Original Paper

Neuropsychobiology

Neuropsychobiology 2009;60:94–103
DOI: 10.1159/000239685

Received: December 12, 2008
Accepted after revision: June 23, 2009
Published online: September 21, 2009

Reduced Response to Reward in Smokers and Cannabis Users

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Key Words
Addiction · Cognitive performance · Mood · Dopamine · Smoking · Cannabis · Reward

Abstract
Background: Cannabis is one of the most commonly used illicit drugs. Reduced neural and behavioral reactions to reward have been demonstrated in other forms of addiction, as expressed by reduced mood reactivity and lack of striatal activation to rewards, but this effect has not yet been investigated in cannabis users. ***Methods:*** We hypothesized that cannabis users and tobacco smokers would evidence lower positive mood ratings in rewarded conditions than control participants and that this reduction would be greater in cannabis users than in smokers. We examined the influence of reward on mood and performance in a group of regular cannabis users, a group of tobacco smokers and a group of nonsmokers while they performed a spatial recognition task with delayed response that incorporated 3 levels of difficulty. Correct responses were either not reinforced or reinforced with money. We measured the accuracy of reactions, reaction times and mood ratings throughout the trials. ***Results:*** Cannabis users rated their mood as significantly worse than the smokers and nonsmokers during the easiest level of the rewarded condition. A significant positive correlation between mood ratings and monetary reward was found in the nonsmokers but not in the cannabis users and smokers. The groups did not differ with regard to task performance. ***Conclusions:*** Our results suggest that regular cannabis use affects certain aspects of motivation and that both tobacco smoking and cannabis use lead to similar motivational changes. However, the use of cannabis seems to affect motivation in a stronger way than does tobacco smoking alone.

Introduction

Cannabis is one of the most commonly used illicit drugs, and its effects are often considered less harmful than the effects of other illicit drugs [1]. However, recent work has showed that behavioral and physical cannabis dependence occurs in about 7–10% of regular users [2]. Furthermore, regular cannabis use seems to be associated with adverse effects on health and with the development or exacerbation of schizophrenia [1, 2]. Additionally, long-term heavy marijuana use is associated with impairment of memory, attention and decision-making [3, 4]. However, the consequences of cannabis use on motivation in humans have not yet been investigated.

There is a strong relationship between cannabis and tobacco use. When smoked, cannabis is mixed with to-

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bacco, so that the consumption of cannabis is often associated with tobacco smoking [5]. Epidemiological studies showed that adolescents who smoked cigarettes were 9–15 times more likely to use cannabis [6, 7]. Recently, a reverse association between cannabis and tobacco was demonstrated. Due to the use of tobacco along with marijuana in joints [8, 9], cannabis use was shown to impede the users' attempts to quit tobacco smoking and to increase the risk of nicotine dependence [8, 9].

The psychoactive substances contained in cannabis, i.e. delta-9-tetrahydrocannabinol (THC), and in tobacco, i.e. nicotine, both increase the dopamine (DA) transmission within the mesolimbic DA system, especially in the nucleus accumbens [10–15]. This mechanism is thought to be one of the common denominators between all substances of abuse [16–19]. Because the mesolimbic DA system is involved in the processing of reward information, it has been postulated that the reinforcing properties of psychoactive drugs could be mediated by this system [16–19]. The cerebral reward system involves a neural circuitry including, among others, the ventral striatum (nucleus accumbens), the amygdala and the orbitofrontal cortex [20–26], which also receives input from neurotransmitters other than DA, such as opioid peptide, gamma-aminobutyric acid and glutamate [27, 28]. Some regions of the reward system, like the ventral tegmental area and the nucleus accumbens, are anatomically interconnected with endogenous brain opioid systems that have a modulatory influence on them [29]. Another neurobiological mechanism common to addictive drugs is that opiate antagonists block or attenuate the enhanced brain reward response produced by these drugs [28, 29]. This effect was also demonstrated for THC. Animal studies showed that the opiate antagonist naloxone attenuated a THC-induced DA increase in the nucleus accumbens [14, 30, 31] and attenuated THC-enhanced DA synthesis [32]. Finally, opioid peptide antagonists significantly attenuated THC self-administration in rats and squirrel monkeys [33, 34].

Because substances of abuse affect reward mechanisms at a neurobiological level, it can be hypothesized that substance users treat rewarding information in a different way than nonusers. Therefore, reward processing offers a promising way to investigate the effects of cannabis use on motivational processes.

Reduced neural and behavioral reactions to reward have been demonstrated in smokers in previous positron emission tomography studies [35, 36]. The difference between smokers and nonsmokers primarily involved brain regions belonging to the mesolimbic DA system, especially the striatum, which was not activated at all by reinforcement in smokers. At a behavioral level, these studies showed that, in contrast to the nonsmokers, reward did not improve the mood ratings of the smokers. Furthermore, there was no correlation between the amount of the reward and the mood ratings of smokers, in contrast to nonsmokers. These results suggest that reward does not elicit the same positive feelings in smokers as in nonsmokers, due to the changes in the cerebral reward system induced by addiction. Similar results were found in a study of opiate addicts [37], leading to the conclusion that both types of addiction are associated with changes in the neural processing of reward. However, so far, no study has investigated the effect of regular cannabis use on reward processing, and the consequences of cannabis use on motivation are still unclear.

