ORIGINAL INVESTIGATION

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Altered orbitofrontal activity and dorsal striatal connectivity during emotion processing in dependent marijuana users after 28 days of abstinence

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Abstract

Rationale Intact cognitive and emotional functioning is vital for the long-term success of addiction treatment strategies. Accumulating evidence suggests an association between chronic marijuana use and lasting alterations in cognitive brain function. Despite initial evidence for altered emotion processing in dependent marijuana users after short abstinence periods, adaptations in the domain of emotion processing after longer abstinence remain to be determined.

Objective and methods Using task-based and resting state fMRI, the present study investigated emotion processing in 19 dependent marijuana users and 18 matched non-using controls after an abstinence period of > 28 days.

Results Relative to the control subjects, negative emotional stimuli elicited increased medial orbitofrontal cortex (mOFC) activity and stronger mOFC-dorsal striatal and mOFC-amygdala functional coupling in dependent marijuana users ($p < 0.022$, FWE-corrected). Furthermore, mOFC-dorsal striatal functional connectivity was increased at rest in marijuana users ($p < 0.03$, FWE-corrected). Yet, processing of positive stimuli and subjective ratings of valence and arousal were comparable in both groups.

Conclusions Together, the present findings provide the first evidence for persisting emotion processing alterations in dependent marijuana users. Alterations might reflect long-term neural adaptations as a consequence of chronic marijuana use or predisposing risk factors for the development of marijuana dependence.

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Introduction

Worldwide, marijuana is among the most frequently used drugs of potential abuse, with an estimated 3.8% of the world population using it regularly (UNODC 2016). Although the majority of regular marijuana users may not develop addictive patterns of use, epidemiological data and increasing rates of treatment demand for marijuana dependence indicate that a significant number of regular users can develop a clinically relevant marijuana use disorder (EMCDDA 2016). Despite the growing treatment demand for problematic marijuana use, current therapeutic options remain limited. Evidence-based pharmacological treatment strategies are lacking (Van den Brink 2012), and although behavioral therapeutic interventions show some efficacy (Gates et al. 2016), the long-term success of interventions in individuals with substance addictions strongly relies on intact cognitive (Stevens et al. 2014) and emotional functioning (Charlet et al. 2014).

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Accumulating evidence regarding non-acute effects of chronic marijuana use suggests cognitive impairments that persist for several days after last use (Broyd et al. 2016) paralleled by altered neural functioning in prefrontal-limbic networks (Martín-Santos et al. 2010). Findings concerning persisting effects of chronic use on cognitive brain function are less consistent. Whereas some studies reported partial recovery of cognitive processing at the behavioral and neural level (Schreiner and Dunn 2012), others observed impairments of executive functions in the context of altered neural processing in prefrontal regions after prolonged abstinence (Martín-Santos et al. 2010), including changes in orbitofrontal cortex (OFC) activation alongside faulty decision-making after 25 days of abstinence (Bolla et al. 2005). Importantly, a dynamic susceptibility contrast MRI study could show that cerebral blood volume is increased in frontal regions in long-term cannabis users after 7 days of abstinence, but normalizes with continued abstinence (Sneider et al. 2008). Together with findings indicating that impairments in functional domains that critically rely on the integrity of the prefrontal cortex, such as motivation, inhibition, and executive function (partly) normalize with prolonged abstinence across drugs of abuse (Verdejo-García et al. 2006), these previous findings emphasize the need to determine functional impairments that persist during prolonged abstinence.

In contrast to the large number of studies examining alterations in cognitive brain function, only a small number of fMRI studies have addressed effects of regular marijuana use on emotion processing. Initial studies investigating effects of chronic marijuana use after short abstinence periods revealed decreased amygdala and cingulate reactivity during implicit emotional processing of masked faces (Gruber et al. 2009), blunted activation during processing of negative words (Heitzeg et al. 2015), and decreased prefrontal activity during explicit evaluation of affective scenes (Wesley et al. 2016). However, the fMRI data was acquired after 12–24 h of marijuana abstinence and therefore subacute effects of cannabinoids and cannabinoid metabolites could not be ruled out. Moreover, study samples consisted of non-dependent marijuana users. A recent behavioral study could show that dependent marijuana users display deficits in both identification and discrimination of facial emotions after a minimum abstinence of 28 days (Bayrakçı et al. 2015). However, neural alterations that underlie altered emotion processing in marijuana dependence after prolonged abstinence remain to be determined.

Early abstinence periods are characterized by withdrawal (Budney et al. 2003), craving (Lee et al. 2014), and emotional distress (Jacobus et al. 2017) which have been shown to decrease over the course of 28 days (Lee et al. 2014; Jacobus et al. 2017). Therefore, longer abstinence periods are of particular relevance when assessing emotional functioning, as negative affective states related to marijuana withdrawal

together with potential subacute effects of the drug may impact the outcome measures during early abstinence.

Against this background, the present fMRI study examined basic emotion processing and subjective emotion perception in marijuana-dependent individuals after an abstinence period of > 28 days. Based on previous findings, suggesting decreased limbic and frontal activity in marijuana users following short abstinence periods (Gruber et al. 2009; Wesley et al. 2016), we expected reduced frontal and limbic activity during processing of emotional scenes in dependent marijuana users relative to matched healthy controls. To further explore alterations in brain networks, differences in functional connectivity during emotion processing and at rest were examined.

Materials and methods

Experimental protocols

Twenty-one volunteers (two females) with marijuana dependence according to DSM-IV criteria and 20 matched healthy non-using volunteers (two females) were enrolled in the study. General study eligibility was assessed via telephone screening. All 41 eligible participants completed two separate study appointments. On the first day, participants were screened for inclusion and exclusion criteria. An experienced clinical psychologist assessed whether marijuana users met the criteria for marijuana dependence according to DSM-IV criteria (SCID interviews; Wittchen et al. 1997). On the second day, all participants completed questionnaires and cognitive tests, as well as a urine screen prior to the fMRI session. Inclusion criteria for all participants were (1) age 18–35 years, (2) right-handedness, and (3) a negative qualitative urine toxicology for marijuana and other prevalent illicit drugs on the day of the experiment (Drug-Screen® Pipette test by Nal van Minden, Moers, Germany, Multi 7TF for amphetamines (500 ng/ml), cocaine (300 ng/ml), methamphetamine (500 ng/ml), THC (50 ng/ml), MDMA/ecstasy (300 ng/ml), opiate (300 ng/ml), methadone (300 ng/ml)). Inclusion criteria for marijuana users were (1) a marijuana dependence according to DSM-IV criteria and (2) marijuana abstinence > 28 days based on a self-report of days since last cannabis use (duration of abstinence in days since last use: $M = 166.95$, SD = 280.08; Median = 42.00, range = 14–1035). One user reported having used marijuana on one occasion 14 days before the experiment but was included due to his negative urine drug screen on the examination day. Control subjects were included if their cumulative lifetime marijuana use was below 10 g. Exclusion criteria for all participants were (1) any profound DSM-IV axis I or axis II disorder, such as psychotic or bipolar disorders (assessed with SCID interviews), (2) a clinically relevant depressive symptom load (Beck Depression Inventory, BDI-II, score > 20 (Beck et al. 1996)), (3) a clinically relevant medical disorder, including

