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Brain reactivity to alcohol and cannabis marketing during sobriety and intoxication

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ABSTRACT

Drugs of abuse stimulate striatal dopamine release and activate reward pathways. This study examined the impact of alcohol and cannabis marketing on the reward circuit in alcohol and cannabis users while sober and intoxicated. It was predicted that alcohol and cannabis marketing would increase striatal activation when sober and that reward sensitivity would be less during alcohol and cannabis intoxication. Heavy alcohol ($n = 20$) and regular cannabis users ($n = 21$) participated in a mixed factorial study involving administration of alcohol and placebo in the alcohol group and cannabis and placebo in the cannabis group. Non-drug users ($n = 20$) served as between group reference. Brain activation after exposure to alcohol and cannabis marketing movies was measured using functional magnetic resonance imaging and compared between groups while sober and compared with placebo while intoxicated. Implicit alcohol and cannabis cognitions were assessed by means of a single-category implicit association test. Alcohol and cannabis marketing significantly increased striatal BOLD activation across all groups while sober. Striatal activation however decreased during intoxication with alcohol and cannabis. Implicit associations with cannabis marketing cues were significantly more positive in alcohol and cannabis users as compared with non-drug using controls. Public advertising of alcohol or cannabis use elicits striatal activation in the brain's reward circuit. Reduction of marketing would reduce brain exposure to reward cues that motivate substance use. Conversely, elevated dopamine levels protect against the reinforcing potential of marketing.

Keywords alcohol, cannabis, craving, cue-reactivity, fmri, marketing.

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INTRODUCTION

Alcohol and cannabis are the most widely used drugs in the western world. It is estimated that around two billion individuals consume alcohol worldwide (World Health Organization 2004). People typically drink alcohol and smoke cannabis to induce euphoria or reduce anxiety. Both drugs facilitate the release of tonic dopamine in reward and motivation circuits in the brain (Anton 1999; Heinz *et al.* 2005; Gilman *et al.* 2008; Bossong *et al.* 2009; Yacubian & Büchel 2009) that accounts for the pleasurable effects of drugs. The hedonic response is often a motive for people to repeat drug use (Franken, Booij, & van den Brink 2005).

Drug-associated cues have also been shown to stimulate dopamine release (Berger *et al.* 1996; Koob & Volkow 2010) and activate the reward circuit of abstinent drug users (Filbey *et al.* 2009; Goudriaan *et al.* 2010; Vollstädt-Klein *et al.* 2010; Cousijn *et al.* 2013). This suggests that drug-related cues may trigger the reward system to a similar extent as do drugs. Consequently, motivations to use alcohol or drugs may increase because of marketing exposure to drug-related cues such as alcohol and drug advertisements. Earlier studies on soft drink brands have shown that brand knowledge influences expressed behavioural preferences and measured brain responses (McClure *et al.* 2004). Likewise, cue-elicited

reactivity to alcohol and cannabis has been shown to activate reward pathways in the brain associated with the neuropathology of addiction (Tapert *et al.* 2003; Filbey *et al.* 2009). Research on alcohol and tobacco marketing has shown that marketing can significantly increase consumption patterns (Tye, Warner, & Glantz 1987; Cassisi *et al.* 1998; Anderson *et al.* 2009; Smith & Foxcroft 2009).

While longitudinal studies consistently show that alcohol and tobacco marketing negatively affect adolescents' drinking and smoking behaviour (Lovato *et al.* 2003; Anderson *et al.* 2009), no research has examined the impact of marketing on brain activity during intoxication. One might expect that the reinforcing properties of marketing cues and actual drug or alcohol use add up to increase the hedonic response. However, current knowledge on the dopaminergic response within the reward system would predict that reinforcing properties of drug and alcohol marketing may actually diminish during drug and alcohol intoxication. Reinforcing stimuli have previously been shown to cause burst firing of midbrain dopamine neurons that leads to a temporary, phasic release of dopamine in the striatum (Schultz 2007). The striatal response or reward sensitivity to such phasic dopaminergic innervations has been posed to vary with the availability of tonic dopamine in the same area (Cools & D´Esposito 2011). Reward sensitivity is high when tonic dopamine is low and vice versa. This implies that a phasic response to marketing may decrease in the presence of elevated tonic dopamine levels induced by alcohol (Gilman *et al.* 2008) and cannabis (Bossong *et al.* 2009).