In this study, we investigated whether there was a reduced influence of monetary reward on the momentary mood, defined as the current subjective feelings of well-being, in cannabis users compared to nonsmokers and smokers. We used a spatial recognition test with 3 difficulty levels adapted from Glahn et al. [38]. Because monetary reinforcement has been shown to have a beneficial effect on performance in healthy participants [39], especially for easy tasks where increased effort can induce better performance [40], and because previous studies [41] showed that smokers evaluated the effort associated with a reinforced memory task as significantly greater than did controls, we decided to include a task with different levels of difficulty in order to test the complex relationship between reinforcement, difficulty and addiction. We included a group of smokers to control for the effect of nicotine use, because cannabis users are mostly smokers. Since previous studies evidenced a positive effect of reward on mood state and because this effect was weakened in smokers [35, 36], we expected a similar but stronger effect in cannabis smokers. We also hypothesized that cannabis users and tobacco smokers would display a reduction of the effect of monetary reward on mood when compared to control participants and that this reduction would be greater in cannabis users than in smokers. Furthermore, we expected the differences between the groups to be greater for the most difficult than for the easiest level of our task. More specifically, we expected no differences between the groups at the easiest level of difficulty, but we postulated that differences would emerge in the difficult conditions. Finally, we expected a significant association between mood ratings and monetary wins in the nonsmokers, but not in the tobacco smokers and cannabis users.

Methods

Participants

Fifty-three participants were included in the study: 19 nonsmokers, 20 smokers and 14 cannabis users. Subjects were recruited through advertisements at the University of Basel (Switzerland) and were all students. All subjects were right-handed. They were tested for neurological or medical disorders and for current medication with a short medical screening. Normal memory and attention performance were required for participation in the experiment; these were tested prior to the trials using the Spatial Recall Test [42] and the d2 test [43], respectively. There were no performance differences between the groups of participants for these tests (Spatial Recall Test: $F_{2, 50} = 0.55$, $p = 0.58$; d2 total score of correct responses: $F_{2, 50} = 0.79$, $p = 0.54$). Candidates with current depression were excluded using the Beck Depression Inventory (BDI) adapted from Beck et al. [44]. There were no significant differences in the depression scores between the groups ($F_{2, 50} = 1.17$, $p = 0.31$). Current and past drug dependence as well as history or presence of psychiatric disorders were assessed using the ICD-10 Symptom Checklist [45]. The severity of nicotine dependence was assessed prior to the testing using the Fagerström questionnaire [46]. We developed a questionnaire to assess cannabis use habits, which included items on the duration of cannabis use, number of joints smoked per week, time of the day when cannabis was used, use of other addictive substances and drug history. To be included in the study, smokers had to consume at least 10 cigarettes per day and had to fulfill the ICD-10 criteria for nicotine dependence. They were excluded if they used any other substance of abuse, including cannabis, or had a past or current history of drug dependence other than nicotine dependence. Cannabis users had to consume cannabis at least 5 times a week. The cannabis subject group used cannabis an average of 5.7 ± 0.7 (mean ± SD) times per week, mostly in the evening. Of the 14 cannabis users, 12 were regular smokers and 2 did not smoke, and none of them fulfilled the criteria for cannabis dependence or abuse according to ICD-10 criteria. They were excluded if they used any substance of abuse other than nicotine or cannabis and if they had a past or current history of drug dependence other than nicotine dependence. They were instructed not to use cannabis on the day of the study. General exclusion criteria were current use of psychopharmacological medication, current or past depression, history of psychiatric and neurological disorders as well as memory and attention performance below the normal range. In addition, nonsmokers were excluded if they had past or current drug dependence or had used any substance of abuse within the previous year. Sample demographics, including gender, age, years of education and BDI and Fagerström scores, as well as the frequency and duration of smoking, are summarized in table 1. The subject groups did not differ with regard to age ($F_{2, 52} = 0.21$, $p = 0.80$) or education ($F_{2, 52} = 0.27$, $p = 0.75$).

The participants were thoroughly informed about the study and gave written informed consent according to the Declaration of Helsinki.

