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Functional Connectivity in Brain Networks Underlying Cognitive Control in Chronic Cannabis Users

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The long-term effect of regular cannabis use on brain function underlying cognitive control remains equivocal. Cognitive-control abilities are thought to have a major role in everyday functioning, and their dysfunction has been implicated in the maintenance of maladaptive drug-taking patterns. In this study, the Multi-Source Interference Task was employed alongside functional magnetic resonance imaging and psychophysiological interaction methods to investigate functional interactions between brain regions underlying cognitive control. Current cannabis users with a history of greater than 10 years of daily or near-daily cannabis smoking ($n = 21$) were compared with age, gender, and IQ-matched non-using controls ($n = 21$). No differences in behavioral performance or magnitude of task-related brain activations were evident between the groups. However, greater connectivity between the prefrontal cortex and the occipitoparietal cortex was evident in cannabis users, as compared with controls, as cognitive-control demands increased. The magnitude of this connectivity was positively associated with age of onset and lifetime exposure to cannabis. These findings suggest that brain regions responsible for coordinating behavioral control have an increased influence on the direction and switching of attention in cannabis users, and that these changes may have a compensatory role in mitigating cannabis-related impairments in cognitive control or perceptual processes.

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Uncorrected Proof

INTRODUCTION

Little is yet known of the long-term consequences of cannabis use on brain function underlying cognitive-control abilities. Cognitive-control processes promote adaptive and dynamic goal-directed behavior by biasing perceptual and information processing within the brain in favor of stimuli and responses relevant to current goals (Botvinick *et al*, 2001; Ridderinkhof *et al*, 2004). These processes include the ability to focus and shift attention, to inhibit inappropriate behavioral responses, and to monitor and change one's behavior in response to ongoing environmental feedback (MacDonald *et al*, 2000; Ridderinkhof *et al*, 2004; Suchy, 2009). Cognitive-control processes support healthy social

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functioning, educational achievement, vocational performance, and activities of daily living (Cahn-Weiner *et al*, 2007; Henry *et al*, 2009; Suchy, 2009; Williams *et al*, 2009). Their impairment, on the other hand, has been linked to the initiation and maintenance of addictive behavior by compromising the effective inhibition of drug-seeking behavior (Fillmore, 2003; Koob and Volkow, 2010; Lubman *et al*, 2004). Elucidating the impact of cannabis use on cognitive control and underlying brain function is therefore relevant to developing appropriate interventions for those with cannabis-use disorders and for further understanding the biological mechanisms governing substance use and abuse.

Available evidence regarding the existence and behavioral significance of cognitive-control impairments, and associated abnormalities in underlying neural correlates, remains equivocal in cannabis-using populations. Neuropsychological studies employing tasks of cognitive-interference resolution, selective attention, and inhibitory control have reported relatively normal or minimally impaired performance in chronic cannabis users assessed in the non-intoxicated state (Fernandez-Serrano *et al*, 2010; Lyons *et al*, 2004; Pope *et al*,

2001; Solowij *et al*, 2002; Takagi *et al*, 2010; Verdejo-Garcia *et al*, 2005). Recent neuroimaging investigations, however, have described functional disruptions within the brain during the performance of cognitive-control tasks, both concurrent with (Abdullaev *et al*, 2010; Battisti *et al*, 2010), and in the absence of behavioral deficits (Eldreth *et al*, 2004; Hester *et al*, 2009; Tapert *et al*, 2007) in similar samples of chronic users. These aberrations have largely been reported within brain regions comprising the cognitive-control network (Cabeza and Nyberg, 2000; Nee *et al*, 2007), including the anterior cingulate, lateral prefrontal, and lateral posterior parietal cortices. However, considerable variability in the laterality, anatomical loci, and even valence (ie, hyper- *vs* hypo-activation) of reported functional abnormalities exists between studies. Impairments may therefore best be described as subtle, targeted to select cognitive domains, and/or dependent on the exact cohort under study.

In the investigation of cannabis-related effects on brain function underlying cognitive control, the current study conferred several advantages to previous research. First, the investigation of non-treatment seeking adults with a long-term and heavy exposure to cannabis, alongside minimal exposure to other drugs and no comorbid mental health issues, increased sensitivity to the biological correlates of cannabis use. Second, by employing the Multi-Source Interference Task (MSIT; Bush and Shin, 2006), multiple domains of cognitive control, including interference resolution and selective attention, were simultaneously taxed, increasing the opportunity to identify subtle and/or specific disruptions. Finally, in addition to investigating the magnitude of task-induced brain activations, the integrity of functional inter-relationships between brain regions mediating cognitive control was also examined. Increased cognitive-control demands have been linked with dynamic increases in functional connectivity between regions forming the cognitive-control network (Egner and Hirsch, 2005a, b; Fan *et al*, 2008; Wang *et al*, 2010), whereas both abnormal increases and decreases in this connectivity have been linked to behavioral impairments in a variety of clinical disorders (eg, Konrad and Eickhoff, 2010; Pettersson-Yeo *et al*, 2011; Rowe, 2010). Investigating the impact of cannabis on both activation and connectivity is particularly compelling, given the high density of endocannabinoid receptors located throughout the cognitive-control network (Eggan and Lewis, 2007) and the well-documented role these receptors have in the modulation of synaptic efficacy (Chevaleyre *et al*, 2006; Kano *et al*, 2009). In one such study, Jacobsen *et al* (2007) identified reduced connectivity between the left inferior parietal cortex and the anterior cingulate, lateral prefrontal, and insular cortices, during performance of a verbal working memory task in abstinent adolescent cannabis users. However, to our knowledge, studies of functional connectivity underlying cognitive control have yet to be undertaken.