The aim of the present study was to assess the impact of alcohol and cannabis marketing on the brain's reward circuit. It was predicted that alcohol and cannabis marketing would increase brain activation in the striatum when sober. In addition, the study aimed to obtain direct evidence for the predicted impact of tonic dopamine (cannabis and alcohol intoxication) on the reward-related phasic dopamine effects (cannabis and alcohol marketing) in a pharmaco functional magnetic resonance imaging (fMRI) paradigm. It was predicted that brain networks that are activated after alcohol/cannabis marketing exposure are similar during sobriety and intoxication, but that reinforcement of the striatum after marketing exposure will be less during intoxication as compared with when sober. An implicit association task was used to register implicit cognitions towards alcohol and cannabis marketing cues during intoxication and while sober.

MATERIALS AND METHODS

Participants

The present study included a group of heavy alcohol users, a group of regular cannabis users and a control group. Heavy alcohol use was defined as using on average 21 to 50 alcoholic drinks a week for men or 15 to 35 alcoholic drinks a week for women during the last year (Cassisi *et al.* 1998). Experimental use of cannabis in the alcohol group was allowed only if it occurred more than a year ago. Regular cannabis use was defined as having used cannabis at least three times a week but no more than 10 times a week, during the previous year (Ramaekers *et al.* 2009). Alcohol use between 1–14 U/week was allowed in the cannabis group. Controls were defined as not currently using cannabis or other drugs; experimental use of cannabis was allowed if it occurred more than a year ago and incidental alcohol use was permitted (1–7 U/week for women and 1–14 U of alcohol/week for men).

Inclusion criteria included: (i) age 18–40 years, (ii) free from psychotropic medication, (iii) good physical health and (iv) body mass index within 18.5–28 kg/m^2. Exclusion criteria included: (i) addiction according to DSM-IV criteria, (ii) presence or history of psychiatric or neurological disorder as assessed by a medical questionnaire, (iii) pregnancy, (iv) cardiovascular abnormalities, (v) excessive smoking (>15 cigarettes per day) and (vi) hypertension.

Five subjects from the alcohol group and two subjects from the cannabis group dropped out because of personal circumstances and one subject from the cannabis group failed to complete the fMRI session during placebo, but otherwise completed both behavioural sessions. The dropouts were replaced, but the behavioural data of the subject with incomplete fMRI session was also added to the final data set. The final dataset therefore consisted of 61 subjects spread among the alcohol and control group ($n = 20$ each) and the cannabis group ($n = 21$). Subjects (35 men, 26 women) were aged between 18 and 28 (mean (SD) 22.5 (2.3) years). Subjects underwent a general medical examination including routine laboratory tests and provided a written informed consent. The study was conducted according to the code of ethics on human experimentation established by the declaration of Helsinki (1964) and amended in Seoul (2008) and approved by the Medical Ethics Committee of the Academic Hospital of Maastricht and Maastricht University (Dutch Trial Register: trial number: NTR3428). A summary of subject demographics and drug use history is given in Table 1.

Design and treatments

Groups of heavy alcohol and regular cannabis users participated in a double-blind, placebo-controlled, mixed-factorial study involving two experimental conditions consisting of alcohol and placebo in the alcohol group and cannabis and placebo in the cannabis group. The order of treatment conditions was balanced over

Table 1 Subject demographics and history of alcohol and drug use.

	Mean	*Minimum*	*Maximum*
Age (years)	22.5 (2.3)	18	28
Weight (kg)	67.9 (10.7)	50	92
Alcohol group ($n = 20$; 10 men, 10 women)			
# of alcohol units/week	24 (7.7)	15	50
Cannabis group ($n = 21$; 15 men, 6 women)			
Frequency of cannabis use /week	4.8 (1.9)	3	7
# of alcohol units/week	4.9 (4.7)	0	14
Control group ($n = 20$; 10 men, 10 women)			
# of alcohol units/week	5.3 (3.5)	1	14
Lifetime use of other drugs	Alcohol group	Cannabis group	Control group
Ecstasy	8	10	2
Amphetamine	2	5	1
Cocaine	1	5	0
LSD	0	3	0
Mushrooms	2	11	0
Other (e.g. truffles and ketamine)	3	8	0

LSD = lysergic acid diethylamide.

participants and sessions. Conditions were separated by a minimum washout period of 7 days to avoid carry-over effects. An age-matched control group of non-drug users was added that received no treatment but the testing day was similar on all other aspects. The alcohol and cannabis group received treatment prior to the fMRI session (T1) and a second dose prior to the implicit association task (T2).

