



## UvA-DARE (Digital Academic Repository)

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

Chye, Y.; Solowij, N.; Suo, C.; Batalla, A.; Cousijn, J.; Goudriaan, A.E.; Martin-Santos, R.; Whittle, S.; Lorenzetti, V.; Yücel, M.

**DOI**

[10.1007/s00213-017-4606-9](https://doi.org/10.1007/s00213-017-4606-9)

**Publication date**

2017

**Document Version**

Final published version

**Published in**

Psychopharmacology

**License**

Article 25fa Dutch Copyright Act

[Link to publication](#)

**Citation for published version (APA):**

Chye, Y., Solowij, N., Suo, C., Batalla, A., Cousijn, J., Goudriaan, A. E., Martin-Santos, R., Whittle, S., Lorenzetti, V., & Yücel, M. (2017). Orbitofrontal and caudate volumes in cannabis users: a multi-site mega-analysis comparing dependent versus non-dependent users. *Psychopharmacology*, 234(13), 1985-1995. <https://doi.org/10.1007/s00213-017-4606-9>

**General rights**

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

**Disclaimer/Complaints regulations**

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

*UvA-DARE is a service provided by the library of the University of Amsterdam (<https://dare.uva.nl>)*

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

Yann Chye<sup>1</sup> · Nadia Solowij<sup>2</sup> · Chao Suo<sup>1</sup> · Albert Batalla<sup>3,4</sup> · Janna Cousijn<sup>5</sup> · Anna E. Goudriaan<sup>6,7</sup> · Rocio Martin-Santos<sup>4</sup> · Sarah Whittle<sup>8</sup> · Valentina Lorenzetti<sup>1,8,9</sup> · Murat Yücel<sup>1</sup>

Received: 23 October 2016 / Accepted: 13 March 2017 / Published online: 1 April 2017  
© Springer-Verlag Berlin Heidelberg 2017

## 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

---

Valentina Lorenzetti and Murat Yücel are joint last author

---

**Electronic supplementary material** The online version of this article (doi:10.1007/s00213-017-4606-9) contains supplementary material, which is available to authorized users.

---

✉ Valentina Lorenzetti  
vlor@liv.ac.uk

✉ Murat Yücel  
murat.yucel@monash.edu

<sup>1</sup> Brain and Mental Health Laboratory, Monash Institute of Cognitive and Clinical Neurosciences, School of Psychological Sciences, Monash University, Melbourne, Australia

<sup>2</sup> School of Psychology and Illawarra Health and Medical Research Institute, University of Wollongong, Wollongong, Australia

<sup>3</sup> Department of Psychiatry, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Centre, Nijmegen, The Netherlands

<sup>4</sup> Department of Psychiatry and Psychology, Hospital Clinic, IDIBAPS, CIBERSAM and Institute of Neuroscience, University of Barcelona, Barcelona, Spain

<sup>5</sup> Department of Developmental Psychology, University of Amsterdam, Amsterdam, The Netherlands

<sup>6</sup> Department of Psychiatry, Amsterdam Institute for Addiction Research, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

<sup>7</sup> Arkin Mental Health Care, Amsterdam, The Netherlands

<sup>8</sup> Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne and Melbourne Health, Melbourne, Australia

<sup>9</sup> School of Psychological Sciences, Institute of Psychology, Health and Society, The University of Liverpool, Liverpool, UK

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 Coupé 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  $\chi^2$  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 <i>N</i> = 121	CB <i>N</i> = 140	$t_{df=259}/\chi^2$	<i>p</i>
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 <sup>a</sup>	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

<sup>a</sup> 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<sup>3</sup>)

		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 <sup>6</sup> )		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 <i>N</i> = 50	CB-dep <i>N</i> = 70	$t_{df=118}\chi^2$	<i>p</i>
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 <sup>a</sup>	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

