users exhibited significantly smaller volume in the medial and the lateral OFC. Lateral OFC volume was particularly smaller in CB-dep females, and reduced volume in the CB-dep group was associated with higher monthly cannabis dosage.
Conclusions Smaller medial OFC volume may be driven by CB dependence-related mechanisms, while smaller lateral OFC volume may be due to ongoing exposure to cannabinoid

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compounds. The results highlight a distinction between cannabis use and dependence and warrant examination of gender-specific effects in studies of CB dependence.

Keywords Cannabis · MRI · Brain structure · Orbitofrontal cortex · Caudate · Dependence · Gender

Introduction

Cannabis (CB) is the most widely used illicit substance worldwide, with 182 million users globally, and set to rise with increasing moves towards legalisation (Volkow et al. 2014a; United Nations Office on Drugs and Crime 2015). These statistics are concerning due to the significant social cost (i.e. health, crime, accident) incurred related to CB use (Moore 2007). CB has long been thought of as relatively harmless, but approximately 10% of users become CB-dependent (Chen et al. 2005; Degenhardt et al. 2007; Elkashef et al. 2008). Up to 21% of admissions to substance abuse treatment services in the USA are due to CB use, with more CB users seeking treatment each year (SAMHSA 2014; UNODC 2014). CB dependence is associated with substantial psychosocial impairment including interference to productivity and interpersonal relationships as a result of continued substance use (Budney and Moore 2002). Additionally, dependent or heavy use is also linked to cognitive deficits (e.g. verbal learning and memory, attention, executive function, processing speed) (Curran et al. 2016; Volkow et al. 2016; Broyd et al. 2016). Much of the harms of CB use may thus be attributable to dependence (Volkow et al. 2016). However, little is understood about the neural correlates of CB dependence, as most neuroimaging studies of regular CB users fail to distinguish between dependent (CB-dep) and non-dependent (CB-nondep) users (Lorenzetti et al. 2016).

The most consistent evidence for structural brain alteration from neuroimaging studies of CB users implicates the hippocampus, amygdala, and prefrontal cortex as key regions in relation to CB use patterns and associated impairment in neurocognitive performance (Lorenzetti et al. 2014). Less is known about the neurocircuitry associated with CB dependence. In particular, the transition from substance use to dependence may be mediated by cortico-striatal regions relevant to normal learning processes, which have yet to be fully explored (Everitt et al. 2008). Learning theory accounts by Everitt and Robbins (2013) suggest that instrumental learning, consisting of goal-directed and habitual processes, contribute to the transition from intentional substance use to more compulsive use (Everitt et al. 2001; Everitt and Robbins 2016). The goal-directed process is a 'planning system', directing intentional action to obtain drug (Redish et al. 2008). This process is sensitive to devaluation and further supports reversal learning necessary to suppressing perseverative tendencies for substance use (Everitt and Robbins 2016). However, a failure in the planning system and the subsequent engagement of a 'habitual system' may mediate the shift to more compulsive drug use (Everitt and Robbins 2016).

Importantly, the former goal-directed process is subserved by diffuse corticostriatal projections that connect the cortical region, such as the orbitofrontal cortex (OFC), to corresponding striatal regions, including the caudate nucleus (dorsomedial striatum) (Haber et al. 1995; Haber 2016). Such projections allow these regions to work in concert to integrate the emotive, motivation and cognitive processes required for appropriate goal-directed behaviour (Haber 2016). Both the OFC and the caudate nucleus are strongly implicated in this process (Redish et al. 2008; Tanaka et al. 2008; Gillan et al. 2011; Gremel and Costa 2013; Ruge and Wolfensteller 2016). Thus, aberrant OFC and caudate function in CB-dep users may underlie an impaired reliance on a flexible, goal-directed process of substance use, devolving into compulsive use reliant on habitual processes (Volkow and Fowler 2000; Schoenbaum et al. 2006).

There is mounting evidence of substance dependence linked to aberrant OFC function. For example, OFC activity may mediate the subjective value of reward from substance use (Kable and Glimcher 2007; Peters and Buchel 2009; Hayashi et al. 2013). OFC resting state activity correlated with greater CB intake (Houck et al. 2013), greater CB cue-elicited craving and CB-related problems (Filbey et al. 2009). OFC hypoactivity may be implicated in CB-dep as it plays a role in substance withdrawal (i.e. up to a few months post-abstinence) and may contribute to relapse upon re-exposure to substance-associated cues (Ahmed and Koob 1998; Volkow and Fowler 2000). However, it is unclear if OFC structural alterations also occur. Studies showing altered OFC morphology (e.g. reduced thickness and volume) in CB and other substance use (Churchwell et al. 2010; Ersche et al. 2011; Battistella et al. 2014; Filbey et al. 2014; Li et al. 2015) have rarely distinguished between CB-nondep and CB-dep users, and changes in OFC morphology specific to CB-dep are unexplored.