Alcohol (96%v/v) was mixed with orange juice to a total volume of 250 ml. Alcohol doses were individually calibrated using the formula of Watson, Watson & Batt (1981) to achieve a blood alcohol concentration (BAC) of 0.8 g/l. Men received between 52–68 ml, and women received between 39 and 48 ml of alcohol depending on their weight. Subjects' BAC was monitored frequently (every 15–20 minutes approximately) with an alcohol breathalyzer (Dräger Alcotest® 6510, Drägerwerk, Lübeck, Germany) and was kept constant by administering maintenance drinks. Maintenance (booster) doses were administered during before behavioural testing. Each subject received a booster dose; the volume depended on their BAC level at the end of the scanning session.

The cannabis group received a total of 300 µg Δ9-tetrahydrocannabinol (THC)/kg bodyweight, divided over two successive doses of 200 and 100 µg THC/kg bodyweight (booster dose) with an interval of approximately 1 hour. THC was administered using a volcano vaporizer produced by Storz-Bickel, Germany (http://www.storz-bickel.com). Hot air would pass through the filling chamber holding the cannabis (containing 12% THC), which caused the THC or placebo to vaporize and blend with the air. The THC molecules or the placebo (vapor) was trapped in a valve balloon. For inhalation, the valve of the balloon was put to subjects' lips, and they were instructed to inhale deeply.

Procedures

Subjects were asked to refrain from drug use at least a week prior to the start and during the study. Subjects were not allowed to use alcohol on the day before an experimental session and were requested to arrive at experimental sessions well rested. Drug and alcohol screens were carried out upon arrival at our testing facilities. Urine drug screens assessed for the presence of benzodiazepines, opiates, cocaine, marijuana, MDMA and (meth) amphetamine. Women were also tested for pregnancy. Study treatments were only administered after negative drug screens, except for marijuana in the cannabis group, and negative pregnancy tests.

Brain activity was measured by means of fMRI during a 1-hour session. Cannabis (or cannabis placebo) and alcohol (or alcohol placebo) administration was completed at 15 and 30 minutes prior to scanning (T_1). The scanning session was followed by a 45 minutes break in which a booster dose was administered. Implicit association was measured by means of implicit association tests between at 15 and 30 minutes after completion of cannabis (placebo) or alcohol (placebo) booster administration (T_2). All subjects received a training session before the onset of the experimental sessions in order to familiarize them with tests and procedures. Blood samples and breath tests were taken at baseline (T_0) and prior to scanning (T_1) and the single category implicit association test (SC-IAT) (T_2).

Functional magnetic resonance imaging Marketing Exposure Task

Brain activity was assessed during a marketing-exposure task using a block design. In this task, marketing clips were randomly presented on a computer screen in blocks of 30 seconds. The clips consisted of three categories, that is, alcohol marketing clips (10×), cannabis-related clips (10×) and neutral clips (10×). Total task duration was approximately 33 minutes. Alcohol clips were mainly non-local advertisement of beers, wines and other alcoholic beverages that were not readily available in the Netherlands and were spoken in foreign languages (e.g. Polish, Spanish or English) that did not correspond to the subjects' native language (Dutch). This was done to ensure that subjects were not reacting to the specific alcohol brand, but to the alcohol itself. Cannabis clips included advertisement for cannabis paraphernalia and a selection of short film fragments where portrayal of cannabis use and marketing practices at cannabis selling points were displayed. The neutral clips consisted of local and non-local advertisement of non-drug-related stimuli (e.g. advertisement for cameras, water, hearing aid etc.).