<sup>a</sup> 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

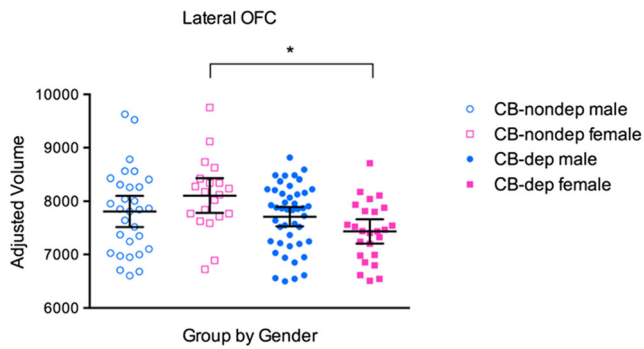
dependence. This may be due to the larger sample and range of users in our large-scale neuroimaging study (previous studies range between 14 and 66 subjects amongst CB-using samples (Tzilos et al. 2005; Medina et al. 2007; Ashtari et al. 2011; Lorenzetti et al. 2012; Gilman et al. 2014; Weiland et al. 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<sup>3</sup>)

		CB-nondep <i>N</i> = 50	CB-dep <i>N</i> = 70	Group effect: CB-nondep vs CB-dep		Hemisphere effect: left vs right		Group × hemisphere effect	
				<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
Intracranial cavity (10 <sup>6</sup> )		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)						

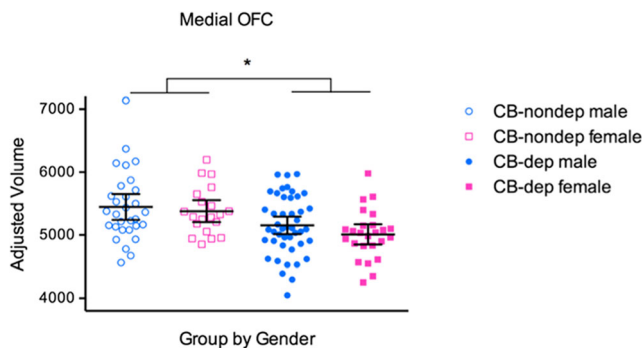
\**p* < .05, \*\**p* < .020 (critical value after FDR correction (Benjamini and Yekutieli 2001))



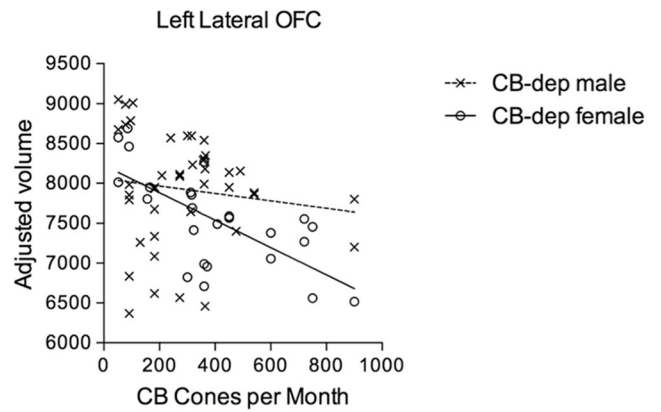
**Fig. 1** Lateral orbitofrontal cortex (OFC) volume in dependent (CB-dep) vs non-dependent (CB-nondep) cannabis users by gender, collapsed across hemispheres, adjusted for intracranial volume (ICV) and age, with bars representing 95% confidence interval; \* $p < .05$

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



**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; \* $p < .05$



**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

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.

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–precommissural dorsal caudate and putamen, postcommissural caudate; limbic–ventral striatum; sensorimotor–postcommissural 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.

**Acknowledgments** The Amsterdam sample was obtained with the support of grants from the Netherlands Organisation for Scientific Research–Health Research and Development, ZON-Mw grant #31180002 and an Amsterdam Brain Imaging Platform grant. The Barcelona sample was obtained with the support of grant PNSD:2011/050, Plan Nacional sobre Drogas. Ministerio de Sanidad y Política Social and grant SGR2014/1114, Generalitat de Catalunya, Spain. The Wollongong sample was obtained with the support of grants from the Clive and Vera Ramaciotti Foundation for Biomedical Research, and the Schizophrenia Research Institute with infrastructure funding from NSW Health. The Melbourne sample was obtained with the support of the National Health and Medical Research Council (NHMRC) of Australia Project Grant (#459111).

