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CHAPTER 7

NEURAL MECHANISMS OF DECISION-MAKING & FUTURE CANNABIS USE

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ABSTRACT

Decision-making deficits are thought to play an important role in the development and persistence of substance use disorders. Individual differences in decision-making and the underlying neurocircuitry may therefore constitute an important predictor for the course of substance use and the development of substance use disorders. Here, we investigated the predictive value of decision-making and the underlying neural mechanisms for future cannabis use and problem severity in a sample of heavy cannabis users. Brain activity during a monetary decision-making task (Iowa Gambling Task) was compared between 32 heavy cannabis users and 41 matched non-using controls using functional magnetic resonance imaging. In addition, within the group of heavy cannabis users, associations were examined between task-related brain activations, cannabis use and cannabis use related problems at baseline, and change in cannabis use and problem severity after a six-month follow-up. Despite normal task performance, heavy cannabis users compared to controls showed higher activations during wins in core areas associated with decision-making. Moreover, within the group of heavy cannabis users, win-related activity and activity anticipating loss outcomes in areas generally involved in executive functions predicted change in cannabis use after six months. These findings are consistent with previous studies and point to abnormal processing of motivational information in heavy cannabis users. A new finding is that individuals who are biased towards immediate rewards have a higher probability of increasing drug use, highlighting the importance of the relative balance between motivational processes and regulatory executive processes in the development of substance use disorders.

INTRODUCTION

Decision-making is a complex multifaceted process. Coming to an appropriate decision requires the evaluation of possible positive and negative consequences, the capacity to retrieve this information from memory, and the capacity to maintain and manipulate the information 'online' (working-memory) (Paulus, 2005). However, the decision process is not simply a cost-benefit analysis as the consequences of decisions are often uncertain (Hsee and Hastie, 2006). Motivational processes also play an important role in guiding our decisions, (subconsciously) biasing them by maximizing reward while minimizing punishment (Naqvi et al., 2006; Paulus, 2005).

Substance use disorders (SUDs) are characterized by maladaptive decisions and motivational processes are often biased towards substance use (Koob and Volkow, 2010; Robinson and Berridge, 2003; Wiers et al., 2007). Indeed, substance-related cues tend to automatically grab attention, induce craving, activate approach tendencies, and are evaluated as more arousing than neutral cues (for reviews see Field et al., 2008; Stacy and Wiers, 2010). In addition, regulatory executive functions directed at minimizing punishment are often compromised. This imbalance between drug-oriented motivational processes and compromised regulatory processes may result in decisions guided by a strong incentive to use, despite awareness of the harmful consequences. Thus, decision-making deficits may play an important role in the development and persistence of SUDs. Indeed, decision-making deficits have been suggested to increase individuals' risk for SUDs and have been linked to relapse (Bowden-Jones et al., 2005; Koob and Volkow, 2010; Paulus et al., 2005).

A task repeatedly used to assess decision-making skills is the Iowa Gambling Task (IGT, originally developed by Bechara et al., 1994). The IGT is a monetary decision-making task that measures decision-making under risk, involving choices between small immediate gains with small long-term losses or large immediate gains with even larger long-term losses. Participants are instructed to select cards from four decks and maximize their profit. Two decks are disadvantageous, yielding large gains but even larger losses and thereby resulting in a net loss. The two other decks are advantageous as they yield small wins but even smaller losses, resulting in a net gain. Normative IGT data shows that healthy individuals start off choosing relatively disadvantageously, but as the task progresses they eventually learn the win/loss contingencies and choose more cards from the advantageous decks (Bechara et al., 1994). However, in patients with a SUD IGT performance is generally impaired (for a review see Buelow and Suhr, 2009).

Regarding cannabis use, decision-making has been found to be impaired in chronic cannabis users compared to healthy controls (Bolla et al., 2005; Fridberg et al., 2010; Wesley et al., 2011; Whitlow et al., 2004; but see Vaidya et al.., 2012) up to four weeks of monitored abstinence (Bolla et al., 2005). Moreover, a dose-related association between cannabis use and poorer IGT performance has been reported (Bolla et al., 2005). One study investigated decision-making in a

group of heavy cannabis users (Hermann et al., 2009). Although performance did not differ between heavy cannabis users and controls, a negative correlation was observed between IGT performance and Δ9-tetrahydrocannabinol (THC) concentration in hair (e.g., cumulative cannabis exposure). However, studies investigating the direct effects of cannabis on IGT performance indicate that IGT performance is relatively insensitive to the acute effects of cannabis intoxication (Ramaekers et al., 2006; Vadhan et al., 2007). Together, these findings suggest that there may be a certain threshold at which cannabis consumption impairs decision-making (e.g., decision-making may only be impaired in more chronic cannabis users).