The caudate is also implicated in substance use and dependence. Activity in the dorsal striatum, in which the caudate resides, has been robustly linked to substance-seeking and taking, and with exposure to substance-related cues including CB (Ng Cheong Ton et al. 1988; Ito et al. 2002; Vollstädt-Klein et al. 2010). In CB users, altered caudate-dependent activity mediating reward-motivated behaviour likely increases perseverative responding for CB reward (Gatzke-Kopp et al. 2009; Jager et al. 2012; Enzi et al. 2015). The caudate is also implicated in chronic substance (heroin) use (e.g. decreased functional connectivity with the anterior cingulate cortex (Ma et al. 2011)). Despite increasing evidence of altered caudate activity in CB use, it remains unclear if structural alterations occur. Only three papers to date have examined caudate volumes separate from the striatum in CB, in

studies limited by small sample sizes (less than 30 CB users per study) (Batalla et al. 2013; Gilman et al. 2014; Yip et al. 2014). It is therefore unclear whether the volume of the caudate is altered in CB use and dependence (Cousijn et al. 2012; Batalla et al. 2013).

In this study, we aimed to disentangle the role of exposure and dependence on the structure of these key regions of interest (ROIs) implicated in substance use and dependence, by examining the grey matter volumes of the OFC (medial and lateral portion) and caudate in CB-nondep and CB-dep users. To this end, we aggregated a large sample of 140 CB users and 121 healthy controls (HC), across four research sites including University of Amsterdam (Amsterdam) (Cousijn et al. 2012), University of Barcelona (Barcelona) (Batalla et al. 2013), University of Wollongong (Wollongong) (Yücel et al. 2008; Solowij et al. 2013) and Monash University (Melbourne) (Yücel et al. 2016). We compared the ROI volumes between CB users and HC first, and then between CB-nondep and CB-dep users segregated from the CB group according to the respective dependence scale used at each research site. In line with general findings of reduced frontal and striatal volumes in CB users, we hypothesised that CB users relative to HC and CB-dep relative to CB-nondep users would show smaller ROI volumes (Churchwell et al. 2010; Smith et al. 2014). Finally, we explored the association between ROI volumes and quantity of CB use and age of onset of use to understand whether other parameters of CB use may be differentially related to ROI alterations in CB-dep and CB-nondep.

Methods

Participants

Participants' MRI data were aggregated from four independently conducted studies across Amsterdam (N = 76), Barcelona (N = 55), Wollongong (N = 30) and Melbourne (N = 100). The final sample consisted of 140 CB and 121 HC in the age range between 18 and 56 years. All participants were instructed to abstain from using any substance at least 12 h prior to the MRI scan. Urine samples were taken to screen for illicit drug use other than CB and as a deterrent against participants using CB prior to the scan. All CB users tested positive for THC metabolites, indicating regular CB use, as urine analysis is insensitive to 12-h abstinence (Huestis 2007). Further inclusion and exclusion criteria, along with assessment measures used by each imaging site, are detailed in Supplementary Table 1.

Measures

Participants' demographic and substance use characteristics were assessed through semi-structured interviews at each individual site. These included age, gender, IQ, monthly tobacco (cigarettes) use, monthly standard alcoholic drinks, monthly and lifetime CB consumption (measured in cones, https://ncpic.org.au/static/pdfs/ assessment-tools/timeline-followback.pdf), age of initiation of regular CB use and CB dependence.

Different measures of CB dependence were only available for Amsterdam (Mini Neuropsychiatry International Interview, MINI) (Lecrubier et al. 1997; Sheehan et al. 1997), Barcelona (Severity of Dependence Scale, SDS) (Gossop et al. 1995) and Melbourne (SDS). For the MINI (Amsterdam), a cut-off of 3 and above was used to classify CB-dep (Lecrubier et al. 1997; Swift et al. 1998), while for SDS, a cut-off of 4 and above (Barcelona and Melbourne) was used to classify CB-dep (van der Pol et al. 2013), based on recommended norms.

Structural image processing

T1-weighted structural MR images were acquired independently at each of the four sites. Scanner details for each imaging site have been detailed previously by the original research groups (Yücel et al. 2008; Cousijn et al. 2012; Batalla et al. 2013; Yücel et al. 2016), and in the Supplementary Table 1.