**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.

## References

- Ahmed SH, Koob GF (1998) Transition from moderate to excessive drug intake: change in hedonic set point. *Science* 282:298–300
- Ashtari M, Avants B, Cyckowski L et al (2011) Medial temporal structures and memory functions in adolescents with heavy cannabis use. *J Psychiatr Res* 45:1055–1066
- Batalla A, Soriano-mas C, López-solà M et al (2013) Modulation of brain structure by catechol-O-methyltransferase Val158Met polymorphism in chronic cannabis users. *Addict Biol* 19:722–732
- Battistella G, Fornari E, Annoni J-M et al (2014) Long-term effects of cannabis on brain structure. *Neuropsychopharmacology* 39:2041–2048
- Benjamini Y, Yekutieli D (2001) The control of the false discovery rate in multiple testing under dependency. *Ann Stat* 29:1165–1188
- Bloomfield MAP, Morgan CJA, Egerton A et al (2014) Dopaminergic function in cannabis users and its relationship to cannabis-induced psychotic symptoms. *Biol Psychiatry* 75:470–478
- Boes AD, Bechara A, Tranel D et al (2009) Right ventromedial prefrontal cortex: a neuroanatomical correlate of impulse control in boys. *Soc Cogn Affect Neurosci* 4:1–9
- Bosson MG, van Berckel BN, Boellaard R et al (2009)  $\Delta^9$ -tetrahydrocannabinol induces dopamine release in the human striatum. *Neuropsychopharmacology* 34:759–766
- Broyd SJ, van Hell HH, Beale C et al (2016) Acute and chronic effects of cannabinoids on human cognition—a systematic review. *Biol Psychiatry* 79:557–567
- Budney AJ, Moore BA (2002) Development and consequences of cannabis dependence. *J Clin Pharmacol* 42:28S–33S
- Cardinal RN, Parkinson JA, Hall J, Everitt BJ (2002) Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. *Neurosci Biobehav Rev* 26:321–352
- Cheetham A, Allen NB, Whittle S et al (2011) Orbitofrontal volumes in early adolescence predict initiation of cannabis use: a 4-year longitudinal and prospective study. *Biol Psychiatry* 71:684–692
- Chen CY, O’Brien MS, Anthony JC (2005) Who becomes cannabis dependent soon after onset of use? Epidemiological evidence from the United States: 2000–2001. *Drug Alcohol Depend* 79:11–22
- Churchwell JC, Lopez-Larson M, Yurgelun-Todd DA (2010) Altered frontal cortical volume and decision making in adolescent cannabis users. *Front Psychol* 1:1–8
- Cousijn J, Wiers RW, Ridderinkhof KR et al (2012) Grey matter alterations associated with cannabis use: results of a VBM study in heavy cannabis users and healthy controls. *NeuroImage* 59:3845–3851
- Craft RM (2005) Sex differences in behavioral effects of cannabinoids. *Life Sci* 77:2471–2478
- Craft RM, Marusich JA, Wiley JL (2013) Sex differences in cannabinoid pharmacology: a reflection of differences in the endocannabinoid system? *Life Sci* 92:476–481
- Curran HV, Freeman TP, Mokrysz C et al (2016) Keep off the grass? Cannabis, cognition and addiction. *Nat Rev Neurosci* 17:293–306
- Degenhardt L, Chiu WT, Sampson N et al (2007) Epidemiological patterns of extra-medical drug use in the United States: evidence from the National Comorbidity Survey Replication, 2001–2003. *Drug Alcohol Depend* 90:210–223
- Downer E, Boland B, Fogarty M, Campbell V (2001) Delta 9-tetrahydrocannabinol induces the apoptotic pathway in cultured cortical neurons via activation of the CB1 receptor. *Neuroreport* 12:3973–3978
- Elkashaf A, Vocci F, Huestis M et al (2008) Marijuana neurobiology and treatment. *Subst Abus* 29:17–29
- Enzi B, Lissek S, Edel M-A et al (2015) Alterations of monetary reward and punishment processing in chronic cannabis users: an fMRI study. *PLoS One* 10:e0119150
- Ersche KD, Barnes A, Simon Jones P et al (2011) Abnormal structure of frontostriatal brain systems is associated with aspects of impulsivity and compulsivity in cocaine dependence. *Brain* 134:2013–2024
- Eskildsen S, Coupe P (2011) Effect of non-local means denoising on cortical segmentation accuracy with FACE. In: Organization for Human Brain Mapping 2011 Annual Meeting, Jun 2011, Canada
- Everitt BJ, Robbins TW (2013) From the ventral to the dorsal striatum: devolving views of their roles in drug addiction. *Neurosci Biobehav Rev* 37:1946–1954
- Everitt BJ, Robbins TW (2016) Drug addiction: updating actions to habits to compulsions ten years on. *Annu Rev Psychol* 67:150807174122003
- Everitt BJ, Dickinson A, Robbins TW (2001) The neuropsychological basis of addictive behaviour. *Brain Res Rev* 36:129–138
- Everitt BJ, Belin D, Economidou D et al (2008) Neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and addiction. *Philos Trans R Soc B Biol Sci* 363:3125–3135
- Fattore L, Fratta W (2010) How important are sex differences in cannabinoid action? *Br J Pharmacol* 160:544–548
- Fattore L, Spano MS, Altea S et al (2009) Cannabinoid self-administration in rats: sex differences and the influence of ovarian function. *Br J Pharmacol* 152:795–804
- Fellhauer I, Zöllner FG, Schröder J et al (2015) Comparison of automated brain segmentation using a brain phantom and patients with early Alzheimer’s dementia or mild cognitive impairment. *Psychiatry Res Neuroimaging* 233:299–305