On the basis of the existing literature examining cognitive-control deficits in cannabis users discussed above, we did not predict impaired behavioral performance on the MSIT paradigm in this population. However, abnormal functional activations throughout the cognitive-control network, including the anterior cingulate, lateral prefrontal, anterior insular (aIns), and posterior parietal cortices were predicted. Moreover, abnormal connectivity within this network, as well as between these regions and additional task-relevant brain areas, including the extrastriate cortices, cerebellum, and basal ganglia, were also hypothesized. Two-sided hypotheses were adopted, as the expectation of directionality cannot be adequately justified at present, given the variability between existing reports of functional impairments in similar tasks and cohorts, a current lack of comparable connectivity-based research, and evidence supporting both increased and decreased activation/connectivity underlying cognitive-control deficits in psychiatric and neurological disorders. However, an earlier age of onset and heavier lifetime cannabis use were hypothesized to positively correlate with greater abnormalities in functional activations and connectivity.

MATERIALS AND METHODS

Participants

Current cannabis users who had smoked on a daily or near-daily basis for no less than 10 years ($n = 21$), and age, gender, and full-scale, IQ-matched non-users, who were naive or had minimal lifetime exposure to cannabis ($n = 21$; Table 1) were recruited from the general community. Substance-use history was assessed by a structured interview that incorporated the Alcohol Use Disorders Identification Test (Allen *et al*, 1997) and a Time-Line Follow-Back procedure (Maisto *et al*, 1982). All cannabis users were abstained for no less than 12 h before testing, based on self-report, and corroborated by analysis of urine and saliva samples (Table 1), minimizing the prevalence of acute subjective and cognitive effects of intoxication (Curran *et al*, 2002; Fant *et al*, 1998; Ramaekers *et al*, 2009). Urinalysis also served to rule out other concurrent recreational drug use. Additionally, all cannabis users endorsed only mild, if any, symptoms of withdrawal as measured using the Marijuana Withdrawal Checklist (Budney *et al*, 1999). The groups were matched for current average monthly alcohol use, but cannabis-using participants smoked a greater number of daily tobacco cigarettes. The median number of cumulative lifetime episodes of other illicit drug use ranged from 0 to 6.5 for each of amphetamines, benzodiazepines, cocaine, ecstasy, hallucinogens, inhalants, and opiates, and no participant reported regular consumption (> 1 use/month for any period of time) of any substance other than cannabis within the past 2 years. The age of onset of regular cannabis use, total estimated joints consumed over the lifetime, and concentrations of urinary and salivary cannabinoids at the time of testing were the primary substance-use measures examined in relation to performance and imaging measures.

All participants were right-handed, had normal or corrected-to-normal visual acuity, and were screened for past and present psychiatric or neurological illness, substance dependence (excepting cannabis dependence in the cannabis group), current use of psychotropic medication, or history of significant head injury, by structured interview including the Structured Clinical Interview for DSM-IV Axis I Disorders. This study was approved by the local Human Research and Ethics Board, and all participants provided written, informed consent before participation.

Table 1 Demographic and Substance Use Measures

	Controls (*n* = 21)	Cannabis (*n* = 21)	*p*-value
Demographics, mean (SD)			
Age (years)	31.0 (11.7)	36.5 (8.8)	0.10
Gender (M/F)	11/10	10/11	0.76
WASI FSIQ	111.8 (9.7)	106.7 (10.9)	0.12
Substance use, median (range)			
Lifetime cumulative dose (number of joints)	2 (0–60)	26 711 (4512–79 200)	
Age of onset, regular use (years)	n/a	16 (12–25)	
Duration of regular use (years)	0	20 (10–38)	
Urinary carboxy-THC:creatinine ratio (ng/mg)	0	410 (0–2568)	
Salivary delta-9-THC (ng/ml)	0	1.7 (0–11)	
Withdrawal (MWCL score)	0	3 (0–17)	
Severity of dependence (SDS score)	0	5 (0–14)	
Tobacco cigarettes (no. per day)	0 (0–15)	5 (0–30)	< 0.001
Alcohol consumption (drinks per month)	10.5 (0–100)	5.25 (0–55)	0.41

Abbreviations: MWCL, Marijuana Withdrawal Checklist; THC, tetrahydrocannabinol; WASI, Wechsler-Abbreviated Scale of Intelligence.

Experimental Design

The MSIT, a well-validated paradigm that provides for robust assay of cognitive-control performance and associated-neural correlates (Bush and Shin, 2006), was utilized. In brief, participants were visually presented with stimuli consisting of three numbers, or triplets, aligned horizontally. The value of each number ranged from 0 to 3, with one number always unique (the 'target') to the other two (the 'distracters'; Figures 1a and b). Participants were instructed to identify the value of the target number by pressing one of three available buttons on an MR-compatible response box, using the first three fingers of the right (dominant) hand. Two active conditions were created by manipulating the composition of the triplets: during congruent trials (Figure 1a), the target number was always spatially aligned with the position of the correct button response (ie, a target of '1' would be presented as the left-most number) and was accompanied by two zeros (which do not represent a response alternative); during incongruent trials (Figure 1b), the target digit was always spatially misaligned and accompanied by distracters that represented an alternative response possibility. Each triplet was presented for 2000 ms with an inter-stimulus interval of 500 ms. Both reaction time (RT) and accuracy were emphasized and recorded.

Correct and efficient responses to incongruent trials relative to congruent trials thus relied on: (i) selective attention mechanisms to filter irrelevant information; (ii) inhibition of prepotent responses to salient, yet incorrect response alternatives; (iii) resolution of response-based conflict created by spatial stimulus–response incongruence (ie, 'Simon' interference; Simon and Berbaum, 1990); and (iv) resolution of stimulus-based conflict created by distracter stimuli (ie, 'Flanker' interference; Eriksen and Eriksen, 1974).