In order to minimise inter-scanner differences between research sites, an optimised preprocessing protocol with additional steps was adopted. A noise removal step was first implemented using the prefiltered rotationally invariant nonlocal means filter (PRINLM) (https://sites.google.com/site/pierrickcoupe/softwares/denoising-for-medical-imaging/mri-denoising), to remove systematic variations due to noise and improve the segmentation of brain regions (Gaser and Coupé 2010; Eskildsen and Coupe 2011; Manjón et al. 2012; Fellhauer et al. 2015).

Subsequently, subcortical and cortical volumetric processing was performed using FreeSurfer image analysis (http://surfer.nmr.mgh.harvard.edu/) version 5.3.0. The automated FreeSurfer pipeline included motion correction (Reuter et al. 2010), non-uniform intensity normalisation (N3) at 500 iterations to correct for intensity non-uniformity artifacts (increase from default number of iterations of 4) (Sled et al. 1998; Zheng et al. 2009), automated Talairach transformation, removal of non-brain tissue (Ségonne et al. 2004) and segmentation of white matter and grey matter volumes (Fischl et al. 2002). Finally, grey matter volumes (lateral OFC, medial OFC and caudate) were extracted from Freesurfer's automated parcellation procedure for further statistical analysis.

Statistical analyses

All statistical analysis was conducted using IBM SPSS Statistics 22.0. Group differences in demographic variables

between CB and HC were assessed using an independent sample *t* test or X^2 test.

All segmented subcortical volumes were corrected for the effect of individual intracranial volume (ICV) using a residual approach prior to analysis (Free et al. 1995). A repeated-measure analysis of covariance (ANCOVA) was subsequently performed to examine the difference in ROI volumes between CB users and HC, with left and right hemisphere comprising the within-subject repeated measure, with imaging site and gender as between-subject factors, and age, IQ, as well as monthly alcohol and tobacco use as covariates. A second repeated-measure ANCOVA was performed to examine the difference in ROI volumes between CB-dep and CB-nondep users for the three sites that obtained dependence measures (Amsterdam, Barcelona, Melbourne). Hemisphere was used as repeated measure, with imaging site and gender as between-subject factors, and age, IQ and monthly cigarettes and standard drinks as covariates. Multiple comparisons were corrected for using Benjamini and Yekutieli's modified false discovery rate (FDR) method (Benjamini and Yekutieli 2001; Narum 2006). Finally, we ran a regression analysis to explore the association between the volumes of the ROIs and CB use variables—age of regular use onset, monthly and lifetime cones.

Results

Sample characteristics

Key demographic and substance use characteristics of participants are presented in Table 1. Further demographic information by imaging site, along with any site effects on ROIs, is discussed in the supplement (Supplementary Tables 2 and 3). CB and HC groups did not differ in age, gender or alcohol use. However, CB users had a significantly lower IQ ($p < .001$) and smoked significantly more cigarettes per month ($p < .001$) than HC. We excluded the influence of these potential confounders (i.e. IQ, monthly cigarettes use) in preliminary correlations with the ROIs in the Supplementary Fig. 1.

OFC and caudate differences between CB users and HC

OFC and caudate volumes in HC and CB groups are presented in Table 2. There was no significant group difference in overall OFC (lateral and medial) or caudate volumes. There was a significant group by hemisphere interaction in the lateral OFC ($F_{1,243} = 5.27$, $p = .023$), with the volume difference between the left and right hemisphere (left bigger than right) being larger in the CB than in the HC group; however, none of the hemisphere or group effect (in either CB or HC group) were significant. There was also a main effect of hemisphere in the caudate ($F_{1,243} = 3.976$, $p = .047$), with the left caudate being larger than the right. The effect of imaging site was significant for each of the ROI volumes: lateral OFC ($F_{3,243} = 12.44$, $p < .001$), medial OFC ($F_{3,243} = 5.85$, $p = .001$) and caudate ($F_{3,243} = 18.68$, $p < .001$) (see Supplementary Table 2). Age also significantly affected each ROI: lateral OFC ($F_{1,243} = 26.23$, $p < .001$), medial OFC ($F_{1,243} = 27.36$, $p < .001$) and caudate ($F_{1,243} = 4.99$, $p = .026$). Reduced volume was associated with older age for all ROIs, as determined through further correlation analysis (range of $r = -.14$ to $-.37$, range of $p = .027$ to $<.001$). There was also a gender effect ($F_{1,243} = 5.41$, $p = .021$) and a site by gender effect ($F_{3,243} = 3.28$, $p = .039$) for the caudate only, with females demonstrating smaller caudate than males in only the Wollongong and Melbourne groups. However, only site-related