neurological, cardiovascular, and internistic disorders, (4) intake of psychotropic medication in the 28 days prior to the fMRI assessment, and (5) MRI contraindications. Attention and general intelligence were assessed using validated measures (d2-Test of attention (Brickenkamp and Zillmer 1998), Wortschatztest, WST assessing approximate verbal IQ level (Metzler and Schmidt 1992), respectively). To control for mood differences that might affect emotion processing, subjects completed the positive and negative affect schedule (PANAS, (Crawford and Henry 2004)) on the day of the assessment. Parameters of marijuana use were documented for marijuana users using a standardized structured interview (Becker et al. 2010) in which participants were asked to specify the age of onset (M ± SD 14.90 ± 1.25 years), frequency of use (M ± SD 27.33 ± 5.94 days per month), and duration of regular use (M ± SD 71.33 ± 34.29 months) (detailed interview form is available upon request from the corresponding author). Experiences with other prevalent licit and illicit drugs of potential abuse were also documented in this interview. Marijuana-dependent individuals were recruited in collaboration with the LVR Clinic Bonn and through advertisements. All subjects gave written informed consent before study inclusion. The study was in accordance with the latest revision of the Declaration of Helsinki, had full ethical approval by the local ethics committee of the medical faculty, University of Bonn (Application Number: 220/12), and was registered as clinical trial (NCT02711371, https://clinicaltrials.gov/ct2/show/NCT02711371).

Emotion processing paradigm

The emotion processing fMRI paradigm included four "negative," four "positive," and four "neutral" blocks, each comprising six negative (M ± SD: valence = 2.71 ± 0.63, arousal = 6.12 ± 0.82), positive (M ± SD: valence = 7.32 ± 0.55, arousal = 4.99 ± 1.37), or neutral pictures (M ± SD: valence = 5.44 ± 0.47, arousal = 3.25 ± 0.50) selected from the International Affective Picture System (IAPS). Each picture was presented for 2 s with a 100-ms inter-stimulus interval. Blocks were presented in a randomized order and interspersed with a jittered inter-block-interval (13–15 s). Subjects were instructed to passively view the pictures. To ensure attention, subjects had to confirm each picture with a button press of the right index finger. The paradigm was presented in two successive runs. Following the fMRI scan, subjects rated their subjective emotional perception of the previously shown stimuli in terms of valence and arousal on the Self-Assessment Manikin (SAM) scale (arousal 0 "lowest arousal"–9 "highest arousal"; valence 0 "very negative"–9 "very positive").

Study sample

Twenty-one dependent marijuana users and 20 non-using healthy controls participated in the fMRI study. $N = 2$ subjects per group were excluded due to excessive head motion (see fMRI preprocessing), resulting in a sample size of 19 marijuana users and 18 control subjects for the fMRI analysis. Post-scan emotional ratings from $N = 1$ subject per group were lost due to technical failure, resulting in a sample size of 18 marijuana users and 17 control subjects for the behavioral data analysis (see Fig. S1).

Behavioral data analysis

For non-normally distributed data, we report the median and range. A repeated measures analysis of variance (ANOVA) was performed on valence and arousal ratings with emotions ("negative," "positive," and "neutral") as a within-subject factor and group (marijuana users vs controls) as a between-subject factor. Significant interactions and main effects were further explored using post hoc Bonferroni-corrected comparisons. The final analysis included 18 marijuana users and 17 controls.

MRI data acquisition

Images were collected using a 3T Siemens TRIO MRI system (Siemens, Erlangen, Germany). fMRI data was acquired using a T2*-weighted echo-planar imaging (EPI) pulse sequence (emotion processing: repetition time = 2500 ms, echo time = 30 ms, number of slices = 37, slice thickness = 3.0 mm, no gap, field of view = 192 × 192 mm^2, resolution = 64 × 64, flip angle = 90°, number of volumes per run = 160; resting state: repetition time = 2580 ms, echo time = 30 ms, number of slices = 47, slice thickness = 3.5 mm, no gap, field of view = 224 × 224 mm^2, resolution = 64 × 64, flip angle = 80°, number of volumes = 180). For the resting state acquisition, subjects were instructed to stay relaxed, close their eyes, and think of nothing in particular while not falling asleep. To exclude subjects with apparent brain pathologies and to improve normalization of the functional EPI images, high-resolution whole-brain volume T1*-weighted images were acquired obliquely using a 3D spoiled gradient echo pulse sequence (repetition time = 1660 ms, echo time = 2.54 ms, flip angle = 9°, field of view = 256 × 256 mm^2, acquisition matrix = 256 × 256, thickness = 0.8 mm, number of slices = 208).

fMRI preprocessing: emotion processing task fMRI

Images were processed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK). The first five volumes of each subject and each run were discarded to allow magnet equilibration. The remaining functional images were realigned to correct for head motion, and subsequently, the mean functional EPI image was co-registered to the T1 image. For normalization, a two-step procedure was applied. First, normalization parameters were determined by

segmenting the T1 image using the default tissue probability maps as priors. Next, normalization parameters were applied to normalize the functional images to the standard anatomical Montreal Neurological Institute (MNI) space resampled at $2.0 \times 2.0 \times 2.0$ mm^3. Normalized images were spatially smoothed with a 6-mm full width at half maximum (FWHM) Gaussian kernel. Four subjects were excluded due to excessive head movement (> 3 mm or $> 3°$; two males per group). The final fMRI analysis included 19 marijuana users and 18 control subjects.

fMRI data analysis: emotion processing task fMRI

The first level design matrix included three experimental regressors ("negative," "positive," "neutral") convolved with the canonical hemodynamic response function and the six realignment parameters to control for head motion. In line with previous studies on emotion processing alterations in marijuana users (Gruber et al. 2009; Wesley et al. 2016), valence-specific contrasts ("negative > neutral," "positive > neutral") were used for between-group comparisons by means of SPM two-sample t tests. Based on our a priori hypothesis and a recent systematic review indicating small to moderate effect sizes (Ganzer et al. 2016) of neural alterations in abstinent marijuana users, the second level analysis was regionally restricted to increase the sensitivity to detect lasting effects of marijuana use. To this end, the second level analysis focused on regions that (1) show particular high densities of endocannabinoid (CB1) receptors (Mackie 2008) and (2) have been translationally determined to be involved in valence processing (Hayes et al. 2014). Regions of interests (ROIs) were structurally defined using standardized brain atlases and included: cingulate cortex, orbitofrontal cortex (OFC), anterior insula (AI), striatum (caudate and putamen combined to a single mask) (Automatic Anatomical Labeling (AAL) atlas), amygdala, and hippocampus (probabilistic maps, Anatomy toolbox 2.1). Results were considered significant at $p < 0.05$ family-wise error corrected (p_{FWE}, peak-level correction). To further examine effects of marijuana dependence on functional coupling within the emotion processing network, a generalized psycho-physiological interaction (gPPI, (McLaren et al. 2012)) analysis was conducted. Seed regions were defined as 6-mm spheres centered at the MNI-coordinates of the maximum t value of between-group differences from the BOLD level analysis. The gPPI toolbox (https://www.nitrc.org/projects/gppi) was used to model psycho-physiological interactions. Two-sample t tests were used to examine group differences of connectivity for the corresponding contrasts. In line with the BOLD level analysis, the analysis focused on the structurally defined masks, and results were considered significant at $p_{FWE} < 0.05$ (SVC), peak-level correction.