The experiment followed an A-R-B-R block design (Figure 1c), where A and B represent active task conditions presented in 30-s blocks, separated by 15-s resting periods (R), during which a fixation cross was displayed. Four
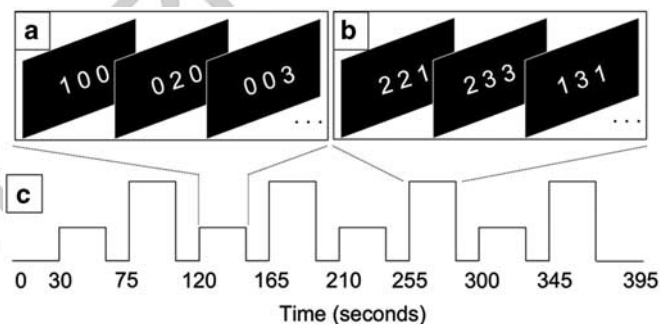

Figure 1 The Multi-Source Interference Task. Examples of congruent (a) and incongruent (b) stimuli, with the correct response '1', '2', and '3' corresponding to the left, middle, and right panels, respectively. The experimental time course (c) depicts the alternating block design with interleaved passive rest periods between each task-active block.

blocks of each condition, containing 12 stimuli each, were presented across a single 6.5-min run. A short practice run consisting of one congruent and one incongruent block preceded scanning. Stimuli were generated and responses recorded using Presentation software (version 14.4, http://nbs.neuro-bs.com/nbs_online). Stimuli were back-projected onto a semi-transparent display at the foot of the scanner bed and viewed through a head-coil mounted mirror.

Image Acquisition

All images were obtained on a 3T Siemens Trio scanner equipped with a 32-channel head coil at the Murdoch Childrens Research Institute, Melbourne, VIC, Australia. Functional data consisted of 157 whole-brain gradient-echo echo-planar images consisting of 36 interleaved, contiguous axial slices (TR = 2400 ms; TE = 40 ms; flip angle = 90°; thickness = 3.0 mm; in-plane resolution = 3.3 mm^2; FOV = 210 mm^2). Three additional whole-brain volumes were

acquired before this functional acquisition to allow magnetization to reach a steady state. High-resolution T1-weighted MPRAGE structural images were acquired for subsequent co-registration (176 sagittal slices; 1.0 mm^3 isotropic voxels; TR = 1900 ms; TE = 2.15 ms; FOV = 256 mm).

Behavioral Data Analysis

Mean RT data from all correct responses were entered into a 2×2 mixed-design ANCOVA, treating task condition (congruent *vs* incongruent) as the within-subject factor, and group (cannabis user *vs* control) as the between-subject factor. Although the groups were matched for age and alcohol consumption, both were added to the model as covariates to control additional residual variance.

To measure the impact of tobacco use, which differed significantly between groups (regular smokers: 1 of 21 controls *vs* 16 of 21 cannabis users), the cannabis group was divided categorically into low ($n = 11$, mean (SD) = 1.6 (2.0) cigarettes per day) and high ($n = 10$, 13.7 (6.6) cigarettes per day) tobacco users. There were no demographic or drug-use differences between these subgroups. The potential effects of past polydrug abuse were similarly assessed by dividing the cannabis group into those with ($n = 10$) and without ($n = 11$) past abuse of alternate illicit substance(s), defined as >1 use/month for any period of time. These subgroups did not differ on demographic or cannabis use metrics, with the exception of a greater concentration of urinary cannabinoid metabolites observed in those with a history of polydrug abuse ($t_{6.7} = 2.43$, $p = 0.047$). However, this latter effect did not survive correction for multiple comparisons and appeared to be driven by one outlier subject. Differences in the condition effect between these categorically defined subgroups and the control cohort were assessed using one-way ANOVAs.

Multiple regression models were additionally employed in the cannabis group to assess relationships between behavioral performance and (i) lifetime cannabis use indices, including cumulative cannabis exposure and age of onset of regular cannabis use; (ii) recent cannabis use indices, including salivary and urine cannabinoid concentrations (assessed in separate models due to correlation); and (iii) acute withdrawal symptoms, as assessed by the Marijuana Withdrawal Checklist. All analyses were undertaken using SPSS (version 18.0).

Although the group-by-condition interaction effect was of primary interest, the main condition effect, collapsed across groups, was also assessed to ensure a significant behavioral effect was elicited by the task. Mean error rates across both conditions (and their log-transformed equivalents) failed to meet assumptions of normality as expected, because of ceiling effects, and were therefore analyzed using equivalent non-parametric methods (Wilcoxon signed rank, Mann–Whitney *U*, and Kruskal–Wallis tests).

Functional Magnetic Resonance Imaging (fMRI) Regional Analysis

All functional analysis was performed using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/). For each subject, the functional images were first spatially aligned to the first volume of the run using a six-parameter rigid-body transformation to correct for head movement. The anatomical scans across all participants were then used to create a study-unique group template using a diffeomorphic registration algorithm designed to improve between-subject registration (DARTEL; Ashburner, 2007). This intermediate group template was normalized to MNI space, and subsequent transformation parameters from both steps, estimated individually for each subject, applied to the motion-corrected, coregistered functional data. Voxel sizes were resampled to 2 mm^3 during normalization, and images spatially smoothed using a Gaussian kernel of 8 mm at FWHM.

The congruent and incongruent task periods were coded as individual regressors within a general linear model (GLM) by first specifying the onset and duration of each task epoch, followed by convolution of the model with a canonical hemodynamic response function to form a model of the predicted task-related BOLD response. A 128 s high-pass filter was applied to remove low-frequency noise, whereas temporal autocorrelations were estimated using a first-order autoregressive model. Resulting regression parameter estimates from each individual were used as summary statistics for group-level random-effects analysis entirely analogous to the 'Behavioral Data Analysis' described above.