Table 1 Demographic and substance use characteristics of healthy controls (HC) and cannabis (CB) users (mean (SD))

	HC *N = 121*	CB *N = 140*	$t_{df=259}/X^2$	*p*
Age	26.12 (9.03)	28.03 (10.25)	1.58	.12
Gender (% M/F)	70.25/29.75	67.14/32.86	0.29	.60
IQ[a]	109.31 (10.54)	103.45 (10.74)	−4.44	<.001**
Alcohol (StDr/mth)	19.87 (23.77)	24.43 (25.18)	1.50	.14
Tobacco (Cig/mth)	30.88 (97.92)	254.96 (233.77)	9.82	<.001**
Cannabis use				
Onset regular use (years)	–	17.84 (3.38)	–	–
Current use (cones/month)	–	334.08 (322.32)	–	–
Lifetime use (cones)	–	57,107 (99,987)	–	–

StDr/mth standard drinks per month, *Cig/mth* cigarettes smoked per month

[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) (Barcelona) (Wechsler 1997), the National Adult Reading Test (NART) (Wollongong) (Nelson 1982) and the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler 1999) (Melbourne)

**$p < .001$

Table 2 Cortical and subcortical volumes of healthy controls (HC) and cannabis (CB) users (mean (SD); mm^3)

		HC *N = 121*	*CB* *N = 140*	Group effect: HC vs CB		Hemisphere effect: left vs right		Group × hemisphere effect	
				F	*p*	*F*	*p*	*F*	*p*
Intracranial cavity (10^6)		1.55 (0.20)	1.52 (0.17)						
Lateral OFC	Left	8070.83 (928.48)	7851.59 (927.51)	0.54	.46	0.41	.52	5.27	.023*
	Right	7738.31 (993.50)	7441.17 (986.43)						
Medial OFC	Left	5235.12 (755.91)	5124.80 (808.05)	0.87	.35	0.63	.43	2.32	.13
	Right	5598.26 (644.68)	5279.79 (696.25)						
Caudate	Left	3945.49 (492.04)	3770.79 (556.22)	0.48	.49	3.98	.047*	0.17	.68
	Right	4078.98 (561.65)	3841.23 (629.13)						

*$p < .05$

group differences remain significant after correcting for multiple comparison using FDR method (critical value = .020).

CB-dependent group differences

Five CB users (four from Barcelona, one from Melbourne) were missing information on dependence status and were omitted from subsequent analysis. CB-nondep and CB-dep users did not differ in age, gender, IQ, alcohol and tobacco use, onset age of CB use and lifetime CB use (Tables 3 and 4). CB-dep users, however, smoked significantly more CB per month ($p = .012$). Further demographic information and ROI volumes in CB-nondep and CB-dep group by imaging site can be found in Supplementary Table 3.

Repeated-measure ANCOVA revealed a significant effect of dependence ($F_{1,106} = 5.81$, $p = .018$, $\eta_p^2 = .052$) and a gender × dependence interaction ($F_{1,106} = 5.90$, $p = .017$, $\eta_p^2 = .009$) in the lateral OFC. CB-dep users had a significantly smaller lateral OFC than non-dependent users ($p = .029$), most prominent in CB-dep females (M = 7393.97, SD = 586.28) relative to CB-nondep females (M = 8002.76, SD = 823.73) (Tukey's HSD, $p = .024$) (Fig. 1). Age was a significant covariate in the model ($F_{1,106} = 6.98$, $p = .009$) and was associated with smaller volume in all further ROIs (lateral and medial OFC, caudate) except the right lateral OFC, as determined through further correlational analysis (range of $r = -.22$ to $-.48$, range of $p = .014$ to $<.001$). Additionally, there was a significant effect of imaging site ($F_{2,106} = 7.96$, $p = .001$), with volume difference being driven by users from Amsterdam (see Supplementary Table 3).

Similarly, we found that the medial OFC was significantly affected by dependence ($F_{1,106} = 7.51$, $p = .007$, $\eta_p^2 = .066$) and age ($F_{1,106} = 10.91$, $p = .001$). CB-dep had a smaller medial OFC than CB-nondep users ($p = .003$), and there was no gender × dependence interaction effect (Fig. 2). Imaging site did not affect medial OFC volume, and the pattern of 'CB-dep < CB-nondep' was found in all sites (visual inspection, see Supplementary Table 3 for volumes by imaging site).