Experimental Task

The participants performed a spatial delayed response task adapted from Glahn et al. [38], which was primarily designed to investigate which brain regions reacted to the systematic increase of cognitive load. The task was programmed using E-Prime software (version 1.1.3, Psychology Software Tools Inc., Pittsburgh, Pa., USA) and presented on a high-resolution color monitor (Samsung SyncMaster P750). The monitor resolution was 1,024 × 768 pixels, and the presentation of the stimuli was synchronized with the refresh rate of the monitor. The display was viewed from a distance of 50 cm. The task comprised 3 levels of difficulty, which were differentiated by the number of items (3, 5 or 7) to be remembered (fig. 1). There were 2 feedback conditions: a rewarded and a baseline condition. All participants had to perform the task with the 3 levels of difficulty under the 2 feedback conditions. The order of feedback conditions was counterbalanced across participants. During the rewarded condition, the participants could earn a monetary reward for every correct response. The monetary reward increased according to the difficulty of the task, i.e. CHF 0.50 (approximately USD 0.40) in the block with 3 circles, CHF 1 (approximately USD 0.80) in the block with 5 circles and CHF 2 (approximately USD 1.60) in the block with 7 circles. Each level of difficulty comprised 12 trials. The participants were informed that they would receive the sum shown at the end of the trials. The maximum reward that could be won was CHF 42 (approximately USD 35). Before the main experiment started, participants underwent a training phase in which they had to achieve at least 70% correct responses to proceed to the main task. The criterion of 70% was chosen to prevent arbitrary guessing and thereby verify understanding of the task.

There was a break of 10 min between the 2 conditions, during which the smokers could smoke 1 cigarette before continuing the trials in order to avoid withdrawal symptoms that could affect mood during the second part of the experiment. All smokers used this possibility and smoked 1 cigarette during the break.

Table 1. Sample demographics for our 3 groups of subjects

	Nonsmokers	Smokers	Cannabis users
Men, n (%)	10 (52.6)	10 (50)	8 (57.1)
Age, years	25.2 ± 1.08	26 ± 1.6	24.6 ± 1.3
Years of education	15.2 ± 0.35	15.3 ± 0.33	14.9 ± 0.41
BDI score	3.6 ± 1.01	3.75 ± 0.89	5.7 ± 1.2
Fagerström scores	–	4.6 ± 0.35	3.36 ± 0.72
Cigarettes per day	–	15.6 ± 0.49	12.3 ± 1.7
Years of cigarette use	–	6.6 ± 0.43	4.9 ± 0.72
Cannabis joints per week	–	–	5.8 ± 0.20
Years of cannabis use	–	–	2.5 ± 0.25

Values shown are means ± standard errors. There were no significant differences between the subject groups with regard to age, education or BDI scores. The smokers and cannabis users did not differ with regard to their Fagerström test scores. The BDI measures the severity of depression with 21 items. A score of 11 is considered to be the cutoff for clinical depression. The maximum score on the Fagerström test is 10. This test differentiates between the following levels of dependence: (1) low (0–2 points), (2) middle (3–5 points), (3) strong (6–7 points) and (4) very strong (8–10 points).

Table 2. Means and standard errors for the amount of received monetary reward, and mood scores in the rewarded and unrewarded conditions, for each level of difficulty of the task

Group	n	Difficulty (number of circles)	Rewarded conditions		Unrewarded conditions
			mood score	monetary win, CHF	mood score
Nonsmokers	19	3	3.68 ± 0.20	5.39 ± 0.16	3.68 ± 0.23
		5	3.42 ± 0.26	9.47 ± 0.40	3.68 ± 0.23
		7	3.36 ± 0.24	15.89 ± 0.76	3.26 ± 0.24
Smokers	20	3	3.80 ± 0.20	5.43 ± 0.12	3.55 ± 0.21
		5	3.55 ± 0.21	9.10 ± 0.46	3.50 ± 0.18
		7	3.20 ± 0.22	15.80 ± 0.65	3.2 ± 0.18
Cannabis users	14	3	2.92 ± 0.37	5.29 ± 0.18	3.14 ± 0.29
		5	2.92 ± 0.32	9.14 ± 0.52	3.14 ± 0.31
		7	3.21 ± 0.32	17.14 ± 0.72	3.28 ± 0.30

The subjects did not differ with regard to their monetary wins. The cannabis users evidenced lower mood scores than both the smokers and the nonsmokers at the easiest level of difficulty of the rewarded conditions at a significance level that did not survive Bonferroni correction, but did show a trend ($p < 0.05$). Mood scores: 1 = bad mood; 5 = good mood. Maximum reward: CHF 6 in the 3-circle condition, CHF 12 in the 5-circle condition and CHF 24 in the 7-circle condition.