Resting state fMRI data acquisition and preprocessing

The emotion processing paradigm was preceded by a 7.54-min resting state fMRI acquisition. The first five volumes were discarded, and remaining volumes were slice-timing corrected, spatially realigned to the first EPI volume, and unwarped to compensate for non-linear distortions caused by head motion or magnetic field inhomogeneity using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). These volumes were further processed using the FMRIB Software Library (FSL, http://www.fmrib.ox.ac.uk/fsl), including non-brain removal using BET (Smith 2002), spatial smoothing using a Gaussian kernel of 6 mm FWHM, and global 4D mean intensity normalization. Note that no temporal filtering was applied at this stage of processing. Registration of functional data to structural images was carried out using affine boundary-based registration as implemented in FSL FLIRT (Jenkinson et al. 2002). Registration from structural to standard space was then refined using FNIRT non-linear registration (Andersson et al. 2007). Additional preprocessing included an independent component analysis for automatic removal of motion artifacts (ICA-AROMA, (Pruim et al. 2015)), removal of mean signals from white matter and cerebrospinal fluid by means of linear regression, and bandpass filtering (0.01–0.1 Hz). In line with Pruim et al. (2015), white matter and CSF time series were derived by determining the mean time series over voxels within predefined subject-specific WM and CSF masks. These masks were obtained by applying FSL FAST to the T1 image with a threshold of 95% and then registered to native EPI space. Likewise, we registered the MNI152 average CSF and WM segmentation maps (priors) which were subsequently masked by the thresholded registered segmentations and finally thresholded (95% of the robust range) to obtain the respective conservative CSF and WM masks.

Confirmatory analysis of fMRI resting state connectivity

The specific aim of the resting state analysis in the present study was to determine whether altered functional connectivity during task emotion processing can also be observed during rest. To this end, a targeted analysis was conducted on the pathways identified in the task-based connectivity analysis. The seed regions were defined as a 6-mm sphere centered at the maximum t value of the group differences determined by the BOLD level analysis of the emotion processing task. Resting state functional connectivity maps were first generated using voxel-wise correlation analysis between the seed and other voxels in the entire brain and subsequently converted to Z-maps (Fisher's z-transformation).

Group differences between marijuana users and controls were determined using two-sample t tests. Given the confirmatory nature of the analysis, statistical comparisons were restricted to the pathways determined by the task-based connectivity analysis. Masks for target regions were defined as 10-mm spheres centered at the maximum t values from the between-group differences determined by the task-based connectivity analysis. A threshold of $p_{FWE} < 0.05$ (SVC) peak-level correction was applied.

Correlation analysis with parameters of marijuana use

To explore whether neural alterations were associated with the severity of marijuana use, percent signal change (BOLD) and parameter estimates (gPPI) extracted from 6-mm spheres centered at the MNI-coordinates of the maximum t value of group differences from the BOLD level analysis (x, y, z: 8, 48, − 2; right mOFC) and gPPI analysis (task-based: − 14, 18, − 6, left caudate; − 22, − 4, − 28, left basolateral amygdala; 14, 44, − 2, right mOFC; resting state: − 18, 15, − 12; left DS) were entered into Pearson correlation analyses with the duration of regular use (months) and cumulative lifetime use (computed as total lifetime amount in gram), as use-based measures of dependence severity. Results were considered significant at $p < 0.05$.

Results

Group characteristics

Marijuana users and healthy controls were comparable in age, years of education, verbal intelligence (WST), d2 concentration performance, and negative affect (PANAS negative affect) (all $p > 0.05$, Table 1). Although marijuana users reported lower positive affect before entering the scanner (PANAS positive affect) ($p = 0.02$, Table 1), both groups scored in the normal range for positive affect (Crawford and Henry 2004), indicating a stable emotional state at the time of the assessment. Importantly, groups did not differ regarding the use of alcohol or nicotine (see Table 2). As expected, marijuana users reported greater lifetime experiences with other illicit drugs than controls (Table 2). Marijuana, however, was the primary substance of abuse, and all users fulfilled the criteria for marijuana dependence according to DSM-IV, but not the criteria for any other previous or current substance dependence (except for nicotine dependence).

Behavior—valence and arousal ratings

Marijuana users rated negative images with a mean valence of 2.91 ± 1.61 and arousal of 5.86 ± 2.49, positive images with a mean valence of 6.38 ± 1.40 and arousal of 4.70 ± 2.41, and

Table 1 Demographic characteristics of marijuana-dependent subjects and controls. Marijuana users: $N = 19$, controls: $N = 18$

Measure	Marijuana users ($N = 19$) M (SD)	Controls ($N = 18$) M (SD)	p
Age	23.79 (3.24)	24.11 (3.14)	0.76
Years of education	14.39 (2.47)	14.89 (2.27)	0.53
WST	29.37 (5.98)	29.56 (3.73)	0.91
D2 concentration performance	176.16 (34.20)	197.11 (51.25)	0.15
PANAS negative affect	13.89 (4.77)	11.56 (1.76)	0.06
PANAS positive affect	29.95 (5.66)	34.78 (5.99)	0.02

neutral images with a mean valence of 5.16 ± 1.18 and arousal of 2.99 ± 2.03. Non-using control subjects rated negative images with a mean valence of 3.21 ± 1.88 and arousal of 5.18 ± 2.70, positive images with a mean valence of 6.37 ± 1.67 and arousal of 3.90 ± 2.56, and neutral images with a mean valence of 5.18 ± 1.48 and arousal of 2.27 ± 1.92 (Table 3).

For valence ratings, a repeated measures ANOVA revealed a significant main effect of emotion ($F_{(2, 66)} = 185.08$, $p < 0.001$). Post hoc tests showed that valence ratings were highest for positive pictures, followed by neutral and negative pictures (all p's < 0.001, 6.49 ± 0.54, 5.33 ± 0.43, 3.07 ± 1.13 for positive, neutral, and negative pictures, respectively). There were no significant group differences (all p's > 0.202). For arousal ratings, there was a significant main effect of emotion ($F_{(2, 66)} = 66.17$, $p < 0.001$). Post hoc tests showed that arousal was highest for negative pictures, followed by positive and neutral pictures (all p's < 0.001, 5.54 ± 1.58, 4.37 ± 1.46, 2.72 ± 1.21 for negative, positive, and neutral pictures, respectively). There were no significant group differences (all $p > 0.073$).

Emotion processing fMRI—BOLD level and task-based connectivity

A group comparison of "negative > neutral" revealed stronger right medial OFC activity (right mOFC, MNI: 8, 48, − 2, $t = 3.95$, $p_{FWE} = 0.022$ (SVC), voxels = 12) to negative stimuli in marijuana users relative to control subjects (Fig. 1a). No significant group differences were observed in other regions of the emotion processing network or during processing of positive pictures ("positive > neutral"). A subsequent analysis of functional connectivity showed increased coupling of the right mOFC with the left dorsal striatum (DS, caudate, MNI: − 14, 18, −6, $t = 4.15$, $p_{FWE} = 0.030$ (SVC), voxels = 4) and the left amygdala (basolateral sub-region, MNI: − 22, − 4, − 28; $t = 3.91$, $P_{FWE} = 0.026$ SVC; voxels = 1; considered as preliminary finding due to the small cluster-extend), as well as decreased connectivity within the right mOFC (MNI: 14, 44, − 2, $t = 4.41$, $p_{FWE} = 0.002$ (SVC), voxels = 9) for the