For caudate volume, we found no dependence effect, but a site × dependence interaction effect ($F_{2,106} = 3.14$, $p = .047$), with CB-nondep Amsterdam users having the largest caudate. There was also a significant effect of hemisphere ($F_{1,106} = 5.73$, $p = .018$; larger right than left) and imaging site on caudate volume ($F_{2,106} = 6.31$, $p = .003$) (Supplementary Table 3).

Association with cannabis use variables

Multiple regression analyses, with variables including imaging site, gender, age, CB use characteristics (i.e. age of regular use, monthly cones, lifetime cones), IQ, alcohol (i.e. standard drinks per month) and tobacco (i.e. cigarettes per month), were conducted to predict caudate and OFC volume in CB-nondep and CB-dep users separately.

In CB-dep users, smaller left lateral OFC was associated with greater CB cones per month (*Beta* = −.40, $t(57) = -2.95$, $p = .005$, $\eta^2 = .10$) (Fig. 3). This association remained significant despite FDR correction (critical value = .017). The only significant cannabis use-related association in CB-nondep users was that greater CB lifetime cones was associated with larger left lateral OFC (*Beta* = .57, $t(40) = 2.23$, $p = .032$) and larger right medial OFC (*Beta* = .57, $t(40) = 2.04$, $p = .048$), but they did not remain significant after FDR correction. No other association between CB-use parameters and ROI volumes was found in CB-dep or CB-nondep users, with range of ($p = .107$–$.999$).

Discussion

In the first multisite structural brain imaging mega-analysis that directly compares HC vs CB, and subsequently CB-nondep vs CB-dep users, we show that the OFC grey matter

Table 3 Demographic and substance use characteristics of non-dependent (CB-nondep) and dependent (CB-dep) cannabis users (Mean (SD))

	CB-nondep $N = 50$	CB-dep $N = 70$	$t_{df=118}/X^2$	p
Age	27.07 (10.33)	26.74 (9.18)	0.18	.86
Gender (% M/F)	60.00/40.00	64.29/35.71	0.23	.70
IQ[a]	103.03 (11.13)	102.13 (10.86)	0.45	.66
Alcohol (StDr/mth)	21.54 (25.03)	21.88 (22.78)	−0.08	.94
Tobacco (Cig/mth)	236.90 (249.97)	219.72 (197.66)	0.42	.68
Cannabis use				
Onset regular use (years)	17.79 (2.66)	17.44 (3.23)	0.61	.54
Current use (cones/month)	229.81 (202.25)	351.64 (290.95)	−2.54	.01*
Lifetime use (cones)	32,375 (47,641)	50,431 (72,812)	−1.54	.13

StDr/mth standard drinks per month, *Cig/mth* cigarettes smoked per month

[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) (Barcelona) (Wechsler 1997) and the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler 1999) (Melbourne)

*$p < .05$

volume is reduced in CB dependence. CB-dep users showed smaller lateral and medial OFC than CB-nondep users, and the smaller lateral OFC was most prominent in CB-dep females relative to CB-nondep females. In line with the OFC's role in supporting goal-directed learning and behaviour (Tremblay and Schultz 1999; Kringelbach and Rolls 2004) which, when disrupted, may contribute to the emergence of compulsive behaviour (Fineberg et al. 2010) (e.g. excessive and persistent substance use, inability or unsuccessful attempt at reducing use, despite physical/physiological problems related to use (Hasin et al. 2013)), we found OFC volume reduction only in CB-dep users. Our structural findings further concur with studies on altered OFC function (related to reward processing and inhibitory control) in CB dependence (Filbey and Yezhuvath 2013; Filbey and Dunlop 2014). Our findings are inconsistent with previous evidence of reduced OFC volume in CB users compared to HC (Churchwell et al. 2010; Battistella et al. 2014; Filbey et al. 2014). We did not find OFC volume reduction specific to CB use, but rather to CB dependence. This may be due to the larger sample and range of users in our large-scale neuroimaging study (previous studies range between 14 and 66 subjects amongst CB-using samples (Tzilos et al. 2005; Medina et al. 2007; Ashtari et al. 2011; Lorenzetti et al. 2012; Gilman et al. 2014; Weiland et al. 2015; Mashhoon et al. 2015)), affording more power to detect subtle but relevant influences such as dependence on neuroanatomy (Turner 2014).