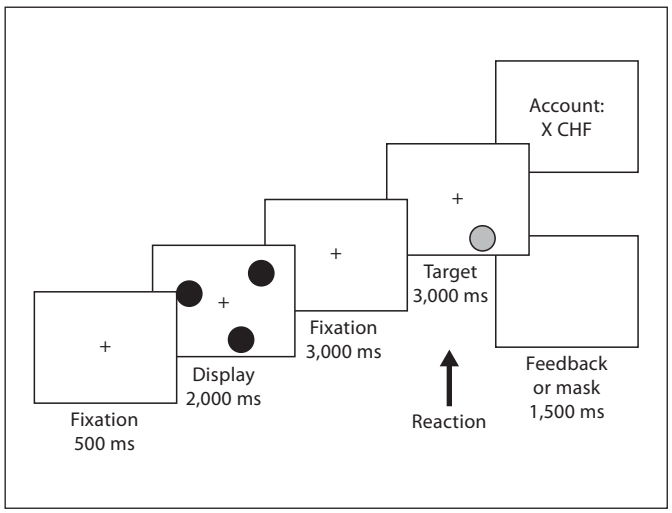

Fig. 1. Schematic representation of a trial of the spatial delayed recall task. In the first display, an array of yellow circles (3, 5 or 7) was presented for 2,000 ms after a fixation time of 500 ms. After a delay of 3,000 ms, a green circle appeared and the subject had 1,500 ms to decide whether the position of the green circle was the same as that of one of the preceding yellow circles. If so, the correct response for the participants was to press a button with their right hand. If not, the participants had to press a button with their left hand. After the response time had elapsed, the circle disappeared and the accumulated amount of money earned appeared on the screen (in the rewarded condition) or the screen remained blank (in the unrewarded condition). The positions of the circles varied randomly and were organized according to a 5 × 5 grid dividing the space into 25 possible positions. The task comprised 3 levels of difficulty determined by the number of circles to remember. During the rewarded condition, the participants could earn a monetary reward for every correct response. The monetary reward increased according to the difficulty of the task.

Rating of Mood and Monetary Wins

The participants were asked to rate their momentary mood on a scale from 1 (bad) to 5 (good) at baseline, at the beginning of the experimental session and after each difficulty block in each condition. In order to control for differences in the evaluation of the monetary earning between the groups of participants, we asked them to rate the value of the amount of money they had won on a scale from 0 (no value) to 10 (high value). Furthermore, the participants were asked at the end of the testing session to rate how strenuous the task was for them.

Data Analysis

Baseline mood ratings were compared among the groups using a 1-factor analysis of variance (ANOVA). If we did not find any significant group differences at baseline, these ratings were not integrated into the further analyses of mood. In order to test our main hypothesis, i.e. that there is a reduced influence of reward on mood states in smokers and cannabis users that is more accentuated in the most difficult level of a task, we performed an ANOVA for repeated measures using mood as a dependent variable, with the 3 following factors: groups of participants (nonsmokers, smokers and cannabis users), feedback conditions (rewarded and not rewarded) and levels of difficulty. The level of difficulty yields indirect information about the influence of the monetary gain on mood for each level of difficulty, since level of difficulty and monetary reward are strongly correlated (nonsmokers: r = 0.89; smokers: r = 0.89; cannabis users: r = 0.91). In addition, we postulated that there would be a significant positive correlation between mood ratings and monetary wins in the rewarded conditions in the nonsmokers, but not in the smokers or

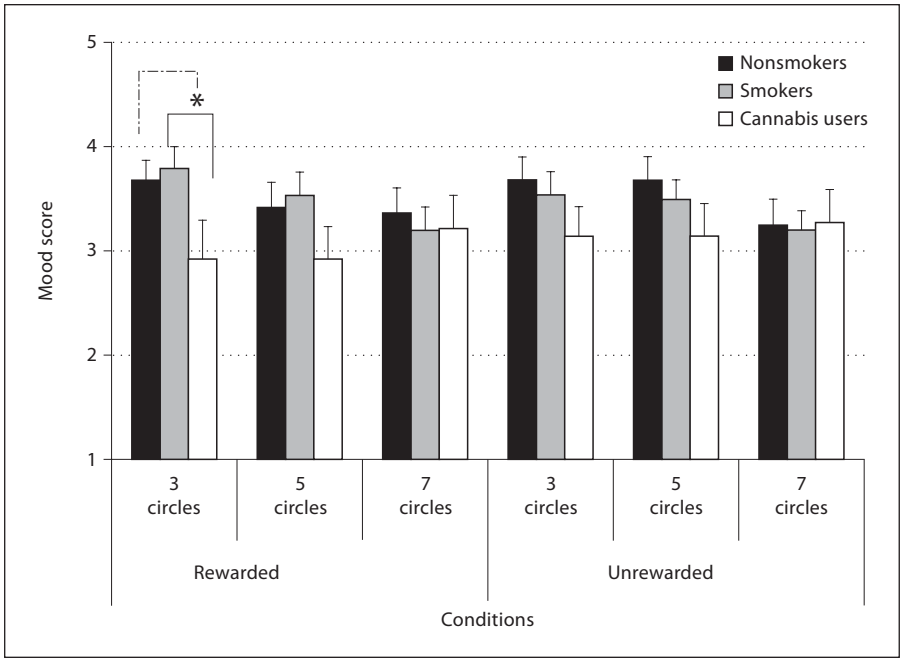

Fig. 2. Mean mood scores at the different levels of difficulty and conditions of reinforcement for each group of participants. Mood was significantly lower in cannabis users than in smokers and nonsmokers, at a significance level that did not survive Bonferroni corrections for multiple comparisons ($p < 0.05$), but did show a trend. Only the mood scores rated during the experimental conditions are presented, because the subjects did not differ in their baseline mood ratings. * $p < 0.05$. Mood scores: 1 = bad mood; 5 = good mood. Dotted line = Comparison showing a trend at $p < 0.06$.