Given the multifaceted nature of decision-making, the origin of the decision-making deficits could be diverse. The neurocircuitry underlying decision-making includes areas involved in working-memory [dorsolateral prefrontal cortex (DLPFC)], areas involved in the processing of internal and external affective information [insula, posterior cingulate cortex (PCC), ventral striatum, amygdala], and integration of affective and cognitive information [anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), ventromedial prefrontal cortex (VMPFC)] (Li et al., 2010; Paulus, 2005). However, only a limited number of studies have investigated the neural mechanisms underlying abnormal decision-making in chronic cannabis users (Bolla et al., 2005; Vaidya et al., 2012; Wesley et al., 2011). Consistently across these studies, and consistent with findings from other SUDs (Diekhof et al., 2008), chronic cannabis use was associated with abnormal functioning of the VMPFC. Moreover, VMPFC activity correlated with the duration of cannabis use (Vaidya et al., 2012). Decreased activity in DLPFC (Bolla et al., 2005) and ACC (Wesley et al., 2011) has also been reported. These minor inconsistencies may be explained by methodological differences between studies; Whereas Bolla et al. (2005) and Vaidya et al. (2012) compared activity during the IGT task with a control task, Wesley et al. (2011) specifically investigated win and loss evaluation during the strategy development phase of the IGT. Wesley's findings suggest that decision-making deficits in chronic cannabis users probably reflect low sensitivity to negative consequences.

Although cross-sectional IGT studies indicate that *chronic* cannabis use is associated with decision-making deficits, very little is known about the predictive relationship between decision-making and cannabis (ab)use. Given the suggested role of decision-making in the development of addictive behaviors, the aim of the present fMRI study was to investigate the predictive value of decision-making and neural mechanisms underlying decision-making for future cannabis use and problem severity in heavy cannabis users. Brain activity patterns anticipating advantageous versus disadvantageous decisions and following wins versus losses during the IGT were compared between a large sample of 32 heavy cannabis users and 41 matched controls. In addition, within the group of heavy cannabis users, we investigated the association between IGT-related activations and change in cannabis use and problem severity after six months. Compared to controls, we expected heavy cannabis users to perform worse on the IGT and show abnormal brain

activation patterns during decision-making. Given the proposed role of abnormal reward processing in SUD (Koob and Volkow, 2010) and that decision-making deficits in cannabis users probably reflect abnormal processing of rewards and losses (Fridberg et al., 2010; Wesley et al., 2011), we specifically expected differences in brain activation during wins and losses to predict changes in cannabis use and problem severity after six months.

MATERIALS AND METHODS

The present study was part of a prospective fMRI study investigating the role of neurocognitive and neuroimaging factors in the course of drug use in heavy cannabis users (Cousijn et al., 2012a; Cousijn et al., 2011; Cousijn et al., 2012b). In the current report only participants with complete IGT data are described. The medical ethical committee of the Academic Medical Centre of the University of Amsterdam approved the study and all participants signed informed consent prior to participation.

Table 1 Sample characteristics

	Heavy cannabis users		**Controls**	
	Baseline	Six-month follow-up	Baseline	Six-month follow-up
N (% female)	32 (34)	30 (33)	41 (37)	41 (37)
Age	21.4 (2.3)	21.9 (2.4)	22.2 (2.4)	22.7 (2.4)
Verbal IQ (Dutch Reading Test)	104.2 (5.5)	--	104.8 (7.4)	--
Alcohol use related problems (AUDIT)	6.1 (3.3)	5.8 (3.2)	5.1 (3.4)	4.9 (3.2)
Cigarette smoking (%)	69	63	17[a]	22[a]
Cigarettes per day	6.5 (6.9)	7.7 (7.0)	1.4 (3.6)[a]	1.3 (3.0)[a]
Nicotine dependence (FTND)	2.8 (2.4)	2.9 (2.5)	.5 (1.2)[a]	.6 (1.2)[a]
Cannabis use lifetime (# joints)	1611.2 (1436.8)	1627.3 (1345.9)	4.6 (9.3)	5.1 (10.2)
Cannabis use related problems (CUDIT)	12.2 (5.7)	9.4 (6.6)[b]	0 (0)	.2 (.5)
Duration heavy cannabis use (year)	2.5 (1.9)	2.9 (2.0)	--	--
Current cannabis use days/week	4.0 (1.5)	4.9 (2.1)	--	--
Current cannabis use gram/week	3.0 (2.3)	3.1 (3.1)	--	--

Means (SD). [a] $p < .001$ for group comparison. [b] $p < .05$ baseline follow-up comparison. SD: standard deviation. AUDIT: Alcohol Use Disorder Identification Test. FTND: Fagerström Test for Nicotine Dependence. CUDIT: Cannabis Use Disorder Identification Test.