Table 2 Parameters of licit and illicit drug use

Measure	Marijuana users M (SD)	Controls M (SD)	p
Licit drugs			
Alcohol units per week	5.38 (6.65)	5.23 (5.50)	0.94
Number of cigarette smokers	$N = 18$	$N = 17$	–
Years of nicotine use	8.67 (4.32)	6.66 (4.29)	0.18
Number of cigarettes per day	9.57 (5.87)	9.88 (6.68)	0.88
Illicit drugs			
Number of participants with past ecstasy use	$N = 12$	$N = 2$	–
Lifetime occasions of ecstasy use	15.13 (22.58)	4.50 (4.95)	
Number of participants with past cocaine use	$N = 10$	$N = 0$	–
Lifetime amount of cocaine use	8.80 (8.20)	–	
Number of participants with past amphetamine use	$N = 14$	$N = 1$	–
Lifetime amount of amphetamine use	17.50 (1–1400)*	6.00	
Number of participants with past hallucinogen use	$N = 6$	$N = 0$	–
Lifetime amount of hallucinogen use	7.17 (11.43)	–	
Number of participants with past opiate use	$N = 2$	$N = 1$	–
Lifetime amount of opiate use	2.5 (2.12)	30.00**	
Number of participants with past marijuana use	$N = 19$	$N = 18$	–
% lifetime marijuana dependence	100%	0%	

Marijuana users: $N = 19$, controls: $N = 18$ (unless indicated otherwise)

* Median

** Prescription medical use

contrast "negative > neutral" in marijuana users relative to controls (Fig. 1b).

Resting state fMRI—intrinsic connectivity of the medial orbitofrontal cortex

Relative to controls, marijuana users showed increased functional connectivity at rest between the right mOFC seed and the left DS (MNI: − 18, 15, − 12, $t = 3.82$, $p_{FWE} = 0.029$ (SVC), voxels = 5). This suggests that marijuana users display alterations in the interplay between these regions beyond negative emotion processing. Examining the right OFC-mOFC and the mOFC-amygdala pathways did not yield significant group differences.

Associations with parameters of marijuana use

We observed no association of neural indices with the duration (months) or cumulative lifetime amount (gram) of marijuana use ($p > 0.05$).

Discussion

The present fMRI study investigated basic emotion processing and perception in dependent marijuana users after 28 days of abstinence. Findings suggest alterations in mOFC neural activity and mOFC-DS coupling in response to negative stimuli and in the absence of task challenge. In contrast, processing of positive content as well as behavioral indices of emotion

Table 3 Valence and arousal ratings of IAPS stimuli (M ± SD) per group and per category

	Negative		Positive		Neutral	
	Valence	Arousal	Valence	Arousal	Valence	Arousal
Marijuana users	2.91 ± 1.61	5.86 ± 2.49	6.38 ± 1.40	4.70 ± 2.41	5.16 ± 1.18	2.99 ± 2.70
Controls	3.21 ± 1.88	5.18 ± 2.70	6.37 ± 1.67	3.90 ± 2.56	5.18 ± 1.48	2.27 ± 1.92

Fig. 1 Neural differences in emotion processing between dependent marijuana users and controls. **a** Greater BOLD signal in the right medial orbitofrontal cortex (MNI: 8, 48, − 2) in marijuana users during processing of negative images, $p_{FWE} < 0.05$ (SVC), peak-level inference. MJ, marijuana users; CON, controls. **b** Stronger functional connectivity between the right medial orbitofrontal cortex (red) and the dorsal striatum (MNI: − 14, 18, − 6) (top green) and the right orbitofrontal cortex (MNI: 14, 44, − 2) (bottom green), $p_{FWE} < 0.05$ (SVC), peak-level inference
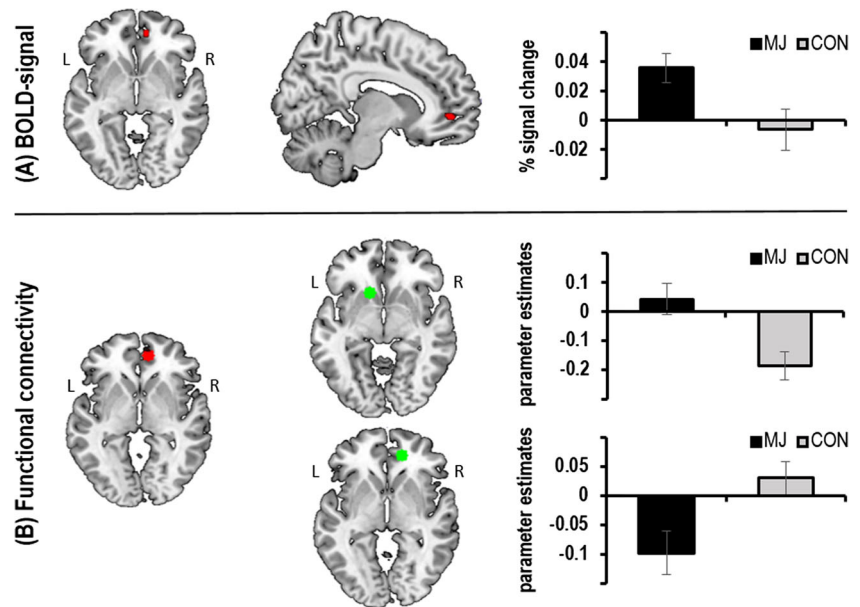
perception were found to be intact. Together, the present findings add to literature on marijuana use associated emotion processing alterations (Gruber et al. 2009; Wesley et al. 2016; Wetherill et al. 2014) and additionally suggest that neural alterations persist with prolonged abstinence in dependent marijuana users.

The present study revealed increased mOFC reactivity to negative stimuli, a region consistently implicated in addiction. However, the heightened regional activation is contrary to the commonly observed decreased activity in response to emotional stimuli in previous studies addressing marijuana-associated alterations in emotion processing (Gruber et al. 2009; Wesley et al. 2016; Wetherill et al. 2014). Differences between studies in the employed task paradigms, sample characteristics, such as the dependence status, and the duration of abstinence might account for the inconsistent findings.

First, whereas we assessed passive viewing of emotional scenes, previous studies revealing decreased activation in marijuana users used paradigms employing emotional face stimuli (Gruber et al. 2009), backward masking procedures (Gruber et al. 2009; Wetherill et al. 2014), or explicit evaluation of emotional scenes (Wesley et al. 2016). FMRI research indicates that the class of emotional stimuli (faces vs scenes) (Sabatinelli et al. 2011) and the level of conscious processing (backward masked vs unmasked) (Phillips et al. 2004) determine the specific emotion networks that engage.

Second, whereas previous studies employing implicit emotion processing paradigms focused on dependent users (Wetherill et al. 2014), the dependence status in the study employing explicit processing of emotional scenes remains unknown (Wesley et al. 2016). Initial evidence for neural indices specifically differentiating dependent from non-dependent drug users (Smith et al. 2014), including marijuana

users (Chye et al. 2017a), emphasize the role of mOFC neuroadaptations in the transition from volitional to dependent patterns of use, suggesting that dependence status may be relevant to our findings.