Functional magnetic resonance images were acquired with a Siemens 3 T head-only scanner (MAGNETOM Allegra, Siemens Medical Systems, Erlangen, Germany). During the cue exposure task, whole brain functional volumes were acquired using gradient-echo echo-planar imaging (GE-EPI, TR = 2000 ms, TE = 30 ms; flip angle (FA) = 90°; FOV 224 mm; matrix size = 64 × 64; voxel size = 3.5 × 3.5 × 3.5 mm). The T1-weighted anatomical scan was acquired using a three-dimensional magnetization-prepared rapid gradient echo (3D MPRAGE; TR = 9.7 ms; TE = 4 ms; FA = 12°; matrix = 256 × 256; voxel size = 1 × 1 × 1 mm^3).

Data preprocessing and analysis were conducted using SPM8 (Welcome Trust Center for Neuroimaging, London, UK). The first two volumes were removed from each fMRI data set to allow for magnetic equilibration. Firstly, framewise displacement (FD) calculations were carried out to quantify head displacement within and across runs (Power *et al.* 2012). In total, two subjects in the alcohol group, one subject in the cannabis group and one subject in the control group were excluded from further processing because of excessive movement (in >20% of the volumes). In addition, motion parameters in the alcohol and cannabis group were then compared with check for motion differences between placebo and active drug/alcohol conditions. These analyses indicated no difference between sessions for the most susceptible motion parameters (Yoo *et al.* 2005; Mayer *et al.* 2007).

Thereafter, the following preprocessing steps were carried out: (1) realignment, (2) slice time correction, (3) individual anatomical data sets were normalized to standard 3D MNI space (voxel size was resampled to 2 × 2 × 2 mm) and (4) spatial smoothing was applied with a FWHM 6-mm Gaussian kernel.

Single category implicit association test

Implicit cognition was assessed by means of the SC-IAT, which measures the strength of evaluative associations (positive versus negative) with a single attitude object (alcohol or cannabis marketing pictures). During the first block of 24 trials (target discrimination), only the target concepts were presented, and subjects had to respond using the corresponding keys (i.e. press left button for positive words and the right button for negative words). In the second block (compatible block) of 72 trials, positive words and drug marketing cues were categorized on the left key, and negative words were categorized on the right key. In the third block (incompatible block) of 72 trials, negative words and drug marketing cues were categorized on the right key, and positive words were categorized on the left key. The rationale behind this task is that if subjects have a positive evaluation for alcohol or cannabis rather than a negative evaluation, they should be quicker to respond when alcohol/cannabis marketing + positive words (compatible block) share the same response key compared with the incompatible block, where alcohol/marketing clips + negative words share the same response key. Target words and marketing cues were presented at random order within each block. Blocks 2 and 3 were counterbalanced across treatments conditions. Data from the first block (practice block) was discarded. Non-responses and responses faster than 350 ms were eliminated and error responses were replaced with the block mean plus an error penalty of 400 ms. Subjects who exceeded an error rate of 20% were excluded. The dependent variable was the D score (Greenwald, Nosek, & Banaji 2003; Karpinski & Steinman 2006), which was calculated by subtracting the mean reaction time (RT) of correct responses in the compatible block from the mean RT of correct responses in the incompatible block, divided by the standard deviation (SD) of all correct responses within the compatible and incompatible block. D scores were log transformed (ln(D score + 1)) before entering statistical analysis.

Pharmacokinetic measures

In the cannabis group, blood samples to determine cannabinoid concentrations (THC and metabolites OH-THC and THC-COOH) were collected at three successive times during each test day, that is, at baseline (T_0) and 0.5 (T_1), 1.5 hours (T_2) after the first dose. The blood samples (8 ml) were centrifuged immediately; serum was transferred into a tube and was stored at −20 °C. Cannabinoid

concentrations were determined by the Institute of Forensic Toxicology, University of Frankfurt, using solid-phase extraction and gas chromatography with mass spectrometric detection with a limit of quantification of 1.0 ng/ml. In the alcohol group, BAC levels were measured throughout the test day with the breathalyzer.

Statistics

Functional magnetic resonance imaging data

Two generalized linear model (GLM) full factorial models were built to calculate marketing cue-related BOLD activations during sobriety (i.e. placebo/no treatment) and how these were affected by cannabis or alcohol intoxication. For both models, contrast images from the individual GLM analysis (first-level) were used as input for the second-level GLMs. Individual analysis consisted of contrast images of cannabis marketing movies versus neutral marketing movies [cannabis marketing; contrast (1–1)] and alcohol marketing movies versus neutral marketing movies [alcohol marketing; contrast (1–1)]. All individual GLMs included the six realignment parameters as regressors.