Volume reduction in the medial OFC in particular may be unique to dependence (relating to individuals' preoccupation with and impaired control over CB use (Gossop et al. 1995; Martin et al. 2006)) and minimally influenced by regular exposure to cannabinoids per se. Both CB-dep and CB-nondep users had comparable ages of use onset and lifetime quantity used, making it unlikely that these factors contributed to the observed differences. Similarly, CB use variables (age of onset, monthly and lifetime dosage) were not negatively associated with medial OFC volume in either the CB-dep or the CB-nondep users in multiple regression analysis. Rather, we

Table 4 Cortical and subcortical volumes of non-dependent (CB-nondep) and dependent (CB-dep) cannabis users (mean (SD); mm^3)

		CB-nondep $N = 50$	CB-dep $N = 70$	Group effect: CB-nondep vs CB-dep		Hemisphere effect: left vs right		Group × hemisphere effect	
				F	p	F	p	F	p
Intracranial cavity (10^6)		1.46 (0.19)	1.53 (0.15)						
Lateral OFC	Left	7945.54 (1007.71)	7713.97 (847.78)	5.81	.018**	0.43	.52	0.38	.54
	Right	7276.50 (913.75)	7414.34 (1038.58)						
Medial OFC	Left	5018.22 (816.76)	5023.97 (797.32)	7.51	.007**	0.01	.98	0.19	.67
	Right	5391.20 (735.97)	5117.39 (627.21)						
Caudate	Left	3711.12 (517.82)	3774.90 (564.10)	0.17	.68	5.73	.018**	0.29	.59
	Right	3812.05 (675.15)	3863.30 (602.51)						

*$p < .05$, **$p < .020$ (critical value after FDR correction (Benjamini and Yekutieli 2001))

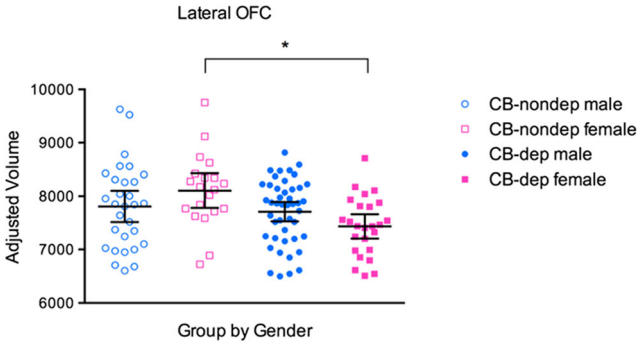

Fig. 1 Lateral orbitofrontal cortex (OFC) volume in dependent (CB-dep) vs non-dependent (CB-nondep) cannabis users by gender, collapsed across hemispheres, adjusted for intracranial volume (ICV) and age, with bars representing 95% confidence interval; *$p < .05$

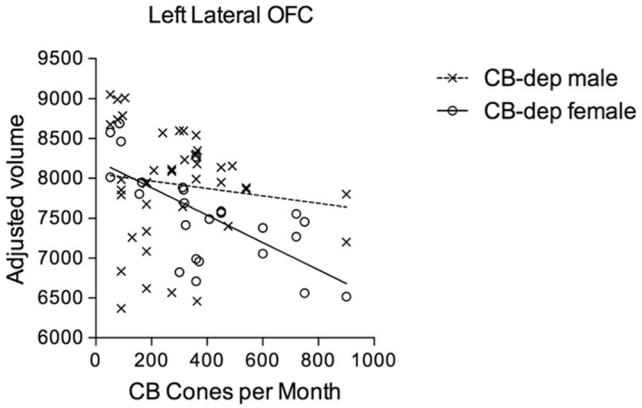

Fig. 3 Left lateral orbitofrontal cortex (OFC) volume by cannabis (CB) use (cones per month) in male and female dependent cannabis users (CB-dep), adjusted for intracranial volume (ICV) and age. This association was not found in recreational cannabis users

observed a possible enlarged medial and lateral OFC in CB-rec users, further highlighting OFC volume to be selectively reduced in CB-dep. On the other hand, the lateral OFC volume was reduced in CB-dep relative to CB-nondep users and most prominently in females, and this reduction was associated with greater monthly CB use in the CB-dep group only. The volume-dosage association may suggest additional cannabinoid toxicity on cortical neurons (Downer et al. 2001) of the lateral OFC in chronic and dependent users. The more pronounced lateral OFC reduction in CB-dep females is in line with evidence of females being more sensitive to the deleterious effects of cannabinoids than their male counterparts (Tseng and Craft 2001; Craft 2005; Fattore and Fratta 2010; Craft et al. 2013)—including faster transition to dependence (Hernandez-Avila et al. 2004) and selective alteration of other brain regions (i.e. amygdala) functionally linked to the OFC in mediating reward and instrumental learning processes (Cardinal et al. 2002; Mcqueeny et al. 2011). Our findings highlight the gender difference in the effect of CB on the brain and the necessity of considering how gender differences may manifest in CB use and dependence.