Third, whereas marijuana users in previous studies underwent short abstinence periods (< 24 h) and provided positive THC screens on the day of the examination (Gruber et al. 2009; Wesley et al. 2016; Wetherill et al. 2014), the present study required an abstinence period of > 28 days prior to the assessment. Notably, studies with short abstinence periods most commonly observed decreased rather than increased neural activity during emotion processing (Gruber et al. 2009; Wetherill et al. 2014), a pattern that partly overlaps with acute THC and CBD-induced attenuated neural activity across domains, including the processing of, particularly negative, stimuli (Rabinak et al. 2012; Bossong et al. 2013), inhibitory control (Bhattacharyya et al. 2017), and salience processing (Bhattacharyya et al. 2012). Within this context, the present findings suggest that marijuana-associated neural alterations during emotion processing change over the course of abstinence. Attenuated neural reactivity to negative stimuli during early stages of abstinence—possibly due to (sub-)acute effects of cannabinoids—might change to exaggerated neural responses with longer periods of abstinence.

In regard to the abovementioned observations, the present findings of increased mOFC neural responsivity to negative stimuli after 28 days of abstinence suggest that marijuana-associated alterations in emotion processing may specifically be related to marijuana dependence and may change during the course of abstinence.

Altered prefrontal functioning in the absence of behavioral differences is commonly observed in studies assessing cognitive brain function in abstinent marijuana users (Bolla et al.

2005; Chang et al. 2006; Schweinsburg et al. 2008; Tapert et al. 2007). Our present findings extend previous literature by suggesting that lasting prefrontal alterations not only affect cognitive brain processes, but may contribute to abnormal emotion processing. Interestingly, regular marijuana users often report gaining control of negative emotions as primary motivational drive to use marijuana (Simons et al. 2000). Thus, altered processing of negative affect may be a predisposing factor contributing to the initiation or later escalation of use. In line with this notion, Chye et al. (2017b) observed an association between a distinctive OFC sulcogyral pattern type, a morphological pattern developed early on in life, and greater lifetime cannabis use. The associated pattern type is above that commonly associated with negative emotionality, both supporting that OFC alterations impacting affective processing may contribute to increased cannabis use. However, the present study design does not allow causal inference.

Increased mOFC activity in the present sample of dependent marijuana users was accompanied by stronger connectivity with the DS during negative processing and at rest. Altered network connectivity has repeatedly been observed in marijuana-dependent subjects after short abstinence periods. Studies focusing on the fronto-striatal circuitry report decreased connectivity at rest following 12 h of abstinence (Blanco-Hinojo et al. 2016), as well as increased connectivity during task challenge following 72 h of abstinence (Filbey and Yezhuvath 2013). Fronto-striatal pathways are modulated by endocannabinoid signaling (Gremel et al. 2016), and an acute pharmacological THC challenge transiently reduces connectivity in these pathways (Bhattacharyya et al. 2015). In contrast, lasting increases in OFC-striatal connectivity at rest have been observed in disorders related to marijuana dependence, such as cocaine dependence (Contreras-Rodriguez et al. 2016) as well as obsessive-compulsive disorder (Beucke et al. 2013). In this context, the current results might reflect a switch from decreased OFC-striatal connectivity during the early course of abstinence to increased connectivity with prolonged abstinence. Neuroplastic changes in this circuitry have been proposed to underlie the development of substance addictions. In particular, the transition from voluntary to habitual drug intake is thought to be reflected in a shift from the ventral to dorsal striatum and deficient prefrontal inhibitory control processes (Everitt and Robbins 2013). Beyond that, altered communication between prefrontal regions with the striatum and the amygdala has been suggested as the neurobiological basis of deficient behavioral and emotional control, a core characteristic of drug addictions (George and Koob 2010).

The OFC has been implicated in a broad range of cognitive and emotional functions, particularly reward (Elliott et al. 2010; Liu et al. 2011) and affective value processing (Shenhav et al. 2013), and decision-making (Cunningham et al. 2009; Lawrence et al. 2009). The OFC and striatum share reciprocal structural and functional connections (Di

Martino et al. 2008; Jarbo and Verstynen 2015), thought to be involved in reward processing (Tanaka et al. 2004) and reinforcement-guided learning (Gremel and Costa 2013). Although disruptions in these functional domains and associated neural indices of OFC-DS functioning have been observed across substance addictions (Everitt and Robbins 2016; Luijten et al. 2017), including marijuana-dependence (Bolla et al. 2005), the present study revealed alterations during processing of negative, rather than positive stimuli.

Recent evidence outlines an increasing role of the DS and OFC not only in positive but also negative emotion processing. Together with the amygdala, the DS, particularly the caudate, exhibits strong reactivity to negative visual stimuli (Carretie et al. 2009) with the OFC being involved in the automatic downregulation of this limbic-striatal reactivity to negative affective stimulation (Ochsner and Gross 2005; Phillips et al. 2008). Furthermore, a recent study revealed altered prefrontal-amygdala coupling associated with regulation of negative affect in regular marijuana users (Zimmermann et al. 2017). In line with this conceptualization, the present connectivity findings might reflect either increased bottom-up signaling or top-down control in response to negative stimuli in dependent marijuana users, with the lack of alterations in the subjective perception of negative stimuli and the preliminary findings on increased mOFC-amygdala connectivity arguing for the latter. However, positive task stimuli in the present study were rated as moderately positive and therefore may not have been sensitive enough to uncover neural adaptations underlying positive emotion processing. Thus, it cannot be excluded that processing of positive stimuli of higher hedonic value, such as monetary rewards, may be impaired in marijuana users, as previously reported (Cousijn et al. 2013; Nestor et al. 2010).

Our findings need to be interpreted in view of several limitations. Abstinence periods were assessed by self-report and negative qualitative urine screenings (cut-off 50 ng/ml) on the day of the fMRI assessment. Although marijuana metabolites remain detectable in urine samples for several weeks after cessation of chronic use (McGilveray 2005) and previous studies found a high reliability of self-reported cannabis use (Martin et al. 1988), we cannot entirely exclude sporadic marijuana use during the assumed 28 days of abstinence. Future studies implementing supervised inpatient abstinence periods would allow to overcome this shortcoming and reliably ensure abstinence. Furthermore, quantitative urine toxicology of marijuana metabolites would allow to infer a lack of subacute affects.

Although negative emotionality plays an important role in the development and maintenance of substance use disorders (Cheetham et al. 2010; Volkow 2004) and emotion perception impairments have been observed in abstinent marijuana users (Bayrakçı et al. 2015; Somaini et al. 2012), neural alterations in the present study were not accompanied by altered emotion perception. This pattern might either reflect a normalization or

neural compensatory mechanism; however, the lacking sensitivity of task stimuli to uncover behavioral changes might also have contributed to the absence of behavioral group differences. In line with previous literature (Wesley et al. 2016), the present findings suggest a higher sensitivity of neural markers to determine marijuana-associated alterations in emotion processing, as has previously been hypothesized for cognitive functions (Cousijn et al. 2014). Alternatively, rating the emotional experience requires cognitive effort and insight into one's actual state of affect and arousal, and a recent study could link low emotional clarity to problematic marijuana use (Boden et al. 2013). Therefore, subjective ratings may not entirely reflect the actual emotional experience. Second, valence and arousal ratings were obtained following the fMRI session. Novelty of emotional stimuli has been shown to play a role in the emotional response (Weierich et al. 2010). Thus, the familiarity of the images may have led to deviations from the initial valence and arousal perception during the imaging session. To overcome these limitations, future studies may use stimuli of higher valence or varying levels of valence and include ratings immediately following the stimulus.

The groups included only a low number of females ($N = 2$); thus, the present findings do not allow to draw conclusions regarding the generalizability of the findings across genders. Following studies might consider specifically addressing this issue.