cannabis users. To test this hypothesis, we used Pearson product-moment correlation and analyzed each group of subjects separately. Two additional ANOVAs for repeated measures were applied using response accuracy and reaction time as dependent variables with the same 3 factors as listed above, in order to test the effect of reward on performance and to control for possible performance differences among the groups of participants. The evaluation of the value of the monetary reward, as well as the ratings of the effort associated with the task, were analyzed using an ANOVA with 1 factor, i.e. the groups of subjects, and the rated value of the monetary gain, or the effort ratings, as the dependent variable. In order to account for multiple comparisons, we used Bonferroni tests as post hoc tests for the one-way ANOVAs and Bonferroni-corrected significance levels for the post hoc tests (t tests) of the ANOVAs with repeated measures. The Bonferroni-corrected significance level was set separately for each analysis using the following formula: $1 - (1 - \alpha)^{1/n}$, where n is the number of possible comparisons of interest to test the hypothesis according to the Holm-Bonferroni method [47].

Results

Reward and Mood

The average mood scores in the rewarded and unrewarded conditions are summarized in table 2. Baseline mood scores were 4.15 ± 0.68 (mean ± SD) for the nonsmokers, 3.95 ± 0.60 for the smokers and 3.64 ± 0.92 for the cannabis users. The results of the 1-factor ANOVA showed no significant difference in mood between the groups at baseline ($F_{2, 50} = 2$, $p = 0.14$).

The 3-factor ANOVA of mood showed a significant effect only for the interaction between groups and levels of difficulty ($F_{4, 100} = 2.44$, $p < 0.05$). Neither the main effects for the factors reward ($F_{1, 50} = 0.18$, $p = 0.66$), difficulty ($F_{2, 100} = 2.34$, $p = 0.10$) and group ($F_{2, 50} = 1.07$, $p = 0.35$) nor the interactions between difficulty and reward ($F_{2, 100} = 0.92$, $p = 0.40$), between group and reward ($F_{2, 100} = 0.69$, $p = 0.50$) and between difficulty, group and reward ($F_{4, 100} = 0.75$, $p = 0.55$) reached significance. Subsequent post hoc tests did not evidence any results that survived the Bonferroni-corrected significance level of 0.016 (corresponding to $\alpha = 0.05$ with 3 comparisons of interest) for the comparison of mood between the rewarded and the unrewarded conditions, when each group of subjects was analyzed separately. Using subsequent independent-sample t tests, we found group differences that showed a trend at the Bonferroni-corrected significance level of 0.01 (corresponding to $\alpha = 0.05$ with 9 comparisons of interest) in the rewarded 3-circle condition. The cannabis users evidenced lower mood scores than both the smokers ($t_{32} = -2.23$, $p < 0.04$) and the nonsmokers ($t_{31} = -1.91$, $p < 0.06$) in this condition (fig. 2). The correlation analyses between mood ratings and monetary wins showed significant results in the easy and middle levels of difficulty [3 circles: $r_{19} = 0.48$, $p < 0.05$ (fig. 3); 5 circles: $r_{19} = 0.60$, $p < 0.01$] and a trend for the most difficult level (7 circles: $r_{19} = 0.42$, $p < 0.07$) in the nonsmoker subjects, but no significant results were found in the