Functional masks for between-group analyses were formed using the global conjunction of the whole-brain-positive effect of condition (incongruent > congruent) from each group, thresholded at $p < 0.05$ uncorrected. The use of global conjunctions and liberal thresholds ensured inclusion of all task-relevant regions across both groups. Voxelwise statistical parametric maps (SPMs; ie, T-statistic maps) inclusively restricted to these regions were then calculated for group-by-condition interactions and cannabis-use regressions using a voxelwise significance threshold of $p < 0.001$ uncorrected, with a 10-voxel minimum cluster extent (K_E).

fMRI Connectivity Analysis

Group differences in task-relevant functional connectivity were analyzed by assessing psychophysiological interactions (PPIs). A PPI indexes task-induced changes in the strength of connectivity between two brain regions, as measured by a change in the magnitude of the linear regression slope between their underlying activities. Significant PPIs indicate dynamic neuromodulation in response to contextual demands, and identify functional interactions that are relevant to the current task demands (Friston *et al*, 1997). Connectivity between each of the seven regions of interest, located in the lateral prefrontal, aIns, and posterior parietal cortices bilaterally, as well as the midline dorsal anterior cingulate cortex (dACC), and all other task-relevant brain regions were assessed for between-group differences. Spheres having a 3-mm radius were defined around the maximum positive main effect of condition for each subject within each region of interest, from which the average time series (first eigenvariate) of activity was extracted. At the individual level, three regressors were created in a GLM representing the deconvolved time course of activity in the seed region (the physiological factor), the task model (the psychological factor), and their cross-product (the PPI), respectively. The voxelwise regression estimates from the interaction term acted as summary statistics that were subsequently entered into one-way ANCOVAs, controlling for potential confounds as described

above. Voxelwise SPMs restricted to task-relevant regions (using inclusive masks, as described above; threshold-$p < 0.001$, $K_E \geqslant 10$) were used to explore group differences in connectivity and associations between cannabis-use measures and connectivity.

RESULTS

Behavior

Analysis of RTs revealed a significant main effect of condition ($F_{1,38} = 21.88$, $p < 0.001$), but a nonsignificant group-by-condition interaction ($F_{1,38} = 2.47$, $p = 0.12$), although covarying for alcohol consumption and current age. No group differences due to history of other illicit drug abuse ($F_{2,37} = 1.22$, $p = 0.31$) or tobacco smoking ($F_{2,37} = 1.23$, $p = 0.31$) were in evidence.

Similar results were found for error rate (main effect of condition: Wilcoxon signed rank test, $Z = -4.34$, $p < 0.001$; group-by-condition interaction: Mann–Whitney U-test, $Z = -1.72$, $p = 0.085$). Although covariates could not be directly included in the models, Spearman correlations between each of alcohol consumption and current age indicated nonsignificant relationships with the condition effect ($p > 0.27$). History of alternate illicit drug abuse (Kruskal–Wallis, $\chi^2 = 3.69$, $p = 0.16$) and tobacco use ($\chi^2 = 3.27$, $p = 0.20$) was also not predictive of error rate.

Taken together, the task was observed to elicited robust behavioral effects with no significant performance differences apparent between groups. See Table 2 for behavioral results.

Evaluation of relationships between lifetime cannabis-use measures and RTs (incongruent–congruent) also failed to support correlations with either of lifetime cannabis dose ($t_{17} = -0.53$, $p = 0.61$) or age of regular cannabis-use onset ($t_{17} = 0.72$, $p = 0.61$). Additionally, neither salivary ($t_{18} = 0.21$, $p = 0.83$) nor urinary ($t_{15} = 0.50$, $p = 0.63$) cannabinoid measures, indexing recent cannabis use, or self-reported symptoms of withdrawal ($t_{19} = -1.59$, $p = 0.13$) were predictive of task effect in the cannabis group.

fMRI: Regional

Significant main effects of condition (collapsed across groups) in *a priori* regions of interest were observed at statistical thresholds corrected for whole-brain analysis (FWE$_{corrected}$, $p < 0.05$) in the dACC, bilateral insula, bilateral superior and inferior parietal lobules, and left lateral prefrontal cortex (PFC). Within the right lateral PFC, significant FWE-corrected activation was also observed within a constrained region-of-interest contralateral to the left-sided, whole-brain-corrected activation (Figure 2, Table 3). Additional task-related activations were also in evidence in the bilateral extrastriate cortex and cerebellum.

Group-by-condition interactions within task-relevant cortical regions did not distinguish significant group differences in the magnitude of functional activations in any region, with or without controlling for the influence of alcohol consumption, tobacco use, history of other illicit drug abuse, RT, or current age. Lifetime cannabis use and age of regular cannabis-use onset were also not associated with task-related activity in the brain. However, greater

Table 2 Group Mean Reaction Time and Median Accuracy Measures

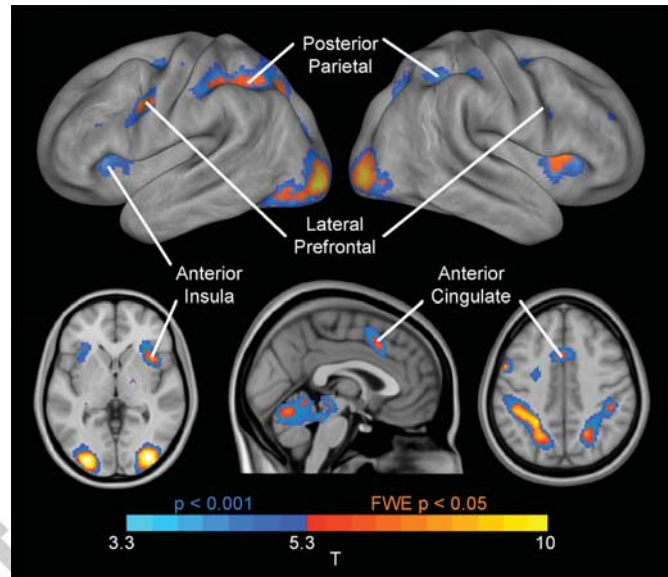|	Controls ($n = 21$)	Cannabis ($n = 21$)
Congruent RT, ms (SD)	650.5 (121.5)	690.2 (193.1)
Incongruent RT, ms (SD)	969.3 (132.3)	1063.0 (194.2)
Congruent accuracy, % (range)	100 (95.8–100)	100 (97.9–100)
Incongruent accuracy, % (range)	97.9 (91.7–100)	95.8 (89.6–100)

Figure 2 Main positive effect of condition. Warm colors indicate activations that meet the threshold for voxelwise familywise error (FWE) correction at a threshold of $p < 0.05$, whereas cool colors represent additional activations at an uncorrected threshold of $p < 0.001$. Labels highlight each of the seven regions –of interest used in subsequent inference.