The first GLM full factorial model focused on BOLD activation during cannabis marketing and alcohol marketing across the three groups while being sober. The model included the factors group (three levels: cannabis group on placebo, alcohol group on placebo and controls) and marketing cue (cannabis marketing and alcohol marketing).

The second GLM full factorial model was designed to assess the influence of cannabis and alcohol intoxication on brain activation during marketing exposure. The model consisted of the following factors: group (two levels: cannabis group and alcohol group); treatment (two levels: placebo and cannabis/alcohol) and marketing cue (two levels: cannabis marketing and alcohol marketing).

For these two models, whole brain analyses were performed to explore general effects of marketing and treatments. Region of interest (ROI) analyses were conducted in order to specifically test our hypotheses that marketing cues and drug intoxication would affect striatal activations within the brain reward network. A striatal ROI was built with the WFU PickAtlas (Tzourio-Mazoyer *et al.* 2002; Maldjian *et al.* 2003; Maldjian, Laurienti, & Burdette 2004) by combining the bilateral putamen, caudate and globus pallidus. Results were considered significant when PFWE-corrected at cluster level <0.05.

Subsequently, we quantified mean percent BOLD signal change in (combined) striatal areas that showed significant brain activation following marketing exposure during sobriety (GLM1) and intoxication (GLM2). Functional striatal masks were created with Marsbar. Mean percent BOLD signal change was quantified for all marketing clips (cannabis, alcohol and neutral) in each group and in each treatment condition using the SPM toolbox rfxplot (Gläscher 2009). Percent BOLD signal change was analyzed in SPSS following the same outline as previous GLMs, with the exception that marketing cue consisted of three levels (cannabis, alcohol and neutral movies).

Implicit cognition

The dependent parameter of the SC-IAT (i.e. D score) was analyzed by means of a GLM univariate ANOVA with a main factor group (three levels: alcohol group on placebo, cannabis group on placebo and control). These were followed by simple group contrast relative to the controls. The effects of the factors alcohol treatment (two levels, alcohol and placebo) and cannabis treatment (two levels; cannabis and placebo) cues were assessed in repeated measures GLMs in the alcohol and cannabis group, respectively. If the sphericity assumption was violated, the Greenhouse–Geisser correction was used. The alpha criterion significance level was set at $P = 0.05$. All statistical tests were conducted with SPSS version 20.0.

Results

Whole brain analyses

Figure 1 shows mean increments in BOLD activation following exposure to cannabis and alcohol marketing cues (versus neutral) collapsed over the three groups while sober and mean decrements in BOLD response to marketing (collapsed over alcohol and marketing movies) while under the influence of cannabis or alcohol.

The first generalized linear model analyses revealed a main effect of Group on BOLD response in the left hippocampus and right precuneus and a main effect of marketing cue in parietal, temporal and frontal brain regions. Overall, exposure to marketing cues increased BOLD activations across these brain regions in the three groups, and more so during alcohol marketing movies. Significant brain clusters associated with main effects of group and marketing cue are given in Supporting Information Table S1.

The second generalized liner model analyses revealed a main effect of group on BOLD response in the cuneus, rolandic operculum, brainstem, insula, amygdala, cerebellum and temporal and frontal clusters. A main effect of marketing cue on BOLD response was found in the postcentral cluster, cingulum, temporal, parietal, frontal and occipital cortex. A main effect of treatment on BOLD response in the right supplementary motor area was observed indicating reduction of marketing induced BOLD