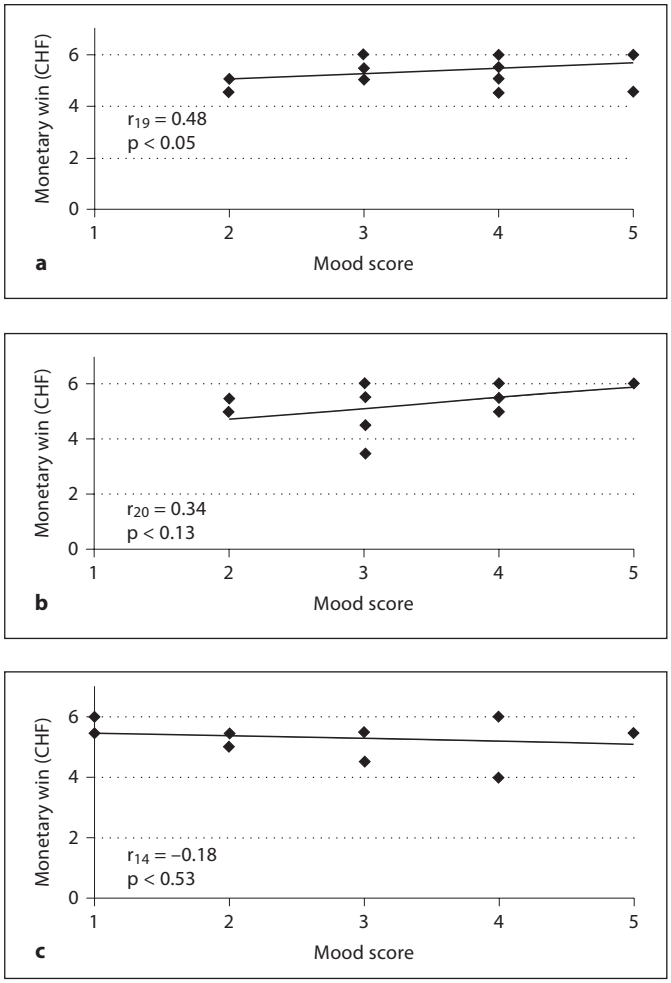

Fig. 3. Correlations between the mean mood scores and the amount of monetary reward received during the task's easiest level of difficulty (3 circles). The comparison of the correlation coefficients showed a trend between the nonsmoker group and the group of cannabis users (p = 0.07). Because in each group of subjects, several subjects showed the same association between mood ratings and monetary wins, they are represented as clouds or groups of subjects (◆) and not as single cases. This is associated with a reduced variance of the data that might influence the results. **a** For the nonsmokers (n = 19) there was a significant positive correlation between mood scores and monetary reward. **b** For the smokers (n = 20) there was no significant correlation. **c** The cannabis users (n = 14) also showed no significant correlation. Mood scores: 1 = bad mood; 5 = good mood.

smoker subjects (3 circles: $r_{20} = 0.34$, p = 0.13; 5 circles: $r_{20} = 0.32$, p = 0.16; 7 circles: $r_{20} = 0.34$, p = 0.14) or in the group of cannabis users (3 circles: $r_{14} = -0.18$, p = 0.53; 5 circles: $r_{14} = 0.46$, $p < 0.09$; 7 circles: $r_{14} = -0.22$, p = 0.43). To test whether these correlation coefficients were significantly different between the groups of subjects, we transformed the coefficients with the Fisher Z transformation and found a trend in the comparison between the nonsmoker group and the group of cannabis users at the easiest level of difficulty (p = 0.07).

As a control measurement, we compared the amount of money earned by the participants in each group using a 1-factor ANOVA and did not find any difference between the groups ($F_{2, 50} = 0.351$, p = 0.70). The ANOVA of the value of monetary earnings at the end of the experiment also showed no difference between the groups of participants ($F_{2, 50} = 1.05$, p = 0.35). However, the rating of the effort associated with the experiment showed group differences ($F_{2, 50} = 3.22$, $p < 0.05$), expressed by lower ratings in cannabis users than in smokers ($p < 0.05$) and lower ratings in smokers than in nonsmokers ($p < 0.05$).

Reward and Performance

The results for reaction accuracy and reaction time for each level of difficulty are summarized in table 3.

The 3-factor ANOVA of reaction accuracy showed a significant effect only for the factor difficulty ($F_{2, 100} = 90.35$, $p < 0.001$). Neither the main effects for the factors reward ($F_{1, 50} = 0.172$, p = 0.68) and group ($F_{2, 50} = 0.092$, p = 0.91) nor any of the interactions tested, including the interaction between difficulty and reward ($F_{2, 100} = 2.51$, p = 0.08), between group and reward ($F_{2, 100} = 0.58$, p = 0.56), between difficulty and group ($F_{4, 100} = 0.51$, p = 0.72) and between difficulty, group and reward ($F_{4, 100} = 0.71$, p = 0.58) reached significance.

The analogous ANOVA of reaction times yielded slightly different results; the main effects for the reward ($F_{1, 50} = 108.06$, $p < 0.001$) and difficulty ($F_{2, 100} = 18.98$, $p < 0.001$) factors, as well as the interaction between the two ($F_{2, 100} = 3.91$, $p < 0.05$), were significant. However, the group factor did not yield any significant results (main effect: $F_{2, 50} = 0.13$, p = 0.87; interaction between group and reward: $F_{2, 50} = 0.55$, p = 0.58; interaction between group and difficulty: $F_{4, 100} = 1.18$, p = 0.32; interaction between group, difficulty and reward: $F_{4, 100} = 0.78$, p = 0.53).

Subsequent post hoc tests evidenced significant results that survived the Bonferroni-corrected significance level of 0.016 (corresponding to $\alpha = 0.05$ with 3 comparisons of interest) in all comparisons between the rewarded and unrewarded conditions in each group of subjects. The reaction times were significantly higher in the unrewarded conditions than in the rewarded conditions for all levels of difficulty (lowest t value: $t_{19} = 3.07$, $p < 0.006$).