- Filbey FM, Dunlop J (2014) Differential reward network functional connectivity in cannabis dependent and non-dependent users. *Drug Alcohol Depend* 140:101–111
- Filbey FM, Yezhuvath U (2013) Functional connectivity in inhibitory control networks and severity of cannabis use disorder. *Am J Drug Alcohol Abuse* 39:382–391
- Filbey FM, Schacht JP, Myers US et al (2009) Marijuana craving in the brain. *Proc Natl Acad Sci U S A* 106:13016–13021
- Filbey FM, Aslan S, Calhoun VD et al (2014) Long-term effects of marijuana use on the brain. *Proc Natl Acad Sci* 111:16913–16918
- Fineberg NA, Potenza MN, Chamberlain SR et al (2010) Probing compulsive and impulsive behaviors, from animal models to endophenotypes: a narrative review. *Neuropsychopharmacology* 35:591–604
- Fischl B, Salat DH, Busa E et al (2002) Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron* 33:341–355
- Free SL, Bergin PS, Fish DR et al (1995) Methods for normalization of hippocampal volumes measured with MR. *Am J Neuroradiol* 16:637–643
- Gaser C, Coupé P (2010) Impact of non-local means filtering on brain tissue segmentation. *Organ. Hum. Brain Mapp.* 2010 Annu. Meet. United States
- Gatzke-Kopp LM, Beauchaine TP, Shannon KE et al (2009) Neurological correlates of reward responding in adolescents with and without externalizing behavior disorders. *J Abnorm Psychol* 118:203–213
- van de Giessen E, Weinstein JJ, Cassidy CM et al (2016) Deficits in striatal dopamine release in cannabis dependence. *Mol Psychiatry* 22:1–8
- Gillan CM, Pappmeyer M, Morein-zamir S et al (2011) Disruption in the balance between goal-directed behavior and habit learning in obsessive-compulsive disorder. *Am J Psychiatry* 168:718–726
- Gilman JM, Kuster JK, Lee S et al (2014) Cannabis use is quantitatively associated with nucleus accumbens and amygdala abnormalities in young adult recreational users. *J Neurosci* 34:5529–5538
- Gossop M, Darke S, Griffiths P et al (1995) The severity of dependence scale (SDS): psychometric properties of the SDS in English and Australian samples of heroin, cocaine and amphetamine users. *Addiction* 90:607–614
- Gremel CM, Costa RM (2013) Orbitofrontal and striatal circuits dynamically encode the shift between goal-directed and habitual actions. *Nat Commun* 4:2264
- Haber SN (2016) Corticostriatal circuitry. *Dialogues Clin Neurosci* 18:7–21
- Haber SN, Kunishio K, Mizobuchi M, Lynd-Balta E (1995) The orbital and medial prefrontal circuit through the primate basal ganglia. *J Neurosci* 15:4851–4867
- Hasin DS, O'Brien CP, Auriacombe M et al (2013) DSM-5 criteria for substance use disorders: recommendations and rationale. *Am J Psychiatry* 170:834–851
- Hayashi T, Ko JH, Strafella AP, Dagher A (2013) Dorsolateral prefrontal and orbitofrontal cortex interactions during self-control of cigarette craving. *Proc Natl Acad Sci U S A* 110:4422–4427
- Hernandez-Avila CA, Rounsaville BJ, Kranzler HR (2004) Opioid-, cannabis- and alcohol-dependent women show more rapid progression to substance abuse treatment. *Drug Alcohol Depend* 74:265–272
- Houck JM, Bryan AD, Feldstein Ewing SW (2013) Functional connectivity and cannabis use in high-risk adolescents. *Am J Drug Alcohol Abuse* 39:414–423
- Huestis MA (2007) Human cannabinoid pharmacokinetics. *Chem Biodivers* 4:1770–1804
- Ito R, Dalley JW, Robbins TW, Everitt BJ (2002) Dopamine release in the dorsal striatum during cocaine-seeking behavior under the control of a drug-associated cue. *J Neurosci* 22:6247–6253