indices of recent cannabis use were predictive of increased activations within small areas of the left lateral PFC (salivary delta-9-THC: $x = -56$, $y = 0$, $z = 32$, $T_{max} = 4.13$, $K_E = 31$; urinary carboxy-THC: $x = -58$, $y = 18$, $z = 22$, $T_{max} = 4.23$, $K_E = 16$).

fMRI: Connectivity

As presented in Figure 3 and Table 4, cognitive-control demands were associated with stronger PPIs (ie, connectivity) in the cannabis group, as compared with controls, between each of the (i) dACC, (ii) left PFC, (iii) left aIns, and (iv) right aIns seed regions, and the left occipitoparietal cortex (OP) located at the junction of the intraparietal sulcus and dorsal extrastriate cortex (Figures 3a and b). A between-group difference was also evident between the right lateral prefrontal seed region and the same area of the left OP at a slightly reduced statistical threshold ($p < 0.002$). Further, cannabis users also demonstrated relatively increased connectivity between the anterior cingulate seed region and the right dorsal extrastriate cortex. These group differences remained significant after accounting for alcohol

Table 3 Positive Main Effect of Condition

Region (BA)		K_E	Coordinates			T_{max}
			x	y	z	
Voxel-wise FWE-corrected p < 0.05 for whole-brain search space						
Extrastriate cortex (18/19)	L	964	−30	−92	−4	10.88
Extrastriate cortex (18/19)	R	784	32	−86	−4	10.55
Superior parietal lobule (7)	L	1284	−26	−48	42	8.55
Inferior parietal lobule (40)			−34	−42	40	8.41
Inferior frontal junction (6/9)	L	200	−56	6	38	8.19
Anterior insula (13)	R	212	34	20	4	7.57
Cerebellum, anterior lobe	L	239	−28	−54	−26	7.49
Cerebellum, anterior lobe	R	736	32	−56	−28	7.18
Inferior parietal lobule (40)	R	78	44	−36	44	6.67
Superior parietal lobule (7)	R	170	22	−60	42	6.5
Anterior cingulate cortex (32)	—	104	−2	14	42	6.49
Caudate tail	L	3	−16	−20	20	5.93
Insula (13)	L	19	−32	24	0	5.9
Dorsal premotor cortex (6)	L	12	−24	−4	54	5.62
Caudate tail	R	4	24	−36	14	5.51
Small volume correction in right lateral prefrontal cortex[a]						
Inferior frontal junction	R	147	42	6	26	5.06[b]

[a]Sphere of 16-mm radius centered at 56, 6, 38, corresponding to contralateral activity.
[b]Significant at FWE-corrected $p < 0.05$ within the search space, and $p = 0.10$ for whole-brain.

and tobacco use, current age, behavioral performance, and history of polydrug use. As depicted in Figure 3c, *post-hoc* exploration indicated significant positive condition effects (ie, increased connectivity alongside increased cognitive-control demand) in the cannabis group at all connections, whereas in the control group, connectivity was either unmodulated (dACC–left OP, left PFC–left OP, left aIns–left OP, and right aIns–left OP) or significantly decreased (dACC–right OP and right PFC–left OP). Furthermore, connectivity was comparable between groups during congruent trials, but diverged during incongruent performance, as illustrated in Figures 3d and 4, suggesting that connectivity differences were principally driven by differing responses to changing cognitive-control demands. Figure 4, in particular, depicts the change in connectivity (ie, regression slope) in the left PFC–left OP connection in two individuals, one from each cohort, whose results most closely replicate group-level findings.

A *post-hoc* region-of-interest analysis was also undertaken at the left OP to determine if significant between-group local activation differences would be apparent. The average contrast estimates ($\beta_{incongruent}−\beta_{congruent}$) from this region across individuals were entered into a two-sample *t*-test; a trend towards a larger activation in the cannabis group was evident ($t_{40} = 1.86$, $p = 0.07$). As such, all five frontal seed regions showed a cannabis-related hyperconnectivity with the left OP, alongside a trend towards greater activation during cognitive control in the same region.

Additionally, with respect to connections exhibiting group differences in magnitude, positive correlations in the cannabis-using group were identified between the magnitude of right PFC–left OP connectivity and both age of onset and lifetime cannabis exposure, and between the magnitude of left PFC–left OP connectivity and age of onset. Biomarkers of recent cannabis use and severity of withdrawal symptoms were not predictive of connectivity strength (Table 4).

DISCUSSION

This study demonstrated that long-term, heavy cannabis use is associated with increased functional connectivity between multiple cognitive-control regions of the frontal cortex, including the dorsal anterior cingulate, lateral prefrontal and aIns cortices, and the OP. Conversely, there were no significant group differences in the magnitude of brain activations during cognitive control in these same core regions of interest, or in task-related performance measures.

Observed increases in the strength of coupling occurred consistently in cannabis users between the frontal cognitive-control regions and the dorsal extrastriate cortex proximal to the ventral intraparietal sulcus and the lateral parieto-occipital sulcus. This region has been variously referred to as the OP (or parieto-occipital), visual area 6, or the dorsomedial visual area (Fattori *et al*, 2009; Galletti *et al*, 2005; Luppino *et al*, 2005). The OP is considered to have a pivotal role in the direction and switching of attention to spatial targets and target features, in guiding stimulus selection, and in tracking self-referential motion, with particular regard to the control of reaching and grasping (Desimone and Duncan, 1995; Galletti *et al*, 1999; Galletti *et al*, 2003; Yantis, 2008). Cognitive-control theories postulate that when the current context presents a requirement for active control processes, such as in novel, challenging, or goal-directed situations, frontal 'executive' regions, including the anterior cingulate and dorsolateral prefrontal cortices, modulate activity within relevant perceptual or motor pathways to bias information processing and response outcomes in favor of current goals (Botvinick *et al*, 2001; Desimone and Duncan, 1995; Egner and Hirsch, 2005a). 'Top-down' modulation therefore serves to optimize behavioral performance and utilization of cognitive resources. The observed task-induced hyperconnectivity may therefore represent increased top-down control influences on selective attention and visual-tracking mechanisms.