Participants

Thirty-two heavy cannabis users and forty-one controls aged 18-25 were recruited through advertisements on the Internet and in cannabis outlets (coffee shops). Groups were matched for age, gender, education, estimated intelligence (Schmand et al., 1991), and alcohol use (Saunders et al., 1993), see Table 1. Heavy cannabis use was defined as using cannabis more than 10 days per month for at least two years and not seeking treatment or having a treatment history for cannabis use. Given their level of cannabis use, age, and that they did not (yet) request treatment, these individuals are at an increased risk for escalating cannabis use. Participants in the control group had smoked less than 50 cannabis joints lifetime and had not used during the last year (5 controls used more than 10 joints lifetime). Drug and alcohol use was controlled for by excluding participants with an Alcohol Use Disorder Identification Test score higher than 10 (AUDIT, Saunders et al., 1993), smoking more than 20 cigarettes daily, a positive urine screen for alcohol, amphetamines, benzodiazepines, opioids or cocaine, or using non-cannabinoid drugs in total on more than 100 occasions (7 participants > 10 occasions, no participant > 25 occasions). Other exclusion criteria were general MRI-contraindications, major physical disorders, and psychiatric disorders, which were assessed with the Mini-International Neuropsychiatric Interview (MINI, Dutch version 5.0.0, Sheehan et al., 1998). All participants were asked to refrain from alcohol and drug use (except for nicotine and caffeine) in the 24-hours before testing (mean self-reported abstinence of cannabis use in heavy users was 1.6 days, SD = 2.2). Although urine analysis of THC metabolites is insensitive to 24-hour abstinence, it increases accuracy of self-reported substance-use (Roese and Jamieson, 1993). The urine samples were taken to control for recent illicit substance use (all heavy cannabis users scored positive for cannabis use and all controls scored negative). Testing took place in late afternoon. Participants received 50 Euro for completing the baseline test-session and 25 Euro for completing the follow-up.

Questionnaires at baseline and follow-up

Problem severity of cannabis use during the last six months was assessed with the Cannabis Use Disorder Identification Test (CUDIT, Adamson and Sellman, 2003). The CUDIT is a screening-instrument for at-risk cannabis use and consists of 10 items on cannabis use-frequency and severity of use-related problems. Severity of nicotine dependence during the last six months was measured with the Fagerström Test for Nicotine Dependence (FTND, Heatherton et al., 1991). In addition, a detailed history on past and present cannabis and nicotine use was taken. After six months participants were contacted for a telephone interview on present drug use and related problems using the same questionnaires.

IGT

Participants performed an fMRI-optimized IGT task during which fMRI-BOLD responses were recorded. The task was identical to the one described by Wesley et al. (2011). During the tasks, participants viewed four decks of cards (A, B, C, D) and were instructed to select cards from any of these decks. After selecting a card they would either win or lose some money. The ultimate goal was to win as much money as possible but avoid losing money. Participants were explicitly instructed that some decks were worse than others and that they could win the most if they stayed away from the worse decks (for a detailed description of the task see Wesley et al., 2011). Thereby emphasis was placed on the role of losses in correctly performing the IGT. Deck A and B resulted in immediate gains of 100 Euro with losses ranging from 250 to 1200 Euro, whereas deck C and D resulted in immediate gains of 50 Euro with losses ranging from 50 to 250 Euro. Deck A and B would eventually lead to a net loss and were therefore considered disadvantageous. Deck C and D would lead to a net gain and were considered advantageous. Participants performed three separate IGT sessions, each consisting of 45 gamble trials and 13 control trials presented in a randomized order. As participants are unaware of the win/loss contingencies of the task, the first session probably assesses decision-making under ambiguity whereas the two later sessions probably assess decision-making under risk (Brand et al., 2007). As real money as opposed to virtual money may increase motivation and performance (Fernie and Tunney, 2006), participants were informed that the individual that performed the best would receive a 50 Euro bonus. Each gamble trial participants viewed the instruction 'select a card' for a fixed period of 2 s during which they had to select a card form any deck. Participants could indicate their choice by pressing a corresponding response-box button. Immediately after this 2 s decision phase participants received feedback on the amount of money won and lost during the trial and the total money won or lost during the previous trials. This evaluation phase of the trial lasted on average 2 s (jittered between 1 and 3 s). On control trials, instructions were to select a specific card as usual after which the feedback 'you neither win nor lose' was given. These control trials require the same sensorimotor actions but no decisions. The task was projected on a screen viewed through a mirror attached to the MRI head coil. Mean time to complete the three sessions was 15 minutes. Prior to scanning the participants shortly practiced the task outside the scanner.

Imaging parameters and data pre-processing

A 3T MRI scanner (Philips Intera, Best, The Netherlands) with a phased array SENSE RF eight-channel receiver head coil was used for image acquisition. At the start of each scan-session a T1 structural image was acquired (T1 turbo field echo, TR 9.6 s, TE 4.6 ms, 182 slices, slice thickness 1.2 mm, FOV 256 x 256 mm, in-plane resolution 256 x 256 mm, flip angle 8°). During the IGT task, BOLD signal was measured with a T2* weighted gradient-echo EPI sequence (TR 2.29 s, TE 30 ms, 38 slices, slice thickness 3 mm, interslice gap .3 mm, FOV 220 x 220 mm, in-plane resolution 96 x

96 mm, flip angle 80°). Data pre-processing was conducted with FEAT (FMRI Expert Analysis Tool) version 4.1, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). First, non-brain tissue and skull was removed with BET (Brain Extraction Tool). Per participant per session images were slice-time aligned, motion corrected, high-pass filtered in the temporal domain (sigma=100s), spatially smoothed with a 5 mm full-with-half-maximum Gaussian kernel, and prewhitened (Woolrich et al., 2001). Next, functional data were registered to the participants' structural image and transformed to MNI space (Montreal Neurological Institute) using FLIRT (FMRIB's Linear Image Registration Tool).