While the exact mechanism underlying the reduced OFC volume is unknown, supporting evidence of a relative shift from goal-directed behaviour towards habit formation, which is quantitatively associated with reduced medial OFC volume in compulsive behaviour (including substance dependence) (Voon et al. 2015), suggests an intimate association between compromised OFC function and its structural deficit. Such OFC volume loss may be the result of neuronal loss and atrophy resulting in compromised function (Rajkowska et al. 1999; Rajkowska 2000; Volkow et al. 2002). However, further means of characterising the cellular and perfusion characteristic of OFC reduction in CB dependence (e.g. magnetic resonance spectroscopy, perfusion imaging, post-mortem neuronal/glia morphometric) will be necessary to uncover the aetiology of this volume reduction. Alternatively, reduced OFC volume may pose as a pre-existing vulnerability factor subsequently observed in our CB-dep sample. In previous studies, reduced medial OFC volume has been linked to earlier CB use onset (Boes et al. 2009; Matsuo et al. 2009; Churchwell et al. 2010), while reduced OFC volume in general has been found to predict initiation of CB use in adolescents (Cheetham et al. 2011). It may be possible that the (medial) OFC's role in supporting goal-directed decision-making and behavioural process, when impaired, may pose as a vulnerability factor for both early use and subsequent misuse (i.e. dependence) of substances such as CB (Volkow and Fowler 2000; Schoenbaum et al. 2006). However, further longitudinal study will be necessary to disentangle the causes and consequences of reduced OFC structure in CB dependence.

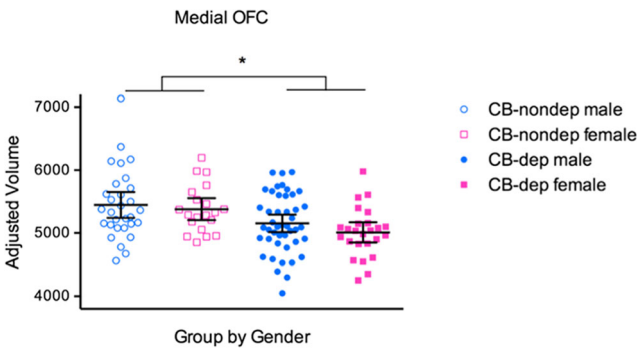

Fig. 2 Medial orbitofrontal cortex (OFC) volume in dependent (CB-dep) vs non-dependent (CB-nondep) cannabis users by gender, collapsed across hemispheres, adjusted for intracranial volume (ICV) and age, with bars representing 95% confidence interval; *$p < .05$

The caudate volume was not affected by either CB use or dependence, in line with previous studies on CB use (Cousijn et al. 2012; Gilman et al. 2014). Despite this, studies examining dependence on substances other than cannabis (meth, alcohol, cocaine, nicotine) have found both enlarged or reduced volumes (Sullivan et al. 2005; Ersche et al. 2011; Morales et al. 2012; Li et al. 2015). A possible explanation is that caudate volume parallels the changes in dopaminergic activity

(DA, a key neurotransmitter mediating reward processing and addictive behaviour) over the course of dependence (i.e. a pre-existing larger caudate that reduces in size with repeated substance use) (Scherk and Falkai 2006; Ersche et al. 2011). This may lead to the disparate findings in previous studies on caudate volume in substance dependence and explain the lack of finding in our study. Indeed, studies demonstrating acute cannabinoid-induced striatal DA release support its reinforcing effect (Voruganti et al. 2001; Bossong et al. 2009). Meanwhile in dependent CB users, evidence of compromised striatal DA synthesis and release capacity suggest DA down-regulation (Bloomfield et al. 2014; Volkow et al. 2014b; van de Giessen et al. 2016), which may inform deficits in corticostriatal behavioural monitoring function (Volkow and Fowler 2000). As such, the evidence demonstrates compromised striatal DA function alongside CB dependence. However, whether this DA alteration is further associated with structural alteration in the caudate is uncertain. While one study demonstrated a positive correlation between dopaminergic binding potential and caudate volume (Woodward et al. 2009), no study has yet specifically examined the association between DA activity and striatal volume within CB-dep users. Additionally, studies in chronic CB users to date have yet been unable to demonstrate a reduction in DA receptor availability, despite compromised DA activity (Volkow et al. 2014b; van de Giessen et al. 2016). Future longitudinal multimodal studies combining PET and MRI in CB-dep vs CB-nondep users and HC are warranted to inform the interrelationship between DA (receptor density and activity) and striatal volume change over the course of dependence, substantiating the role of DA on corticostriatal structure and function.