Finally, dependence status was determined according to DSM-IV diagnostic criteria, yet more detailed measures of marijuana dependence were not documented. For instance, the severity of dependence may impact the extent of neurobiological alterations. Beyond that, the subjective judgment of one's dependence may be a crucial factor as well. This study included an extensive profile of marijuana use patterns which serve as indirect indicators of the severity of dependence. Yet, future studies would benefit from including more elaborate data on dimensional measures of marijuana dependence.

Together, these findings on altered orbitofrontal reactivity and orbitofrontal-striatal connectivity during processing of negative stimuli and at rest suggest emotion processing alterations in marijuana-dependent individuals that persist with prolonged abstinence. Alterations might reflect neural adaptations as a consequence of chronic marijuana use or predisposing risk factors for the development of marijuana dependence.

References

Andersson JL, Jenkinson M, Smith S (2007) Non-linear registration, aka spatial normalisation FMRIB technical report TR07JA2 2007. FMRIB Analysis Group of the University of Oxford, 2

Bayrakçı A, Sert E, Zorlu N, Erol A, Sarıçiçek A, Mete L (2015) Facial emotion recognition deficits in abstinent cannabis dependent patients. Compr Psychiatry 58:160–164. https://doi.org/10.1016/j.comppsych.2014.11.008

Beck AT, Steer RA, Brown GK (1996) Beck depression inventory-II. Psychological Corporation, San Antonio, TX

Becker B, Wagner D, Gouzoulis-Mayfrank E, Spuentrup E, Daumann J (2010) The impact of early-onset cannabis use on functional brain correlates of working memory. Prog Neuro-Psychopharmacol Biol Psychiatry 34(6):837–845. https://doi.org/10.1016/j.pnpbp.2010.03.032

Beucke JC, Sepulcre J, Talukdar T, Linnman C, Zschenderlein K, Endrass T, Kaufmann C, Kathmann N (2013) Abnormally high degree of connectivity of orbitofrontal cortex in obsessive-compulsive disorder. JAMA Psychiatry 70(6):619–629. https://doi.org/10.1001/jamapsychiatry.2013.173

Bhattacharyya S, Crippa JA, Allen P, Martín-Santos R, Borgwardt S, Fusar-Poli P et al (2012) Induction of psychosis by Δ9-tetrahydrocannabinol reflects modulation of prefrontal and striatal function during attentional salience processing. Arch Gen Psychiatry 69(1):27–36. https://doi.org/10.1001/archgenpsychiatry.2011.161

Bhattacharyya S, Falkenberg I, Martín-Santos R, Atakan Z, Crippa JA, Giampietro V et al (2015) Cannabinoid modulation of functional connectivity with regions processing attentional salience. Neuropsychopharmacology 40(6):1343–1352. https://doi.org/10.1038/npp.2014.258

Bhattacharyya S, Atakan Z, Martin-Santos R, Crippa JA, Kambeitz J, Malhi S et al (2017) Impairment of inhibitory control processing related to acute psychomimetic effects of cannabis. Eur Neuropsychopharmacol 25:26–37

Blanco-Hinojo L, Pujol J, Harrison BJ, Macia D, Batalla A, Nogue S et al (2016) Attenuated frontal and sensory inputs to the basal ganglia in cannabis users. Addict Biol e-pub ahead of print 3 March 2016; doi: https://doi.org/10.1111/adb.12370

Boden MT, Gross JJ, Babson KA, Bonn-Miller MO (2013) The interactive effects of emotional clarity and cognitive reappraisal on problematic cannabis use among medical cannabis users. Addict Behav 38(3):1663–1668. https://doi.org/10.1016/j.addbeh.2012.09.001

Bolla KI, Eldreth DA, Matochik JA, Cadet JL (2005) Neural substrates of faulty decision-making in abstinent marijuana users. NeuroImage 26(2):480–492. https://doi.org/10.1016/j.neuroimage.2005.02.012

Bossong MG, van Hell HH, Jager G, Kahn RS, Ramsey NF, Jansma JM (2013) The endocannabinoid system and emotional processing: a pharmacological fMRI study with delta-9-tetrahydrocannabinol. Eur Neuropsychopharmacol 23(12):1687–1697. https://doi.org/10.1016/j.euroneuro.2013.06.009

Brickenkamp R, Zillmer E (1998) The d2 test of attention, 1st U.S. Edn. eds Hogrefe and Huber, WA, Seattle

Broyd SJ, van Hell HH, Beale C, Yücel M, Solowij N (2016) Acute and chronic effects of cannabinoids on human cognition—a systematic review. Biol Psychiatry 79(7):557–567. https://doi.org/10.1016/j.biopsych.2015.12.002

Budney AJ, Moore BA, Vandrey RG, Hughes JR (2003) The time course and significance of cannabis withdrawal. J Abnorm Psychol 112(3): 393–402. https://doi.org/10.1037/0021-843X.112.3.393

Carretie L, Rios M, de la Gandara BS, Tapia M, Albert J, Lopez-Martin S et al (2009) The striatum beyond reward: caudate responds intensely to unpleasant pictures. Neuroscience 164(4):1615–1622. https://doi.org/10.1016/j.neuroscience.2009.09.031

Chang L, Yakupov R, Cloak C, Ernst T (2006) Marijuana use is associated with a reorganized visual-attention network and cerebellar hypoactivation. Brain 129(5):1096–1112. https://doi.org/10.1093/brain/awl064

Charlet K, Schlagenhauf F, Richter A, Naundorf K, Dornhof L, Weinfurtner CE et al (2014) Neural activation during processing of aversive faces predicts treatment outcome in alcoholism. Addict Biol 19(3):439–451. https://doi.org/10.1111/adb.12045

Cheetham A, Allen NB, Yücel M, Lubman DI (2010) The role of affective dysregulation in drug addiction. Clin Psychol Rev 30(6):621–634. https://doi.org/10.1016/j.cpr.2010.04.005

Chye Y, Solowij N, Suo C, Batalla A, Cousijn J, Goudriaan AE, Martin-Santos R, Whittle S, Lorenzetti V, Yücel M (2017a) Orbitofrontal and caudate volumes in cannabis users: a multi-site mega-analysis comparing dependent versus non-dependent users. Psychopharmacology (Berli) e-pub ahead of print 1 April 2017; doi:https://doi.org/10.1007/s00213-017-4606-9

Chye Y, Solowij N, Ganella EP, Suo C, Yücel M, Batalla A, Cousijn J, Goudriaan AE, Martin-Santos R, Whittle S, Bartholomeusz CF, Lorenzetti V (2017b) Role of orbitofrontal sulcogyral pattern on lifetime cannabis use and depressive symptoms. Prog Neuro-Psychopharmacol Biol Psychiatry 79(Pt B):392–400. https://doi.org/10.1016/j.pnpbp.2017.07.017

Contreras-Rodriguez O, Albein-Urios N, Vilar-Lopez R, Perales JC, Martinez-Gonzalez JM, Fernandez-Serrano MJ et al (2016) Increased corticolimbic connectivity in cocaine dependence versus pathological gambling is associated with drug severity and emotion-related impulsivity. Addict Biol 21:709–718

Cousijn J, Wiers RW, Ridderinkhof KR, van den Brink W, Veltman DJ, Porrino LJ, Goudriaan AE (2013) Individual differences in decision making and reward processing predict changes in cannabis use: a prospective functional magnetic resonance imaging study. Addict Biol 18(6):1013–1023. https://doi.org/10.1111/j.1369-1600.2012.00498.x