Statistical analysis

Demographics and behavior: Demographics, scores on questionnaires (for an overview of these variables see Table 1), and IGT behavioral performance were compared between groups with standard univariate analysis of variance procedures in SPSS for Windows (v.16.0). IGT behavioral performance was assessed in terms of a net performance score of advantageous minus disadvantageous choices per session, a total net performance score over sessions, and an improvement score over sessions (net score session 3 - net score session 1). Thereby a positive net score indicated more advantageous compared to disadvantageous choices and a positive improvement score indicated more advantageous choices in the third session compared to the first session. Within the group of heavy cannabis users Pearson correlations were calculated to investigate associations between IGT behavioral performance and measures of baseline cannabis use, baseline cigarette smoking, change in weekly use (follow-up grams per week - baseline grams per week), and change in problem severity (follow-up CUDIT - baseline CUDIT).

fMRI: fMRI time-series analysis was carried out with FILM (FMRIB's Improved Linear Model) with local autocorrelation correction. The three IGT sessions were first analyzed separately per participant. Explanatory variables were created for advantageous choices (first 2 s of C/D deck selection trials), disadvantageous choices (first 2 s of A/B deck selection trials), win evaluation (feedback phase of win trials), loss evaluation (feedback phase of loss trials), and control trials by convolving timing parameters with a double gamma hemodynamic response function. Second, the three IGT sessions were pooled with a fixed-effects analysis to calculate the participants mean response over sessions. Higher-level group analyses of contrast-images were conducted using FLAME (FMRIB's local analysis of mixed effects) stages 1 and 2. Primary contrasts of interest were advantageous versus disadvantageous decisions and win versus loss evaluations (bidirectional). These contrasts enable investigation of the relationship between measures of cannabis use and neural activation patterns associated with decision-making and reward/punishment sensitivity. Additionally, the decision versus control trials contrast was investigated for descriptive purposes.

Activity was considered significant if $Z > 2.3$, with a whole-brain cluster correction at $p < .05$ (Worsley et al., 1992). Clusters of activation were localized with the Talairach Daemon database implemented in FSL and the LONI probability atlas (Shattuck et al., 2008).

IGT activation patterns were first compared between heavy cannabis users and controls. Second, within heavy cannabis users, multiple regression analyses were performed to investigate associations between activation patterns and history of cannabis use, using baseline weekly use (grams), lifetime use (number of joints), duration of heavy use (years), and baseline problem severity (CUDIT) as dependent variables. Third, to assess possible confounding effects of nicotine use, associations between IGT activation patterns and FTND scores and cigarettes per day were investigated and smoking heavy users were compared to non-smoking heavy users. Fourth, multiple regression analyses were performed to investigate associations between IGT activation patterns at baseline and change in cannabis use and problem severity after six months, using change in weekly use (follow-up grams per week - baseline grams per week) and change in problem severity (follow-up CUDIT - baseline CUDIT) as dependent variables. For descriptive purposes activation in significant clusters was quantified for each participant by extracting the percent BOLD signal change for the advantageous versus disadvantageous and win versus loss contrast with Featquery (implemented in FSL).

RESULTS

IGT behavioral performance

Participants correctly selected a card 95 % of the trials (range = 73-99 %) with no difference between groups. Mean reaction times (RTs) did not differ between groups (t_{71}= .07, p = .94). Net performance scores (number of advantageous – disadvantageous decisions) were analyzed using a mixed ANOVA with Group as between-subject factors and IGT session as within subject factor with three levels. There was a main effect of session, $F_{2,70}$ = 6.24, p = .003, η^2 = .15, but this effect did not differ between Groups, $F_{2,70}$ = .78 , p = .61, indicating a significant shift towards more advantageous decisions in both heavy cannabis users and controls over time (mean improvement score session 1 to 2: cannabis users = 9.7, SD = 21.6; controls = 4.2, SD = 17.2, t_{71} = 1.22, p = .23; session 1 to 3: cannabis users = 10.4, SD = 24.9; controls = 6.7, SD = 16.5, t_{71} = .76, p = .45; Figure 1). However, post-hoc analysis showed that the net score of the final session in both groups did not significantly deviate from zero (cannabis users, t_{31} = .63, p = .54; controls, t_{40} = .34, p = .74).

Within the group of cannabis users, total net score over sessions and improvement score did not significantly correlate with measures of cannabis use and cigarette smoking ($r < .25$, $p > .16$) at baseline, change in weekly cannabis use after six months ($r < .20$, $p > .30$), and change in cannabis problem severity after six months ($r < .17$, $p > .38$).

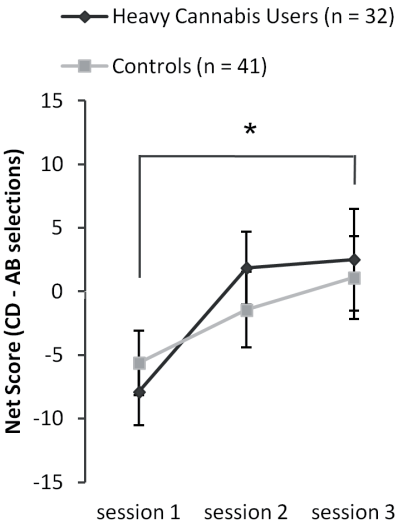

Figure 1 IGT behavioral performance is expressed in a net score of advantageous selections (deck CD) minus disadvantageous selections (deck AB) per session in heavy cannabis users and controls. Performance improved over sessions: both groups made more advantageous selections in the third session compared to the first session (* $p < .05$).