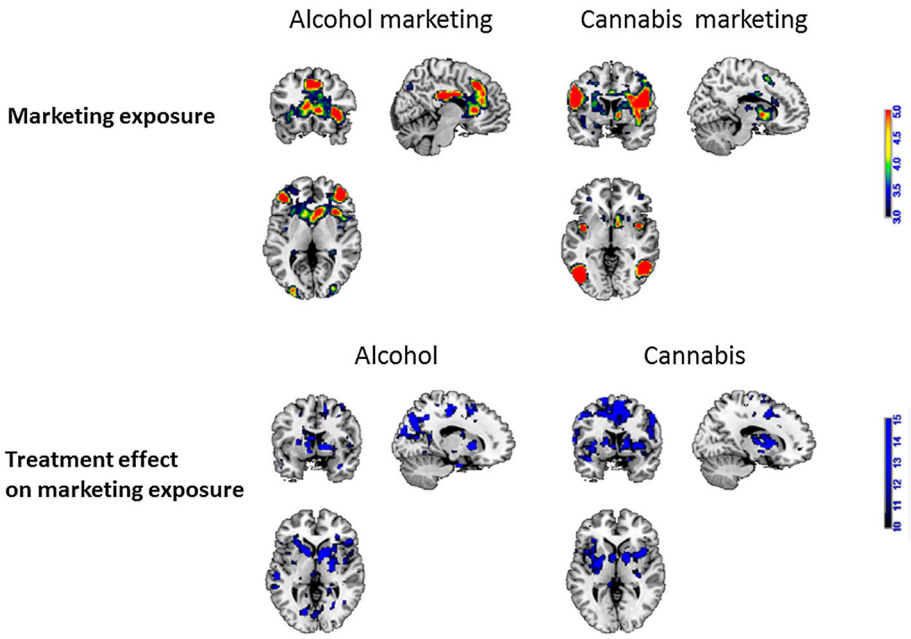

Figure 1 The upper panel shows BOLD activation (red) following cannabis and alcohol marketing exposure (versus neutral) collapsed over all three groups while sober. The lower panel shows how alcohol and cannabis intoxication deactivates (blue) the BOLD response to marketing exposure (collapsed across alcohol and cannabis marketing cues) relative to placebo

activation. Significant brain clusters associated with main effects of Group, Treatment and Marketing cue are given in Supporting Information Table 1.

ROI analyses striatum

The first generalized linear model revealed a main effect of group on BOLD response in the left pallidum during marketing exposure across all groups. The factor marketing cue did not differentially affect BOLD response in the striatum. The GLM2 analysis revealed a main effect of group on BOLD response in the right caudate. The factor treatment caused an overall decrease in the BOLD response in the bilateral pallidum and right caudate. The factor marketing cue did not differentially affect BOLD response in the striatum. Significant brain clusters associated with main effects of group, treatment and marketing cues for the GLM analyses are given in Table 2.

Percent signal change striatum

The first generalized linear model revealed a main effect of Marketing cue ($F_{2,52} = 12.8$; $P < .001$). Simple contrast indicated that cannabis marketing cues ($P < .001$) and alcohol marketing cues ($P < .001$) increased BOLD activation in the striatum, relative to neutral marketing cues (Fig. 2). The factors group and group × marketing cue did not reach significance.

The second generalized linear model revealed main effects of treatment ($F_{1,35} = 4.18$; $P = .048$) and marketing cue ($F_{2,34} = 14.6$; $P < .001$). Treatment with alcohol and cannabis generally reduced BOLD activation in the striatum relative to placebo ($P = .048$) whereas cannabis ($P = 0.014$) and alcohol ($P < .001$) marketing cues generally increased BOLD activation, relative to neutral cues. The interactions between treatment, group and marketing cue did not reach significance.

Implicit cognition

Overall, implicit associations (SC-IAT) following exposure to cannabis cues significantly differed between groups during sobriety ($F_{2,58} = 4.16$; $P = .021$). Simple groups contrast revealed that D scores following cannabis cues were more positive in the cannabis ($P = .012$) and alcohol group ($P = .020$) relative to controls. Overall, implicit associations with alcohol cues did not differ between groups. Simple contrasts revealed that associations with alcohol cues tended to be higher in the alcohol group as compared with the group of controls ($P = .058$).

During intoxication with alcohol and cannabis, mean D scores were less relative to placebo but failed to reach statistical significance. Mean D scores obtained in the cannabis group, alcohol group and controls following alcohol and cannabis cues are shown in Fig. 3.

Pharmacokinetics

Mean (SE) alcohol concentrations in breath and cannabinoid concentrations in serum for the alcohol and cannabis treatment conditions are shown in Table 3.

Table 2 Striatal areas showing changes in BOLD activation during marketing exposure while being sober (GLM1) and while intoxicated (GLM2).