- Jager G, Block RI, Luijten M, Ramsey NF (2012) Tentative evidence for striatal hyperactivity in adolescent cannabis-using boys: a cross-sectional multicenter fMRI study. *J Psychoactive Drugs* 45:156–167
- Kable JW, Glimcher PW (2007) The neural correlates of subjective value during intertemporal choice. *Nat Neurosci* 10:1625–1633
- Kringelbach ML, Rolls ET (2004) The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. *Prog Neurobiol* 72:341–372
- Kühn S, Schubert F, Gallinat J (2010) Reduced thickness of medial orbitofrontal cortex in smokers. *Biol Psychiatry* 68:1061–1065
- Leclercubier Y, Sheehan DV, Weiller E et al (1997) The MINI International neuropsychiatric interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. *Eur Psychiatry* 12:224–231
- Li Y, Yuan K, Cai C et al (2015) Reduced frontal cortical thickness and increased caudate volume within fronto-striatal circuits in young adult smokers. *Drug Alcohol Depend* 151:211–219
- Lorenzetti V, Solowij N, Fomito A et al (2012) P.I.B.003 the impact of regular cannabis use on human brain structure. *Eur Neuropsychopharmacol* 22:S164–S165
- Lorenzetti V, Solowij N, Fomito A et al (2014) The association between regular cannabis exposure and alterations of human brain morphology: an updated review of the literature. *Curr Pharm Des* 20:2138–2167
- Lorenzetti V, Solowij N, Whittle S et al (2015) Gross morphological brain changes with chronic, heavy cannabis use. *Br J Psychiatry* 206:77–78
- Lorenzetti V, Cousijn J, Solowij N et al (2016) The neurobiology of cannabis use disorder: a call for evidence. *Front Behav Neurosci* 10:1–3
- Ma N, Liu Y, Fu XM et al (2011) Abnormal brain default-mode network functional connectivity in drug addicts. *PLoS ONE* 6:e16560
- Manjón JV, Coupé P, Buades A et al (2012) New methods for MRI denoising based on sparseness and self-similarity. *Med Image Anal* 16:18–27
- Martin G, Copeland J, Gates P, Gilmour S (2006) The severity of dependence scale (SDS) in an adolescent population of cannabis users: reliability, validity and diagnostic cut-off. *Drug Alcohol Depend* 83:90–93
- Martinez D, Slifstein M, Broft A et al (2003) Imaging human mesolimbic dopamine transmission with positron emission tomography. Part II: amphetamine-induced dopamine release in the functional subdivisions of the striatum. *J Cereb Blood Flow Metab* 23:285–300
- Mashhoon Y, Sava S, Sneider JT et al (2015) Cortical thinness and volume differences associated with marijuana abuse in emerging adults. *Drug Alcohol Depend* 155:275–283
- Matsuo K, Nicoletti M, Nemoto K et al (2009) A voxel-based morphometry study of frontal gray matter correlates of impulsivity. *Hum Brain Mapp* 30:1188–1195
- Mcqueeny T, Padula CB, Price J et al (2011) Gender effects on amygdala morphometry in adolescent marijuana users. *Behav Brain Res* 224:128–134
- Medina KL, Schweinsburg AD, Cohen-Zion M et al (2007) Effects of alcohol and combined marijuana and alcohol use during adolescence on hippocampal volume and asymmetry. *Neurotoxicol Teratol* 29:141–152
- Moore TJ (2007) Monograph no. 14: working estimates of the social costs per gram and per user for cannabis, cocaine, opiates and amphetamines. National Drug and Alcohol Research Centre, Sydney
- Morales AM, Lee B, Hellemann G et al (2012) Gray-matter volume in methamphetamine dependence: cigarette smoking and changes with abstinence from methamphetamine. *Drug Alcohol Depend* 125:230–238
- Narr KL, Woods RP, Thompson PM et al (2007) Relationships between IQ and regional cortical gray matter thickness in healthy adults. *Cereb Cortex* 17:2163–2171