IGT fMRI

Baseline: Heavy cannabis users showed significantly higher activity related to win versus loss evaluation in the right OFC, right insula, and left superior temporal gyrus compared to controls (Figure 2, Table 2, see Supplementary Figure 1 for IGT main effect per group). No significant group differences were observed for loss versus win evaluations, advantageous versus disadvantageous decisions, disadvantageous versus advantageous decisions, and all decisions versus control trials.

Within the group of heavy cannabis users, a significant positive relation was observed between weekly cannabis use (grams) and activity related to win versus loss evaluation in the right insula, right caudate, and right VLPFC (Figure 3a, Table 2). No significant relations were found between IGT activation patterns and baseline problem severity, lifetime cannabis use, or duration of heavy cannabis use.

Heavy cannabis users scored higher on measures of nicotine use (percentage smokers, X^2 = 20.05, $p < .001$; cigarettes per day, $t_{71} = 4.10$, $p < .001$) and nicotine dependence (FTND, $t_{71} = 5.38$, $p < .001$; Table 1). However, IGT activation patterns did not differ between smoking and non-smoking heavy cannabis users and were not associated with nicotine dependence.

Association change in cannabis use and problems after six months: Six months after baseline a 97 % follow-up rate was achieved (two non-responders among the heavy cannabis users). Average cannabis problem severity significantly decreased in heavy cannabis users ($t_{29} = 2.23$, $p = .034$; Table 1). Weekly cannabis use and measures of alcohol and nicotine use did not change in heavy cannabis users or controls (Table 1). During the past six months, none of the heavy cannabis users sought treatment for their cannabis use.

Within the group of heavy cannabis users, increased activity related to disadvantageous versus advantageous decisions in the bilateral lateral frontal pole and bilateral middle and superior temporal gyrus was associated with an increase in weekly cannabis use. Similarly, higher activity related to win versus loss evaluation in the right superior frontal gyrus (SFG) was associated with an increase in weekly cannabis use. However, IGT activation patterns were not significantly associated with change in problem severity.

Table 2 IGT activation patterns: group differences and associations baseline and future cannabis use in heavy cannabis users.

Clustersize (voxels)	Brain region	Hemisphere	MNI coordinates			Z_{max}
			x	*y*	*z*	
Heavy cannabis users > controls						
Win > Loss evaluation						
545	Orbitofrontal cortex	R	38	24	-10	3.93
	Insula	R	38	14	-2	3.52
539	Posterior superior temporal gyrus	L	-48	-36	10	3.47
Within heavy cannabis users						
Positive association weekly use						
Win > Loss evaluation						
747	Insula	R	44	12	-8	3.89
	Caudate nucleus	R	12	14	12	3.54
799	Insula	R	32	18	6	4.14
	Ventrolateral prefrontal cortex	R	48	36	2	3.32
Positive association change weekly use						
Disadvantageous > Advantageous decisions						
1133	Lateral frontal pole	R	48	44	6	3.24
1431	Lateral frontal pole	L	-46	52	0	3.73
592	Middle temporal gyrus	R	54	-32	-8	3.61
1896	Middle temporal gyrus	L	-62	-48	-8	3.42
	Inferior temporal gyrus	L	-48	-58	-20	4.30
434	Inferior temporal gyrus	R	54	-60	-20	3.69
Win > Loss evaluation						
436	Superior frontal gyrus	R	4	32	52	4.31

L, left; R, right; MNI, Montreal Neurological Institute; MNI coordinates and *Z*-scores of local maxima are shown for each cluster; Statistical threshold: $Z > 2.3$, whole-brain cluster-corrected at $p < .05$.

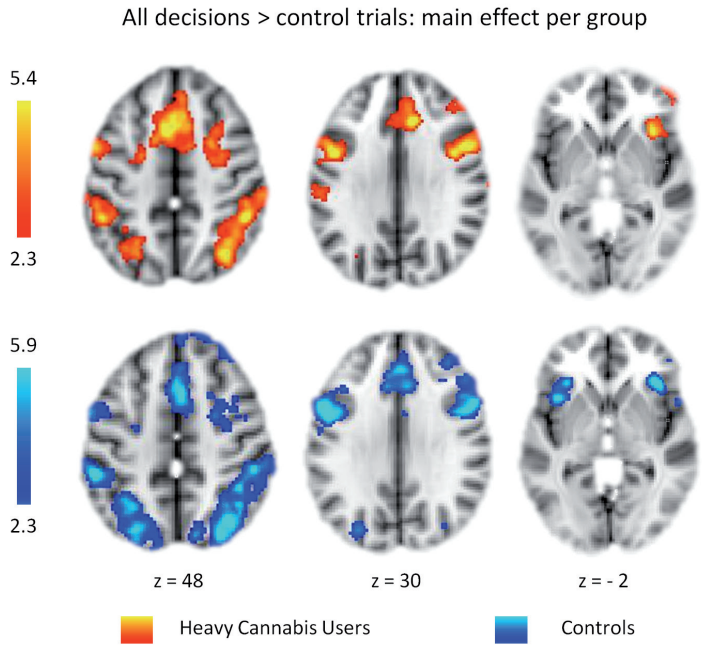

Figure 2 IGT-related activity (all decisions > control trials) in heavy cannabis users and controls. Clusters of significant activation ($Z > 2.3$, whole-brain cluster-corrected at $p < .05$) are overlaid on a standard MNI brain. Right side of the brain is depicted at right side.