A significant increase in reaction times over the 3 levels of difficulty was evidenced only in the unrewarded conditions. In the smoker group, this increase was sig-

Table 3. Means and standard errors for reaction accuracy and reaction time during the spatial delayed recall task

Group	n	Difficulty (number of circles)	Rewarded conditions		Unrewarded conditions	
			correct responses, n	reaction time, ms	correct responses, n	reaction time, ms
Non-smokers	19	3	10.79 ± 0.32	933.33 ± 35.14	10.32 ± 0.32	1,055.52 ± 51.59
		5	9.47 ± 0.40	968.64 ± 42.51	9.95 ± 0.36	1,122.71 ± 57.53
		7	7.95 ± 0.38	1,008.75 ± 51.86	8.05 ± 0.47	1,192.14 ± 53.02
Smokers	20	3	10.85 ± 0.24	920.83 ± 45.46	10.6 ± 0.22	1,025.18 ± 55.67
		5	9.10 ± 0.46	952.74 ± 51.89	9.70 ± 0.36	1,098.85 ± 54.2
		7	7.90 ± 0.32	967.38 ± 53.04	7.80 ± 0.40	1,208.48 ± 71.82
Cannabis users	14	3	10.57 ± 0.36	940.05 ± 35.25	10.5 ± 0.37	1,097.98 ± 51.47
		5	9.14 ± 0.52	979.66 ± 50.99	9.36 ± 0.41	1,204.65 ± 61.09
		7	8.57 ± 0.36	976.02 ± 50.54	7.50 ± 0.59	1,180.85 ± 44.91

Accuracy is measured as the number of correct responses, with a maximum of 12 correct responses for each block. Significant results were found in all comparisons between the rewarded and the unrewarded conditions in each group of subjects. The reaction times were significantly higher in the unrewarded conditions than in the rewarded conditions for all levels of difficulty (lowest p value: <0.01). Significant increases in reaction times between the 3 levels of difficulty were evidenced only in the unrewarded conditions as follows: (1) smokers: significant increase between all levels of difficulty (lowest p value: <0.01); (2) nonsmokers: significant increase only in the comparison between the 3-circle and 7-circle conditions ($t_{18} = -4.39$, $p < 0.001$); (3) cannabis users: significant increase only in the comparison between the 3-circle and 5-circle conditions ($p < 0.05$).

nificant at a Bonferroni-corrected significance level of 0.016 (corresponding to $\alpha = 0.05$ with 3 comparisons of interest) between all the levels of difficulty (lowest t value: $t_{19} = -3.11$, $p < 0.006$). In the nonsmoker group, this increase was significant only in the comparison between the 3-circle and 7-circle conditions ($t_{18} = -4.39$, $p < 0.001$). In the group of cannabis users, this increase was significant only in the comparison between the 3-circle and 5-circle conditions ($t_{13} = -2.75$, $p < 0.016$).

In summary, these results confirm that monetary reinforcement, as well as the level of difficulty, influenced specific aspects of performance, i.e. reaction times, in a similar way in all groups of participants and that there were no performance differences between the groups of participants.

Discussion

The main aim of the present study was to investigate whether cannabis use influenced the effect of a monetary reward on mood ratings. We hypothesized that cannabis users and tobacco smokers would show a reduction in the effect of a monetary reward on mood ratings compared to control participants and that this reduction would be greater in cannabis users than in smokers. We used a spatial delay task including 3 levels of difficulty in order to test the relationship between reinforcement, effort and addiction. We expected the group differences to be greater for the most difficult than for the easiest conditions of our task.

Our results indicate a reduced influence of monetary reward on momentary mood ratings in cannabis users. However, contrary to our hypothesis, this effect was found in the easiest condition of our task rather than in the most difficult. At the easiest level of difficulty of the rewarded condition, the cannabis users rated their momentary mood as significantly lower than the smokers and nonsmokers. These results are in contradiction with our hypothesis but are in agreement with the conclusions of Camerer and Hogarth [40] that a monetary reward principally influences easy tasks. In addition, our results support the hypothesis of a positive correlation between monetary wins and mood ratings in the group of nonsmokers that was not significant in the group of cannabis users or tobacco smokers. Taken together, these results suggest, on the one side, a reduced association between mood and reward in the groups of substance users and, on the other side, a reduced effect of reward on mood in cannabis users only.

The nonsignificant association between mood ratings and reward in the group of smokers is in agreement with

previous findings in smokers that showed reduced behavioral and neural reactions to reward [35, 36]. These observations were explained by drug-induced dysfunction of the cerebral reward system, which led to a lack of activation of the striatum in response to reward. This explanation is supported by the fact that striatal activation has been shown to correlate positively with reward-induced mood changes [36] as well as with amphetamine-induced feelings of euphoria [48, 49]. Our results are in agreement with current neurobiological theories which postulate that addiction is associated with persistent changes in motivation and in brain motivational systems [50]. More specifically, it is hypothesized that there is a molecular or cellular neuroadaptation within the neural reward circuitry that compensates for the overactivity of hedonic feelings associated with addiction or repeated drug intake and finally results in a decrease in reward function. The emotional dysregulation accompanying withdrawal symptoms is also associated with a decreased reward function, an enhanced sensitization for drug stimuli and a reduced response to natural rewards [51] that is thought to be related to the activation of an anti-reward system [50]. The neural correlates for this emotional dysregulation are thought to be partly similar to the ones underlying anxiety and involve the extended amygdala [52], a neuroanatomical entity that is thought to integrate brain arousal stress systems with hedonic processing systems [50]. The extended amygdala is an anatomically and neurochemically interconnected system in the basal forebrain consisting of the bed nucleus of the stria terminalis, the central nucleus of the amygdala and the shell of the nucleus accumbens [53]. Taking drugs to alleviate the negative effects associated with withdrawal works as a negative reinforcer. This negative reinforcement mechanism is thought to underlie the shift from regular drug use to compulsive drug use [54].