An issue that may have restricted our ability to observe CB-related effect relates to our choice of defining the caudate as an ROI based on structural (rather than functional) mapping of striatal subregions (i.e. dorsomedial striatum; Fischl et al. 2002). As multiple parallel corticostriatal circuits subserving unique functions ranging from emotion, motivation, higher cognition and motor planning, converge in overlapping zones on the striatum (Haber 2016), structural segmentation within the caudate based on anatomical division may not parse out the morphology corresponding to the different functional subdivisions of the striatum. Alternatively, striatal segmentation corresponding to the OFC-striatal projections (i.e. medial caudate, ventromedial putamen, and central and lateral ventral striatum (Haber et al. 1995; Haber 2016)) or corresponding to purported function (i.e. associative–precommisural dorsal caudate and putamen, postcommisural caudate; limbic–ventral striatum; sensorimotor–postcommisural putamen (Martinez et al. 2003)) may provide more information on CB-dep-related effect.

Another limitation in our investigation was the significant group difference in IQ and tobacco use levels—with lower IQ level and higher tobacco use in CB users than HC. This is relevant as prior studies have suggested an association of IQ and tobacco use with grey matter volumes (Narr et al. 2007; Wetherill et al. 2015). Nevertheless, our preliminary correlations demonstrated no association between IQ or tobacco use and ROI volumes (Supplementary Fig. 1). We also controlled for the confounding influence of IQ and tobacco use in all our group analyses and found no significant effect in any of the results, suggesting that these variables did not drive the OFC volume reduction in CB-dep users relative to CB-nondep users. Of note, neither IQ nor tobacco use differed between CB-dep and CB-nondep groups and therefore cannot explain the differences we observed in relation to cannabis dependence. Nevertheless, other studies have found reduced OFC GM and OFC-related functional deficits with regular tobacco use, suggesting that similar dysfunction in reward and decision-making circuits occur in chronic cigarette smokers and CB users (Spinella 2002; Kühn et al. 2010). As our CB user sample smoked considerably less cigarettes than smokers whose primary substance of choice is tobacco (i.e. 250 vs 400+ cigs/month) (Kühn et al. 2010; Wetherill et al. 2015), we might not have been able to observe a tobacco-related effects.

A further limitation arises from our collating pre-existing datasets in the form of a mega-analysis. Different imaging sites adopted different instruments in measuring CB-dep. This precluded direct comparison of level of dependence severity with ROIs across sites. However, we adopted validated cut-offs (Lecrubier et al. 1997; Swift et al. 1998; van der Pol et al. 2013) for separating CB-dep and CB-nondep users, allowing us to consistently investigate the relevance of CB-dep in ROI volume across sites, despite the different dependence scales adopted by each site. Finally, the significant influence of imaging site cannot be excluded. For example in our study, users from Amsterdam drove the group difference in lateral OFC volume between CB-dep and CB-nondep users. Differences in demographic (i.e. age, gender), amount of cannabis use and scanner-related differences (i.e. scanner strength and sequence) may drive site-related differences, such that not all findings may be robustly observed across all sites. Inconsistent findings are not unusual with regards to structural alterations in CB users (Mcqueeny et al. 2011; Lorenzetti et al. 2015; Weiland et al. 2015; Mashhoon et al. 2015), and understanding how various factors (e.g. age, gender, CB dosage) may moderate the neuroanatomical alteration in CB use and dependence is necessary.

In conclusion, our findings show that CB dependence and recreational use have distinct and region-specific effects. Dependence-related medial OFC volume reduction was robust across all examined imaging sites. Lateral OFC volume reduction meanwhile was associated with monthly CB dosage and stronger in female CB-dep users, in line with evidence of gender-dependent differences towards the various physiological, behavioural and reinforcing effect of CB (Craft 2005;

Fattore et al. 2009; Fattore and Fratta 2010). Future studies should explore further neural markers specific to dependence, alongside their functional relevance to the dependence process, which may distinguish the mechanisms of non-problematic regular CB use vs dependent use. Our findings highlight the need to consider the interactive influence of demographic factors (i.e. gender) and CB use pattern in informing CB dependence-related structural alterations, to allow for more targeted diagnosis and treatment of CB dependence.

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Compliance with ethical standards This study was approved by the Monash University Human Research Ethics Committee. All participants provided written informed consent.

Conflict of interests M.Y. was supported by a National Health and Medical Research Council of Australia Fellowship (App#1117188) and the David Winston Turner Endowment Fund. The authors declare that they have no conflict of interest.

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