DISCUSSION

The goal of the present study was to investigate the predictive value of decision-making and neural mechanisms underlying decision-making for future cannabis use and problem severity in heavy cannabis users. In contrast to our hypothesis, heavy cannabis users and controls performed equal on the IGT and IGT performance was not predictive of cannabis use or problem severity in the group of heavy cannabis users. Also, brain activations during the decision phase of the task did not differ between heavy cannabis users and controls. However, heavy cannabis users did show higher activation for win evaluation in core areas associated with decision-making (e.g., the right OFC and insula, and in the posterior part of the superior temporal gyrus). Moreover, within the group of heavy cannabis users, weekly cannabis use was positively associated with win related activity in the insula, VLPFC, and caudate. These findings are generally in line with previous studies (Bolla et al., 2005; Vaidya et al., 2012; Wesley et al., 2011) and indicate that although behavioral IGT performance in heavy cannabis users did not (yet) deviate from normal controls, they do show functional differences in the underlying neurocircuitry. In addition, higher win-related activity in

the SFG and higher activity during the anticipation of disadvantageous decisions in the frontal pole and ventral temporal lobe were found to be associated with an increase in cannabis use after six months. Thus, regional brain function during IGT performance could be an early risk indicator for increasing cannabis use, underscoring the importance of executive functions in the development and maintenance of SUD (Koob and Volkow, 2010; Wiers et al., 2007).

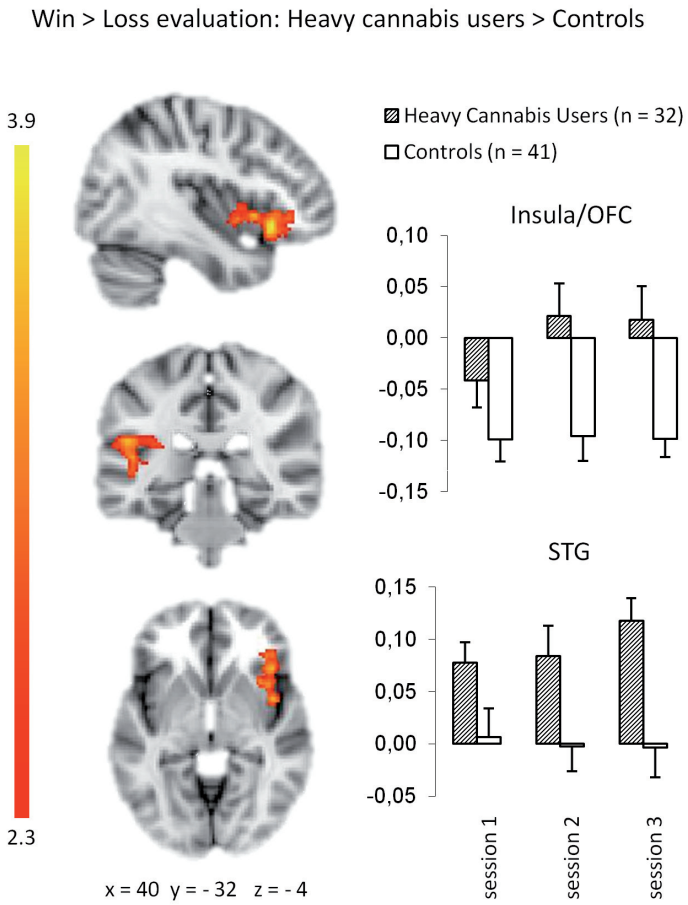

Figure 3 Clusters in right OFC, right insula, and left superior temporal gyrus in which heavy cannabis users showed higher activity related to win versus loss evaluation compared to controls. Clusters of significant activation (Z > 2.3, whole-brain cluster-corrected at p < .05) are overlaid on a standard MNI brain. Right side of the brain is depicted at right side.

On the group level, weekly cannabis use did not change whereas cannabis use related problems decreased after six months in the heavy cannabis users. This is in line with normative trajectories of cannabis use and abuse in young adults, as these tend to wax and then wane during the transition into adulthood (Schulenberg et al., 2005). There is great variability in the vulnerability to develop a SUD (Swendsen and Le Moal, 2011). Although heavy substance use is prerequisite, epidemiological studies estimated that only one out of ten heavy cannabis users develops a cannabis use disorder (Perkonigg et al., 2008). On the individual level, some of the heavy cannabis users in this study increased their cannabis use while some decreased or remained stable, indicating that heavy cannabis use is not necessarily associated with an eventual increase in cannabis use and cannabis related problems. The predictive relationship between IGT-related brain activations and change in cannabis use after six months suggests that these brain activation patterns may indicate which heavy cannabis users are especially at risk for increasing their cannabis use.