- Narum SR (2006) Beyond Bonferroni: less conservative analyses for conservation genetics. *Conserv Genet* 7:783–787
- Nelson HE (1982) National adult reading test. NFER-Nelson, Windsor
- Ng Cheong Ton JM, Gerhardt GA, Friedemann M et al (1988) The effects of delta 9-tetrahydrocannabinol on potassium-evoked release of dopamine in the rat caudate nucleus: an in vivo electrochemical and in vivo microdialysis study. *Brain Res* 451:59–68
- Peters J, Buchel C (2009) Overlapping and distinct neural systems code for subjective value during intertemporal and risky decision making. *J Neurosci* 29:15727–15734
- Rajkowska G (2000) Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. *Biol Psychiatry* 48:766–777
- Rajkowska G, Miguel-Hidalgo JJ, Wei J et al (1999) Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. *Biol Psychiatry* 45:1085–1098
- Redish AD, Jensen S, Johnson A (2008) A unified framework for addiction: vulnerabilities in the decision process. *Behav Brain Sci* 31:415–437 **487**
- Reuter M, Rosas HD, Fischl B (2010) Highly accurate inverse consistent registration: a robust approach. *NeuroImage* 53:1181–1196
- Ruge H, Wolfensteller U (2016) Distinct contributions of lateral orbitofrontal cortex, striatum, and fronto-parietal network regions for rule encoding and control of memory-based implementation during instructed reversal learning. *NeuroImage* 125:1–12
- Scherk H, Falkai P (2006) Effects of antipsychotics on brain structure. *Curr Opin Psychiatry* 19:145–150
- Schmand B, Bakker D, Saan R, Louman J (1991) The Dutch reading test for adults: a measure of premorbid intelligence level. *Tijdschr Gerontol Geriatr* 22:15–19
- Schoenbaum G, Roesch MR, Stalnaker TA (2006) Orbitofrontal cortex, decision-making and drug addiction. *Trends Neurosci* 29:116–124
- Ségonne F, Dale AM, Busa E et al (2004) A hybrid approach to the skull stripping problem in MRI. *NeuroImage* 22:1060–1075
- Sheehan DV, Lecrubier Y, Sheehan KH et al (1997) The validity of the MINI International neuropsychiatric interview (MINI) according to the SCID-P and its reliability. *Eur Psychiatry* 12:232–241
- Sled JG, Zijdenbos AP, Evans AC (1998) A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imaging* 17:87–97
- Smith MJ, Cobia DJ, Wang L et al (2014) Cannabis-related working memory deficits and associated subcortical morphological differences in healthy individuals and schizophrenia subjects. *Schizophr Bull* 40:287–299
- Solowij N, Walterfang M, Lubman DI et al (2013) Alteration to hippocampal shape in cannabis users with and without schizophrenia. *Schizophr Res* 143:179–184
- Spinella M (2002) Correlations between orbitofrontal dysfunction and tobacco smoking. *Addict Biol* 7:381–384
- Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality (2014) Treatment episode data set (TEDS): 2002–2012. National admissions to substance abuse treatment services. BHSIS Series S-71, HHS Publication No. (SMA) 14–4850., Rockville, MD
- Sullivan EV, Deshmukh A, De Rosa E et al (2005) Striatal and forebrain nuclei volumes: contribution to motor function and working memory deficits in alcoholism. *Biol Psychiatry* 57:768–776
- Swift W, Copeland J, Hall W (1998) Choosing a diagnostic cut-off for cannabis dependence. *Addiction* 93:1681–1692
- Tanaka SC, Balleine BW, O'Doherty JP (2008) Calculating consequences: brain systems that encode the causal effects of actions. *J Neurosci* 28:6750–6755
- Tremblay L, Schultz W (1999) Relative reward preference in primate orbitofrontal cortex. *Nature* 398:704–708