	Number of voxels	*Peak MNI coordinates*	*F* value	*P*-value FWE corrected
ROI analysis (GLM1)				
Group				
Left pallidum	22	−24, −8, −6	13.22	0.006
ROI analysis (GLM2)				
Group				
Right caudate	32	18, 8, 22	16.87	0.035
Treatment				
Right pallidum	1672	16, 6, 2	39.45	0.000
Left pallidum	1533	−26, −6, −2	33.25	0.000
Right caudate	6	20, −24, 20	16.76	0.037

GLM = generalized linear model

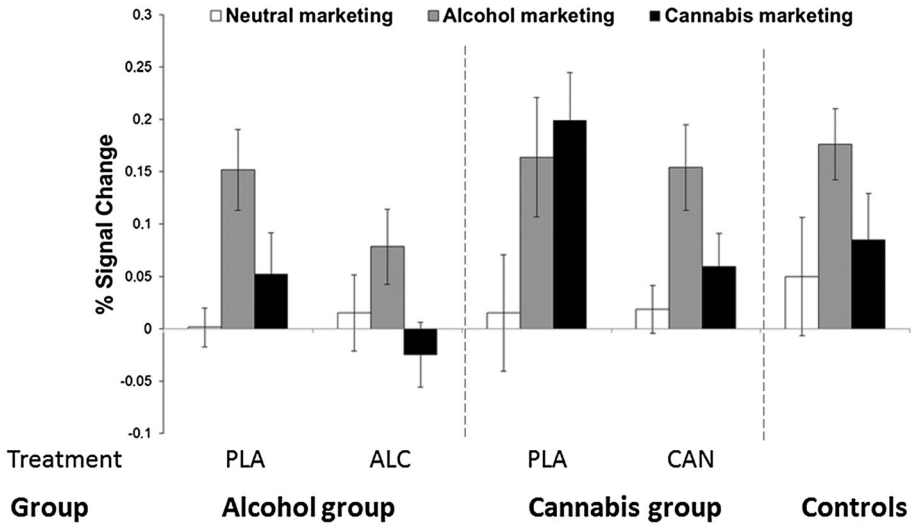

Figure 2 Mean (SE) percent signal change in the striatum separately for each group, treatment condition (PLA = placebo, ALC = alcohol and CAN = cannabis) and marketing cue

DISCUSSION

Whole brain analysis generally revealed increased BOLD activation during marketing exposure in a large number of cortical networks and in all groups while being sober. ROI analysis of the striatal region furthermore indicated a strong increase in BOLD activation in the pallidum. These results are consistent with those from studies that reported wide-spread brain activations in reward, motivation and memory circuits in drug users compared with non-drug users after exposure to drug-cues (e.g. (Myrick *et al.* 2004; McClernon *et al.* 2005; Smolka *et al.* 2006; Goldstein *et al.* 2009; Zijlstra *et al.* 2009; Janes *et al.* 2010; Cousijn *et al.* 2013)). Activation of striatal and cortical networks following exposure to marketing movies of cannabis and alcohol use strongly suggests that such marketing can trigger similar brain responses that have also been observed during drug use or drug craving (Volkow *et al.* 2006; Wong *et al.* 2006; Martín-Santos *et al.* 2010).

Whole brain and striatal ROI analysis revealed decrements in BOLD activation in the right supplementary motor area and the striatum during intoxication with alcohol or cannabis. Overall, cannabis and alcohol marketing movies significantly increased percent signal changes in the striatum relative to neutral marketing movies during placebo treatments. Administration of alcohol and cannabis significantly decreased percent signal change. Together, these results indicate that alcohol and cannabis marketing movies can stimulate striatal parts of the human reward system when drug users are not under the influence of drugs or alcohol, and the reinforcing effects of marketing movies are reduced during alcohol or cannabis intoxication. The present data seem to fit well with our hypothesis that the phasic dopaminergic response (i.e. reward sensitivity) to marketing cues