Interestingly, the predictive association between brain function and change in cannabis use appears to reflect individual differences in brain areas involved in more general cognitive/executive functions rather than specific to decision-making. Both the SFG and the lateral frontal pole are involved in working-memory (Du Boisgueheneuc et al., 2006; Koechlin, 2011), e.g., a central executive function involved in many different cognitive processes (Kane and Engle, 2002). The ventral part of the temporal lobe is mainly involved in higher order visual processing (Bullier, 2001). Indeed, a recent study in our lab showed that working-memory network function, including the frontal pole and superior frontal gyrus, also predicted cannabis use (Cousijn, Wiers, Goudriaan, submitted). Moreover, besides decision-making various other executive functions have been linked to the development and maintenance of SUDs (Grenard et al., 2008; Houben and Wiers, 2009; Thush et al., 2008). In the present study, activity during evaluation of wins compared to losses in the SFG and activity anticipating disadvantageous compared to advantageous decisions in the lateral frontal pole was positively related to degree of change in cannabis use between baseline and follow-up: higher activity was associated with an increase in cannabis use However, activity in these areas did not significantly differ from controls, suggesting that a stronger bias towards immediate rewards (e.g., a stronger difference in brain activations to wins relative to losses) during decision-making may generally predispose individuals to develop a SUD.

In line with previous studies (Bolla et al., 2005; Vaidya et al., 2012), the present findings also suggest a dose-related association between cannabis use and function of the decision-making neurocircuitry: weekly cannabis use was positively associated with activity in the insula, caudate, and VLPFC. This association and the observed group differences in the OFC, insula, and superior temporal gyrus were specific for reward evaluation relative to punishment, not for the phase anticipating a decision. Taking a close look at the core areas associated with decision-making, the insula is important for the translation of internal affective information into conscious experiences