As PPIs do not predict directionality of the influence between interacting brain regions, the possibility that increased connectivity may alternatively represent greater bottom-up information flow from visual to frontal regions must also be considered. However, this interpretation is not well supported. As illustrated in Figure 4, increased connectivity in the cannabis group was indexed by an increase in the strength of the proportional relationship characterizing activity in the OP and frontal cortex. This connectivity change came alongside comparable functional activations between the groups in frontal regions and a trend towards greater activation in the cannabis group in the OP. This result would be predicted by a top-down perspective, in which a comparable unit change in activity between the groups in the seed (ie, frontal) region, alongside a cannabis-specific
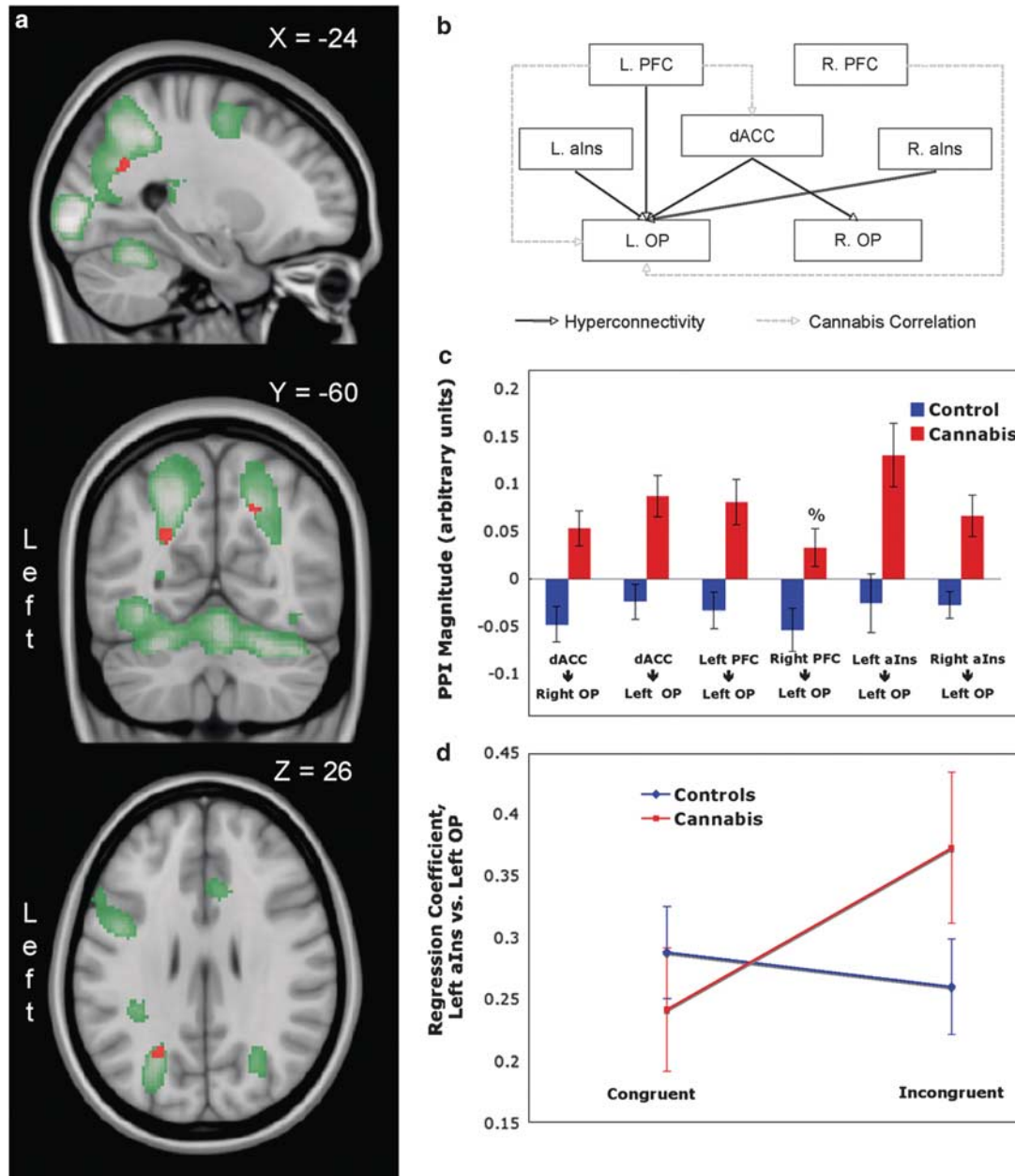
Q7
Q8

Figure 3 Increased functional connectivity in cannabis users from frontal lobe regions to the occipitoparietal (OP) cortex. The relevant region of the OP (red) and the main positive effect of condition (green) are overlayed onto sagittal, coronal, and axial brain slices (a; top to bottom). The corresponding circuit diagram depicts the connections in which a between-group difference is apparent, as well as those exhibiting a correlation with cannabis-use measures (b; PFC = prefrontal cortex; aIns = anterior insula; dACC = dorsal anterior cingulate cortex). The magnitude of the group-averaged connection strengths is also depicted (c; error bars = SEM). The right PFC to left OP interaction has been included (%) for completeness, even though this effect does not reach established significance thresholds. An interaction plot for the Left aIns to Left OP connection is additionally included to highlight that group differences are driven by connectivity differences during incongruent processing (d; error bars = SEM).

increase in connectivity, would result in greater activation in the cannabis group in the target (ie, occipitoparietal) region (Figure 4). From a bottom-up perspective, the slightly greater activation in the seed (ie, occipitoparietal) region in cannabis users would be magnified by the increase in connectivity, resulting in a group activation difference in target (ie, frontal) regions as well. However, the latter eventuality was not observed. Furthermore, results were restricted to task-relevant brain regions; that is to say, regions that were activated by increases in cognitive-control demands. As such, this region of

the OP was likely engaged by mechanisms mediating cognitive control, specifically, the anterior cingulate and lateral prefrontal cortices (MacDonald *et al*, 2000; Ridderinkhof *et al*, 2004), and as such is not likely to be their precursor. Lastly, the OP has not been implicated in visual perception or detection of cognitive conflict, but rather in the control of visual attention (Galletti *et al*, 1999; Galletti *et al*, 2003; Yantis, 2008). As the direction and switching of visual attention are under the control of prefrontal mechanisms (Desimone and Duncan, 1995), alterations in activity within