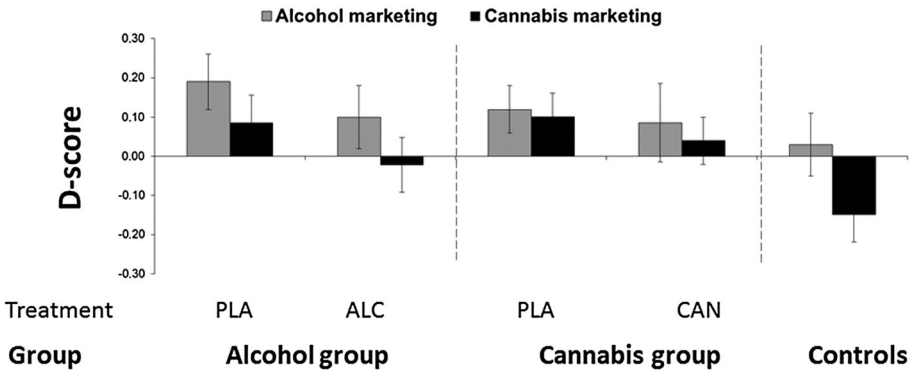

Figure 3 Mean (SE) D scores following alcohol and cannabis marketing cues in each group and each treatment condition (PLA = placebo; ALC = alcohol and CAN = cannabis)

Table 3 Mean (SE) concentrations of THC and metabolites in serum in the cannabis group and blood alcohol concentrations (BAC) levels in the alcohol group, at the different time points.

	Cannabis group			*Alcohol group*
	THC (μg/l)	*THC-OH (μg/l)*	*THC-COOH (μg/l)*	*BAC (g/l)*
Baseline (T_0)	1.24 (.45)	.44 (.28)	15.89 (1.36)	.00 (.00)
Prior to scanning (T_1)	46.48 (1.59)	3.93 (.26)	27.66 (0.84)	.76 (.03)
Prior to SC-IAT (T_2)	24.17 (1.46)	3.16 (.28)	27.34 (1.02)	.79 (.02)

SC-IAT = single-category implicit association test.

decreases when tonic dopamine levels in the striatum are high.

Performance during the cannabis SC-IAT differed significantly between the alcohol and cannabis users and controls while sober. The control group had negative bias scores, which contrasted with positive bias scores of the alcohol and cannabis group indicating positive implicit association for cannabis-related stimuli in cannabis and alcohol users. Performance during the alcohol SC-IAT tended to differ between the three groups during sobriety. Alcohol and cannabis users did display higher alcohol bias scores during placebo as compared with controls, but these differences just failed to reach significance in the alcohol group ($P = 0.058$). In general, these results are in line with previous reviews indicating that a positive, implicit attitude towards drug-related cues is a characteristic of alcohol and substance users (Field & Cox 2008; Field *et al.* 2010). Performance during the alcohol and cannabis SC-IAT decreased during cannabis and alcohol intoxication, but failed to reach significance. This strongly suggests that implicit attitudes towards cannabis and alcohol marketing cues do not change during acute intoxication, even when the actual experience or expectancy of brain 'reward' during marketing exposure decreases.

The main strengths include the placebo-controlled administration of cannabis and alcohol to assess brain reactivity to marketing exposure of alcohol and cannabis. It should be noted however that participants were always exposed to the same set of marketing clips on the first or second day of treatment, even though the order of clips was randomized. This may have mitigated some of the marketing effects because of practice or repeated exposure. If present however, such practice effects were equally balanced between placebo and active treatment sessions.

Policy and clinical implications are twofold. The present data confirm that public advertising of alcohol or cannabis use elicits striatal activation in the brain's reward circuit that are similar to those seen after primary rewards such as liquids, drugs and food. Alcohol and cannabis marketing thus increases reward sensitivity for these substances and increases motivation for actual use. A reduction of alcohol and drug marketing would diminish its impact, particularly in regular alcohol and cannabis users, by reducing brain exposure to reward cues that motivate and prepare for alcohol or drug use. Conversely, the present dataset also demonstrates that high tonic levels of dopamine protect against the reinforcing potential of alcohol and cannabis marketing. This suggests that prescription drugs that increase tonic dopamine levels, such as methylphenidate, may be of prophylactic value to alcohol and cannabis abusers to defy alcohol and cannabis marketing exposure in our society.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Brain areas showing changes in BOLD activation during marketing exposure while being sober (GLM1) and while intoxicated (GLM2)