- Tseng AH, Craft RM (2001) Sex differences in antinociceptive and motoric effects of cannabinoids. *Eur J Pharmacol* 430:41–47
- Turner JA (2014) The rise of large-scale imaging studies in psychiatry. *Gigascience* 3:29
- Tzilos GK, Cintron CB, Wood JBR et al (2005) Lack of hippocampal volume change in long-term heavy cannabis users. *Am J Addict* 14:64–72
- United Nations Office on Drugs and Crime (2014) World drug report 2014. United Nations publication, Sales No. E.14.XI.7
- United Nations Office on Drugs and Crime (2015) World drug report 2015. United Nations publication, Sales No. E.15.XI.6
- van der Pol P, Liebrechts N, de Graaf R et al (2013) Reliability and validity of the severity of dependence scale for detecting cannabis dependence in frequent cannabis users. *Int J Methods Psychiatr Res* 22:138–143
- Volkow ND, Fowler JS (2000) Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. *Cereb Cortex* 10:318–325
- Volkow ND, Fowler JS, Wang G-J, Goldstein RZ (2002) Role of dopamine, the frontal cortex and memory circuits in drug addiction: insight from imaging studies. *Neurobiol Learn Mem* 78:610–624
- Volkow ND, Baler RD, Compton WM, Weiss SRB (2014a) Adverse health effects of marijuana use. *N Engl J Med* 370:2219–2227
- Volkow ND, Wang G-J, Telang F et al (2014b) Decreased dopamine brain reactivity in marijuana abusers is associated with negative emotionality and addiction severity. *Proc Natl Acad Sci* 111:E3149–E3156
- Volkow ND, Swanson JM, Evins AE et al (2016) Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: a review. *JAMA psychiatry* 73:292–297
- Vollstädt-Klein S, Wichert S, Rabinstein J et al (2010) Initial, habitual and compulsive alcohol use is characterized by a shift of cue processing from ventral to dorsal striatum. *Addiction* 105:1741–1749
- Voon V, Derbyshire K, Rück C et al (2015) Disorders of compulsivity: a common bias towards learning habits. *Mol Psychiatry* 20:345–352
- Voruganti LNP, Slomka P, Zabel P et al (2001) Cannabis induced dopamine release: an in-vivo SPECT study. *Psychiatry Res - Neuroimaging* 107:173–177
- Wechsler D (1997) WAIS-III administration and scoring manual. The Psychological Corporation, San Antonio
- Wechsler D (1999) Wechsler abbreviated scale of intelligence (WASI) manual. Psychological Corporation, San Antonio
- Weiland XBJ, Thayer RE, Depue XBE, et al (2015) Daily marijuana use is not associated with brain morphometric measures in adolescents or adults. *J Neurosci* 35:1505–1512
- Wetherill RR, Jagannathan K, Hager N et al (2015) Cannabis, cigarettes, and their co-occurring use: disentangling differences in gray matter volume. *Int J Neuropsychopharmacol* 18:1–8
- Woodward ND, Zald DH, Ding Z et al (2009) Cerebral morphology and dopamine D2/D3 receptor distribution in humans: a combined [18F]fallypride and voxel-based morphometry study. *NeuroImage* 46:31–38
- Yip SW, DeVito EE, Kober H et al (2014) Pretreatment measures of brain structure and reward-processing brain function in cannabis dependence: an exploratory study of relationships with abstinence during behavioral treatment. *Drug Alcohol Depend* 140:33–41
- Yücel M, Solowij N, Respondek C et al (2008) Regional brain abnormalities associated with long-term heavy cannabis use. *Arch Gen Psychiatry* 65:694–701
- Yücel M, Lorenzetti V, Suo C et al (2016) Hippocampal harms, protection and recovery following regular cannabis use. *Transl Psychiatry* 6:e710
- Zheng W, Chee MWL, Zagorodnov V (2009) NeuroImage improvement of brain segmentation accuracy by optimizing non-uniformity correction using N3. *NeuroImage* 48:73–83