Cousijn J, Wiers RW, Ridderinkhof KR, van den Brink W, Veltman DJ, Goudriaan AE (2014) Effect of baseline cannabis use and working-memory network function on changes in cannabis use in heavy cannabis users: a prospective fMRI study. Hum Brain Mapp 35(5): 2470–2482. https://doi.org/10.1002/hbm.22342

Crawford JR, Henry JD (2004) The positive and negative affect schedule (PANAS): construct validity, measurement properties and normative data in a large non-clinical sample. Br J Clin Psychol 43(3):245–265. https://doi.org/10.1348/0144665031752934

Cunningham WA, Kesek A, Mowrer SM (2009) Distinct orbitofrontal regions encode stimulus and choise valuation. J Cogn Neurosci 21(10):1956–1966. https://doi.org/10.1162/jocn.2008.21148

Di Martino A, Scheres A, Marguelies DS, Kelly AM, Uddin LQ, Shehzad Z et al (2008) Functional connectivity of the human striatum: a resting state FMRI study. Cereb Cortex 18(12):2735–2747. https://doi.org/10.1093/cercor/bhn041

Elliott R, Agnew Z, Deakin JF (2010) Hedonic and informational functions of the human orbitofrontal cortex. Cereb Cortex 20(1):198–204. https://doi.org/10.1093/cercor/bhp092

European Monitoring Centre for Drugs and Drug Addiction (2016) European Drug Report: Trends and Developments. http://www.emcdda.europa.eu/system/files/publications/2637/TDAT16001ENN.pdf

Everitt BJ, Robbins TW (2013) From ventral to the dorsal striatum: devolving views of their roles in drug addiction. Neurosci Biobehav Rev 37(9):1946–1954. https://doi.org/10.1016/j.neubiorev.2013.02.010

Everitt BJ, Robbins TW (2016) Drug addiction: updating to actions to habits to compulsions ten years on. Annu Rev Psychol 67(1):23–50. https://doi.org/10.1146/annurev-psych-122414-033457

Filbey F, Yezhuvath U (2013) Functional connectivity in inhibitory control networks and severity of cannabis uses disorder. Am J Drug Alcohol Abuse 39(6):382–391. https://doi.org/10.3109/00952990.2013.841710

Ganzer F, Bröning S, Kraft S, Sack PM, Thomasius R (2016) Weighing the evidence: a systematic review on long-term neurocognitive effects of cannabis user in abstinent adolescents and adults. Neuropsychol Rev 26(2):186–222. https://doi.org/10.1007/s11065-016-9316-2

Gates PJ, Sabioni P, Copeland J, Le Foll B, Gowing L (2016) Psychosocial interventions for cannabis use disorder. Cochrane Database Syst Rev 5:CD005336. https://doi.org/10.1002/14651858.CD005336.pub4

George O, Koob GF (2010) Individual differences in prefrontal cortex function and the transition from drug use to drug dependence. Neurosci Biobehav Rev 35(2):232–247. https://doi.org/10.1016/j.neubiorev.2010.05.002

Gremel CM, Costa RM (2013) Orbitofrontal and striatal circuits dynamically encode the shift between goal-directed and habitual actions. Nat Commun 4:2264. https://doi.org/10.1038/ncomms3264

Gremel CM, Chancey JH, Atwood BK, Luo G, Neve R, Ramakrishnan C, Deisseroth K, Lovinger DM, Costa RM (2016) Endocannabinoid modulation of orbitofrontal circuits gates habit formation. Neuron 90(6):1312–1324. https://doi.org/10.1016/j.neuron.2016.04.043

Gruber SA, Rogowska J, Yurgelun-Todd DA (2009) Altered affective response in marijuana smokers: an fMRI study. Drug Alcohol Depend 105(1-2):139–153. https://doi.org/10.1016/j.drugalcdep.2009.06.019

Hayes DJ, Duncan NW, Xu J, Northoff G (2014) A comparison of neural responses to appetitive and aversive stimuli in humans and other mammals. Neurosci Biobehav Rev 45:350–368. https://doi.org/10.1016/j.neubiorev.2014.06.018

Heitzeg MM, Cope LM, Martz ME, Hardee JE, Zucker RA (2015) Brain activation to negative stimuli mediates a relationship between adolescent marijuana use and later emotional functioning. Dev Cogn Neurosci 16:71–83. https://doi.org/10.1016/j.dcn.2015.09.003

Jacobus J, Squeglia LM, Escobar S, McKenna BM, Hernandez MM, Bagot KS et al (2017) Changes in marijuana use symptoms and emotional functioning over 28-days of monitored abstinence in adolescent marijuana users. Psychopharmacology (Berl.) e-pub ahead of print 12 September 2017; doi:https://doi.org/10.1007/s00213-017-4725-3

Jarbo K, Verstynen TD (2015) Converging structural and functional connectivity of orbitofrontal, dorsolateral prefrontal, and posterior parietal cortex in the human striatum. J Neurosci 35(9):3865–3878. https://doi.org/10.1523/JNEUROSCI.2636-14.2015

Jenkinson M, Bannister P, Brady M, Smith S (2002) Improved optimization for the robust and accurate linear registration and motion correction of brain images. NeuroImage 17(2):825–841. https://doi.org/10.1006/nimg.2002.1132

Lawrence NS, Jollant F, O'Daly O, Zelaya F, Phillips ML (2009) Distinct roles of prefrontal cortical subregions in the Iowa Gambling Task. Cereb Cortex 19(5):1134–1143. https://doi.org/10.1093/cercor/bhn154

Lee D, Schroeder JR, Karschner EL, Goodwin RS, Hirvonen J, Gorelick DA, Huestis MA (2014) Cannabis withdrawal in chronic, frequent cannabis smokers during sustained abstinence within a closed residential environment. Am J Addict 23(3):234–242. https://doi.org/10.1111/j.1521-0391.2014.12088.x

Liu X, Hairston J, Schrier M, Fan J (2011) Common and distinct networks underlying reward valence and processing stages: a meta-analysis of functional neuroimaging studies. Neurosci Biobehav

Rev 35(5):1219–1236. https://doi.org/10.1016/j.neubiorev.2010.12.012

Luijten M, Schellekens AF, Kühn S, Machielse MW, Sescousse G (2017) Disruption of reward processing in addiction: an image-based analysis of functional magnetic resonance imaging studies. JAMA Psychiatry e-pub ahead of print 1 April 2017; doi:https://doi.org/10.1001/jamapsychiatry.2016.3084

Mackie K (2008) Cannabinoid receptors: where they are and what they do. J Neuroendocrinol 20(Suppl 1):10–14. https://doi.org/10.1111/j.1365-2826.2008.01671.x

Martin GW, Wilkinson DA, Kapur BM (1988) Validation of self-reported cannabis use by urine analysis. Addict Behav 13(2):147–150. https://doi.org/10.1016/0306-4603(88)90004-4

Martín-Santos R, Fagundo AB, Crippa JA, Atakan Z, Bhattacharyya S, Allen P, Fusar-Poli P, Borgwardt S, Seal M, Busatto GF, McGuire P (2010) Neuroimaging in cannabis use: a systematic review of the literature. Psychol Med 40(03):383–398. https://doi.org/10.1017/S0033291709990729