Table 4 Group Differences in Connectivity

Seed region	Target region	MNI coordinates x, y, z	Peak Z	Voxels, (K_E)	Cannabis correlations: Pearson 'r' (p-value) Dose[a]	Onset[b]	Saliva[c]	Urine[d]	Withdrawal[e]
Cannabis users > controls									
Anterior cingulate	Right occipitoparietal cortex	20, −58, 38	3.70	34	0.04 (0.85)	−0.11 (0.66)	−0.19 (0.41)	0.06 (0.82)	0.10 (0.67)
	Left occipitoparietal cortex	−24, −62, 26	3.62	23	0.11 (0.66)	0.30 (0.21)	0.15 (0.53)	0.12 (0.67)	−0.25 (0.29)
Left lateral prefrontal	Left occipitoparietal cortex	−26, −62, 26	3.54	10	0.11 (0.65)	**0.51 (0.025)**	0.13 (0.60)	0.10 (0.70)	−0.30 (0.18)
Right lateral prefrontal	Left occipitoparietal cortex	−26, −64, 28	2.96	f	**0.52 (0.024)**	**0.68 (0.001)**	0.13 (0.57)	0.09 (0.75)	−0.34 (0.13)
Left insula	Left occipitoparietal cortex	−26, −64, 24	3.40	6	0.02 (0.94)	0.09 (0.73)	0.18 (0.44)	−0.15 (0.58)	−0.35 (0.12)
Right insula	Left occipitoparietal cortex	−26, −62, 24	3.47	16	−0.25 (0.29)	0.15 (0.53)	0.24 (0.30)	−0.22 (0.41)	−0.22 (0.33)
Controls > cannabis users									
None									

[a] Total lifetime cannabis use, controlling for onset age and current age.
[b] Age of onset of regular cannabis use, controlling for dose and current age.
[c] Delta-9 THC concentration by volume in saliva.
[d] Carboxy-THC:creatinine ratio in urine.
[e] Withdrawal symptoms based on Marijuana Withdrawal Checklist.
[f] No voxels were significant at $p < 0.001$ (peak voxel: $p = 0.002$).

this region are likely the consequence of top-down influences.

Accepting that fronto-occipitoparietal connections represent top-down control influences, the observed increases in connectivity may conceivably suggest that cannabis users require greater control over attentional and perceptual resources in cognitively demanding contexts. Acute cannabis intoxication has been linked to decreased occipital activity and disrupted perceptual processing during visual attention (Bocker *et al*, 2010; Weinstein *et al*, 2008), suggesting that cannabis may impair effective filtering and processing of sensory information. In addition, acute intoxication has been linked to hyperactivity in anterior cingulate, lateral prefrontal, and insular cortices during tasks of attention (O'Leary *et al*, 2007; Weinstein *et al*, 2008), suggesting either acute disruption of frontal attention and executive systems and/or the need for greater effortful activation of executive mechanisms to exact adaptive control over behavior. In response to chronic cannabis exposure, increased synaptic efficacy defining the interactions between prefrontal and occipital cortices may therefore compensate, at least partially, for deficits at either level (frontal executive or occipital perceptual) by magnifying the influence of control signals on perceptual processes by which to mitigate deficits in behavior output and brain activity. The presence of such an adaptive mechanism is consistent with the growing line of evidence, indicating that heavier or longer-term users may become increasingly tolerant to the detrimental cognitive effects of intoxication, particularly within the domains of behavioral control and attention (Hart *et al*, 2001; Nordstrom and Hart, 2006; Ramaekers *et al*, 2009). In addition, as a result of varying degrees of progressive compensatory synaptic alteration within targeted networks, the findings of individual investigations exploring the impact of cannabis on cognitive control (and cognition in general) may be dependent on both the cohort (ie, long-term *vs* short-term users) and/or task (ie, selective attention *vs* response inhibition) under investigation. Such variance may help explain the current mixture of evidence for chronic cognitive impairments following extended cannabis use, with respect to both biological and behavioral indices of (dys)function (Crean *et al*, 2011; Martin-Santos *et al*, 2010).