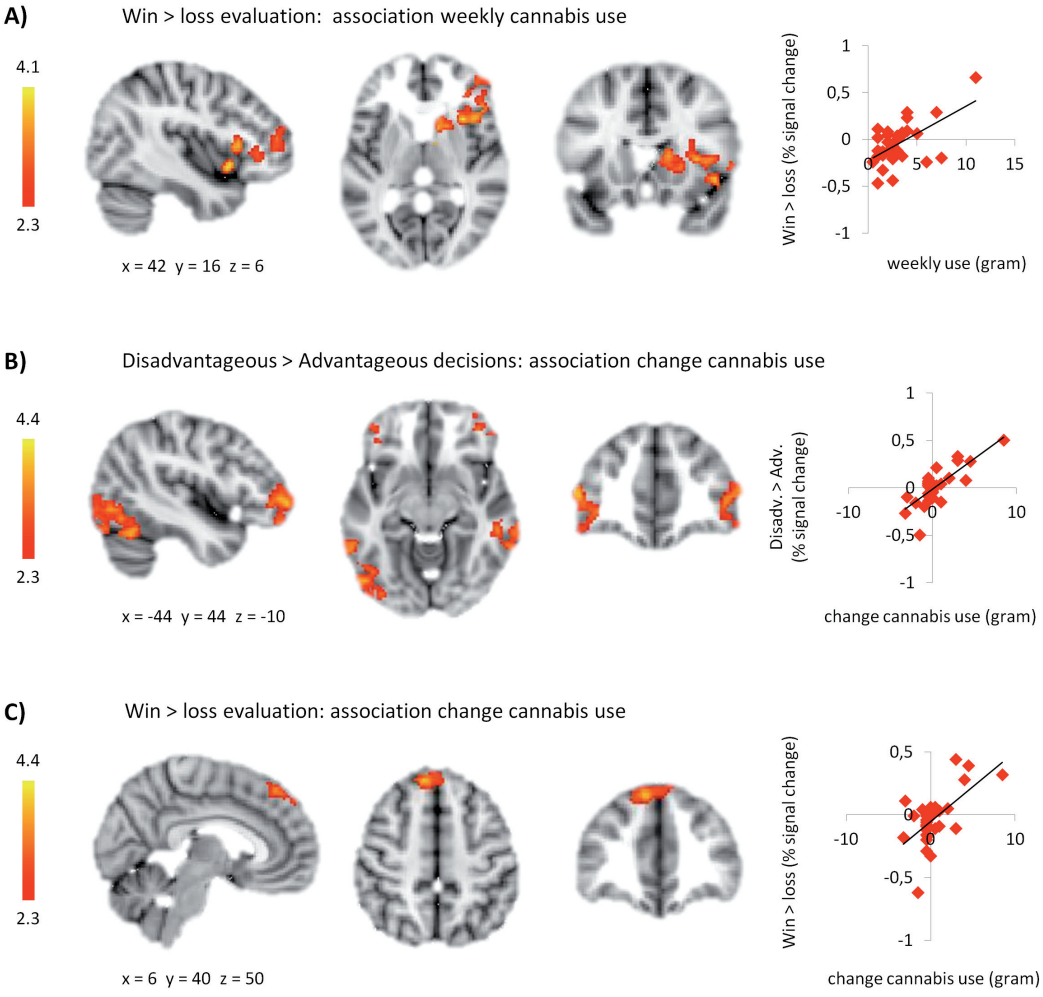

Figure 4 Relation between neural IGT activation patterns and individual characteristics of baseline and future cannabis use in heavy cannabis users. **(A)** Activity related to win versus loss evaluation in right insula, right caudate, and right VLPFC was positively associated with weekly cannabis use. **(B)** Activity related to disadvantageous versus advantageous decisions in bilateral frontal pole and bilateral middle and superior temporal gyrus was positively associated with change in weekly cannabis use. **(C)** Activity related to win versus loss evaluation in right superior frontal gyrus was positively associated with change in weekly cannabis use. Clusters of significant activation ($Z > 2.3$, whole-brain cluster-corrected at $p < .05$) are overlaid on a standard MNI brain. Right side of the brain is depicted at right side. Graphs show association average percent signal change extracted from significant clusters with dependent variable of interest.

like craving (Naqvi and Bechara, 2009), whereas the OFC involves reward evaluation and integrating affective information into the decision process (Koob and Volkow, 2010). The caudate is involved in reward prediction error (Haruno and Kawato, 2006). Thereby, in line with previous studies (Fridberg et al., 2010; Wesley et al., 2011), the present findings suggest that (chronic heavy) cannabis use may impair decision-making through influencing motivational processes rather than general executive processes.

Important to note, however, these inferences are post hoc. It cannot be concluded from the present data that cannabis indeed impairs the decision-making process. Also, although the IGT has been considered a reliable behavioral measure of risky decision-making the task may be too complex and coarse to investigate separate processes underlying decision-making (Buelow and Suhr, 2009). To specifically attribute decision-making deficits to abnormal motivational processes in cannabis users more studies are needed. Moreover, the present design cannot establish a causal relationship between brain function and change in cannabis use. Future longitudinal studies (preferably with a measurement before the onset of cannabis use) are needed to investigate the causal relation between brain function and SUDs.

Regarding IGT behavioral performance, chronic cannabis use has repeatedly been associated with impaired decision-making (Bolla et al., 2005; Fridberg et al., 2010; Wesley et al., 2011; Whitlow et al., 2004). Moreover, quantitative cannabis use appears to be inversely associated with IGT performance (Bolla et al., 2005; Hermann et al., 2009). However, similarly to a behavioral IGT study in heavy cannabis users not seeking treatment (Hermann et al., 2009), IGT performance in the present group of heavy cannabis users did not deviate from controls. The level of IGT performance indicated that both groups did not learn over time that the CD decks were the advantageous decks, indicating a relatively disadvantageous choice strategy in both groups. Compared to studies in chronic cannabis users, the heavy cannabis users in the present study and in the study of Hermann et al. (2009), which both reported similar performance in cannabis groups and control groups, were relatively young and duration of heavy cannabis use was relatively short, supporting the idea that there is a threshold at which cannabis impairs decision-making.

Some potential limitations must be taken into account. First, there were more smokers among heavy cannabis users and almost all cannabis users (90 %) smoked cannabis combined with tobacco [by far the most common form of cannabis use in the Netherlands (Bennett, 2008)]. However, because the heavy cannabis users were relatively light smokers and nicotine use was not significantly associated with IGT performance or IGT related brain activity in heavy cannabis users, it is unlikely that nicotine use accounts for the observed effects. Moreover, post-hoc whole brain regression analyses with FTND-score as additional covariate showed that nicotine dependence did not affect the (predictive) relationship between brain activity and change in cannabis use (each cluster reported in Table 2 remained significant, MNI coordinates and Z-scores of local maxima were unaffected). Nonetheless, it may still be worthwhile to include a group of cannabis naive

cigarette smokers in future studies in order to better distinguish cannabis from nicotine effects. Second, abstinence among the heavy cannabis users was on average 1.6 days. Although IGT performance is relatively insensitive to the acute effects of cannabis intoxication (Ramaekers et al., 2006; Vadhan et al., 2007) this possibility cannot be fully excluded. Third, it should be noted that we excluded potential participants if they had a history of a psychiatric disorder; a less stringently selected but more ecologically valid group may display considerable co-morbid externalizing pathology. Therefore, the extent to which the results generalize to all heavy cannabis users remains to be tested. Finally, as sensitivity for (immediate) rewards has been found to be increased in individuals with a SUD (Reynolds, 2006), the heavy cannabis users may have been more motivated to perform the IGT in order obtain the 50 Euro bonus. This may have diminished the potential to find differences in responsiveness to rewards and losses between the cannabis users and the healthy control group.

In summary, the current fMRI study is the first to demonstrate a predictive relationship between decision-making related brain activation patterns and cannabis use in experienced cannabis users. Moreover, these heavy cannabis users processed wins differently in the brain compared to controls, despite a task performance equal to the control group. Together, these findings suggest that individuals who are strongly biased towards immediate rewards during decision-making may have a higher probability of increasing substance use. Furthermore, these findings emphasize the importance of reward and regulatory executive processes in SUDs.

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