McGilveray IJ (2005) Pharmacokinetics of cannabinoids. Pain Res Manag 10:15–22

McLaren DG, Ries ML, Xu G, Johnson SC (2012) A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standard approaches. NeuroImage 61(4):1277–1286. https://doi.org/10.1016/j.neuroimage.2012.03.068

Metzler P, Schmidt KH (1992) Wortschatztest (WST). Beltz Test GmbH, Weinheim

Nestor L, Hester R, Garavan H (2010) Increased ventral striatal BOLD activity during non-reward anticipation in cannabis users. NeuroImage 49(1):1133–1143. https://doi.org/10.1016/j.neuroimage.2009.07.022

Ochsner KN, Gross JJ (2005) The cognitive control of emotion. Trends Cogn Sci 9(5):242–249. https://doi.org/10.1016/j.tics.2005.03.010

Phillips ML, Williams LM, Heining M, Herba CM, Russell T, Andrew C, Bullmore ET, Brammer MJ, Williams SCR, Morgan M, Young AW, Gray JA (2004) Differential neural responses to overt and covert presentations of facial expressions of fear and disgust. NeuroImage 21(4):1484–1496. https://doi.org/10.1016/j.neuroimage.2003.12.013

Phillips ML, Ladouceur CD, Drevets WC (2008) A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. Mol Psychiatry 829:833–857

Pruim RH, Mennes M, van Rooij D, Llera A, Buitelaar JK, Beckmann CF (2015) ICA-AROMA: a robust ICA-based strategy for removing motion artifacts from fMRI data. NeuroImage 112:267–277. https://doi.org/10.1016/j.neuroimage.2015.02.064

Rabinak CA, Sripada CS, Angstadt M, de Wit H, Phan KL (2012) Cannabinoid modulation of subgenual anterior cingulate cortex activation during experience of negative affect. J Neural Transm (Vienna) 119(6):701–707. https://doi.org/10.1007/s00702-011-0747-x

Sabatinelli D, Fortune EE, Li Q, Siddiqui A, Krafft C, Oliver WT, Beck S, Jeffries J (2011) Emotional perception: meta-analyses of faces and natural scene processing. NeuroImage 54(3):2524–2533. https://doi.org/10.1016/j.neuroimage.2010.10.011

Schreiner AM, Dunn ME (2012) Residual effects of cannabis use on neurocognitive performance after prolonged abstinence: a meta-analysis. Exp Clin Psychopharmacol 20(5):420–429. https://doi.org/10.1037/a0029117

Schweinsburg AD, Nagel BJ, Schweinsburg BC, Park A, Theilmann RJ, Tapert SF (2008) Abstinent adolescent marijuana users show altered fMRI response during spatial working memory. Psychiatry Res 163(1):40–51. https://doi.org/10.1016/j.pscychresns.2007.04.018

Shenhav A, Barrett LF, Bar M (2013) Affective value and associative processing share a cortical substrate. Cogn Affect Behav Neurosci 13(1):46–59. https://doi.org/10.3758/s13415-012-0128-4

Simons J, Correia CJ, Carey KB (2000) A comparison of motives for marijuana and alcohol use among experienced users. Addict Behav 25(1):153–160. https://doi.org/10.1016/S0306-4603(98)00104-X

Smith SM (2002) Fast robust automated brain extraction. Hum Brain Mapp 17(3):143–155. https://doi.org/10.1002/hbm.10062

Smith DG, Simon Jones P, Bullmore ET, Robbins TW, Ersche KD (2014) Enhanced orbitofrontal cortex function and lack of attentional bias to cocaine cues in recreational stimulant users. Biol Psychiatry 75(2):124–131. https://doi.org/10.1016/j.biopsych.2013.05.019

Sneider JT, Pope HG Jr, Silveri MM, Simpson NS, Gruber SA, Yurgelun-Todd DA (2008) Differences in regional blood volume during a 28-day period of abstinence in chronic cannabis smokers. Eur Neuropsychopharmacol 18(8):612–619. https://doi.org/10.1016/j.euroneuro.2008.04.016

Somaini L, Manfredini M, Amore M, Zaimovic A, Raggi MA, Leonardi C, Gerra ML, Donnini C, Gerra G (2012) Psychobiological responses to unpleasant emotions in cannabis users. Eur Arch Psychiatry Clin Neurosci 262(1):47–57. https://doi.org/10.1007/s00406-011-0223-5

Stevens L, Verdejo-García A, Goudriaan AE, Roeyers H, Dom G, Vanderplasschen W (2014) Impulsivity as a vulnerability factor for poor addiction treatment outcomes: a review of neurocognitive findings among individuals with substance use disorders. J Subst Abus Treat 47(1):58–72. https://doi.org/10.1016/j.jsat.2014.01.008

Tanaka SC, Doya K, Okada G, Ueda K, Okamoto Y, Yamawaki S (2004) Prediction of immediate and future rewards differentially recruits cortico-basal ganglia loops. Nat Neurosci 7(8):887–893. https://doi.org/10.1038/nn1279

Tapert SF, Schweinsburg AD, Drummond SP, Paulus MP, Brown SA, Yang TT et al (2007) Functional MRI of inhibitory processing in abstinent adolescent marijuana users. Psychopharmacology 194(2):173–183. https://doi.org/10.1007/s00213-007-0823-y

United Nations Office on Drugs and Crime (2016) World Drug Report. http://www.unodc.org/doc/wdr2016/WORLD_DRUG_REPORT_2016_web.pdf

Van den Brink W (2012) Evidence-based pharmacological treatment of substance use disorders and pathological gambling. Curr Drug Abuse Rev 5(1):3–31. https://doi.org/10.2174/1874473711205010003

Verdejo-García A, Bechara A, Recknor EC, Pérez-García M (2006) Executive dysfunction in substance dependent individuals during drug use and abstinence: an examination of the behavioral, cognitive and emotional correlates of addiction. J Int Neuropsychol Soc 12(3):405–415

Volkow ND (2004) The reality of comorbity: depression and drug abuse. Biol Psychiatry 56(10):714–717. https://doi.org/10.1016/j.biopsych.2004.07.007

Weierich MR, Wright CI, Negreira A, Dickerson BC, Barrett LF (2010) Novelty as a dimension in the affective brain. NeuroImage 49(3):2871–2878. https://doi.org/10.1016/j.neuroimage.2009.09.047

Wesley MJ, Lile JA, Hanlon CA, Porrino LJ (2016) Abnormal prefrontal cortex activity in heavy cannabis users during conscious emotional evaluation. Psychopharmacology 233(6):1035–1044. https://doi.org/10.1007/s00213-015-4180-y

Wetherill RR, Childress AR, Jagannathan K, Bender J, Young KA, Suh JJ, O'Brien CP, Franklin TR (2014) Neural responses to subliminally presented cannabis and other emotionally evocative cues in cannabis-dependent individuals. Psychopharmacology 231(7):1397–1407. https://doi.org/10.1007/s00213-013-3342-z

Wittchen HU, Zaudig M, Fydrich T (1997) Strukturiertes Klinisches Interview für DSM-IV. Achse I und II. Hogrefe, Göttingen

Zimmermann K, Walz C, Derckx RT, Kendrick KM, Weber B, Dore B, Ochsner KN, Hurlemann R, Becker B (2017) Emotion regulation deficits in regular marijuana users. Hum Brain Mapp 38(8):4270–4279. https://doi.org/10.1002/hbm.23671