Crucially, the magnitudes of task-induced connectivity change between several sets of task-relevant brain regions were also correlated with cannabis-use measures. The right prefrontal-to-left occipitoparietal connection strength was positively correlated with lifetime cannabis use. This result supports assertions argued above that increased cannabis use may be associated with greater compensatory changes in connectivity. Additionally, the magnitude of connectivity between both lateral prefrontal regions and the left OP were positively associated with the age of onset of regular cannabis use. This latter finding indicates that a later age of onset was associated with greater differences in cortical connectivity within control networks. The age of onset in our sample ranged from 12 to 19 years of age (plus one outlier at 25 years), representing a cross-section of substantial maturation within the frontal and parietal association cortices of the brain (Gogtay *et al*, 2004), and continued development of top-down control mechanisms (Adleman *et al*, 2002; Luna *et al*, 2001; Rubia *et al*, 2000). It is therefore
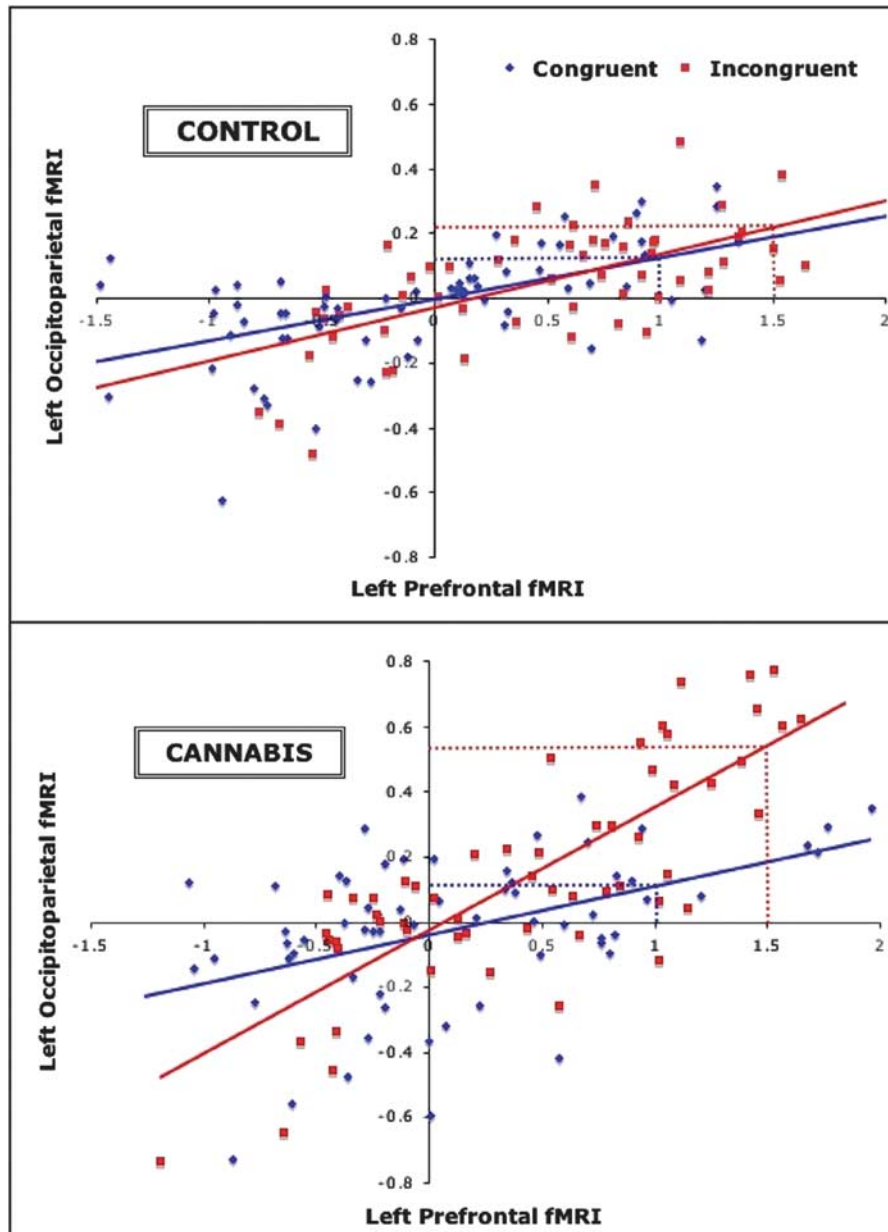
Figure 4 Psychophysiological interactions between the left prefrontal and left occipitoparietal cortices in representative individuals from the 'CONTROL' (top) and 'CANNABIS' (bottom) groups. Each data point represents a functional magnetic resonance imaging (fMRI) signal measurement during congruent (blue) and incongruent (red) task performance, fitted with linear trend lines. Extrapolating to group-level results, the dotted lines illustrate how a comparable average unit change in activation between conditions in the seed region (*x* axis) can drive a between-group activation difference in the target region (*y* axis) due to group differences in connectivity change.

possible that neurodevelopmental trajectories are altered in younger starters in response to chronic cannabis exposure within the plastic brain, bearing in mind that this cohort maintained a level of near daily cannabis consumption from their onset through to the present. Conversely, the more mature brains of older starters may rely on alterations in synaptic efficacy once neural pathways are more established. Put more simply, changes may be hard-wired in younger starters, whereas older starters invoke more dynamic compensatory adjustments in synaptic functioning. These findings are consistent with observations that cognitive deficits may be more persistent in younger starters following

abstinence in later adulthood (Pope *et al*, 2003), and parallel reports that younger onset is associated with more detrimental cognitive outcomes (Jager and Ramsey, 2008; Solowij *et al*, 2011; Solowij *et al*, 2012).

CONCLUSIONS

In summary, we report increased functional connectivity between executive regions of the PFC and areas of the OP, mediating the direction of attention in a cohort of current adult cannabis users during a task of cognitive control. We

suggest that these findings may reflect a mechanism of compensatory top-down control mitigating abnormal attention and visual processing following chronic cannabis exposure. This is the first study to report connectivity disturbances underlying cognitive control in cannabis use, and among the first employing analysis of task-related functional connectivity to the study of illicit substance use.

Several limitations must be considered with respect to this study. The use of a retrospective approach limits the ability to make definitive causal inferences with respect to observed differences; future longitudinal studies will be necessary to disentangle the time course of connectivity changes with certainty. In this study, we aimed to assess cannabis users in an unintoxicated state (greater than 12 h since last use), yet one in which withdrawal symptoms would not confound the results (within the first 24 h since last use; Budney *et al*, 2003). However, it is possible that observed discrepancies are because of the residual effects of cannabis, (see Crean *et al*, 2011 for review) rather than enduring dysfunction. Further research will be required to confirm the presence of similar effects after extended abstinence.

Future research extensions of this work include the application of functional connectivity analyses to additional cognitive domains and, due to the relevance of this work to understanding mechanisms of addiction and other harmful behaviors, to additional recreational substances, with the goal of determining the relative specificity of findings, and the longitudinal nature of effects (particularly with respect to long-term abstinence). Further experimentation exploring the role of top-down connectivity in addiction-related processes, such as selective attention biases, would also be valuable in understanding cognitive-control deficits that may be specific to drug-relevant contexts.

DISCLOSURE

DL has received a speaking honorarium from Astra Zeneca Pharmaceuticals, and CP has provided consultancy for Janssen-Cilag, Eli Lilly, Hospira (Mayne), and Astra Zeneca, Pfizer, Schering Plough, and Lundbeck, and has undertaken investigator-initiated studies supported by Eli Lilly, Hospira, Janssen Cilag, and Astra Zeneca. These activities are unrelated to the present work. Otherwise, except for income received from our primary employers and funding bodies listed in Acknowledgements, no financial support or compensation has been received from any individual or corporate entity over the past three years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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