Because the smokers in our study could smoke before and during the experiment, our results were not influenced by the mood changes associated with withdrawal. However, prolonged exposure to drugs causes long-term neuronal and behavioral changes, including increased anxiety that involves noradrenergic and corticotrophin-releasing factor transmission [55], which could explain the lack of association between reward and mood in smokers. Interestingly, this finding held true even for our group of modestly addicted smokers.

Similar results were evidenced in the cannabis users, suggesting that cannabis use affects reward processing at a behavioral level. This could be explained by a similar dysfunction of the brain motivational systems, especially of the extended amygdala, in cannabis users as in smokers, and could indicate that cannabis use affects motivation, and that different substances of abuse elicit similar motivational changes at a behavioral level. The high density of cannabinoid receptors observed in regions involved in emotional regulation, such as the amygdala, as well as the anxiolytic effects associated with enhancement of endocannabinoid signaling, corroborate this hypothesis [56]. Furthermore, neuroimaging studies in humans showed a direct influence of THC on the amygdala response to emotional stimuli [57, 58].

In addition to the lack of a significant positive association between monetary wins and mood ratings, the group of cannabis users also showed lower mood ratings in response to monetary rewards than tobacco smokers and nonsmokers, suggesting that cannabis use more strongly affects the relationship between reward and mood than does tobacco use. This could be related to reduced emotional regulation in cannabis users, as suggested in a study by Dorard et al. [59], who reported higher anhedonia and alexithymia scores in cannabis users than in healthy controls. The most frequent reasons for cannabis use are related to enhancement of affective states [60, 61], including relaxation, an increase in pleasure and being high, thus supporting the hypothesis of impaired emotional regulation in cannabis users. Because the group differences were specific for one particular condition of the task, and because there were no group differences in baseline mood ratings, these findings cannot be explained by a generally lower mood in cannabis users.

The mood differences observed between cannabis users, tobacco smokers and nonsmokers also cannot be explained by differences in the task performance. Thus, reward had the same effect on the performance of all participants, which consisted of decreased reaction times in the rewarded trials when compared to the unrewarded trials. This finding is consistent with the meta-analytical study of Jenkins et al. [39], in which the authors concluded that reward enhances performance, especially in regard to quantitative aspects. Furthermore, the reaction times were slower at the more difficult levels of the tasks than at the easiest ones for all groups of subjects in the unrewarded conditions only. The effect of increased working memory load on performance is consistent with the results of Glahn et al. [38] obtained with the original version of the task used in this study. Interestingly, no similar effect was found in the rewarded condition, suggesting that reward can attenuate the effect of increased cognitive effort on performance. These results did not confirm our hypothesis of a stronger effect of effort in the groups of

substance users, since the findings were the same in the groups of substance users and healthy controls.

The use of only one scale for the assessment of momentary mood states is certainly a limitation of the present study, and we are aware that a single-item scale might not be sensitive enough to capture subtle mood changes over time. However, a more extensive assessment of mood would have delayed the time between the presentation of the monetary reward and the mood ratings. Furthermore, we assessed baseline mood ratings prior to the experiment and did not find any group differences. The fact that the groups of subjects did not differ in their baseline mood ratings, but differed then in their mood ratings in response to reward, suggests that these changes are elicited by the experimental conditions. Because several subjects showed the same association between their mood ratings during the easiest experimental condition and their monetary wins for this condition, the data considered in the correlation analysis showed a reduced variance that might have affected the results. Another limitation of the study is the lack of biological tests for the control of urine THC levels. Since the cannabis users needed to consume cannabis at least 5 times a week in order to be included in the study, these tests would have been positive in all cases. They would have given little information on whether the participants were under the influence of cannabis during the experiment. Furthermore, smoker subjects were allowed to smoke before and during the experiment in order to avoid negative feelings associated with withdrawal. Therefore, the results could be interpreted as a direct effect of nicotine or cannabis use. However, since our results show differences between tobacco smokers and cannabis users, and because these results were in agreement with the results of previous studies, it can be postulated that they are related to changes induced by the regular use of these psychoactive substances and not by their direct psychopharmacological effect.

In conclusion, our results indicate a reduced effect of reward on positive mood states in cannabis users. Since a similar result was observed in the group of smokers, this suggests that both substances of abuse lead to similar motivational changes. However, the use of cannabis seems to affect mood ratings in a stronger way than tobacco smoking alone. Finally, these results suggest that regular cannabis use affects certain aspects of motivation.

Acknowledgements

This study was supported by the Faculty of Psychology at the University of Basel and the Freie Akademische Gesellschaft. We thank Krystle Barhaghi for checking the English.

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