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Cannabis with high Δ^9-THC contents affects perception and visual selective attention acutely: An event-related potential study

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ABSTRACT

Objective: Cannabis intake has been reported to affect cognitive functions such as selective attention. This study addressed the effects of exposure to cannabis with up to 69.4 mg Δ^9-tetrahydrocannabinol (THC) on Event-Related Potentials (ERPs) recorded during a visual selective attention task. Methods: Twenty-four participants smoked cannabis cigarettes with four doses of THC on four test days in a randomized, double blind, placebo-controlled, crossover study. Two hours after THC exposure the participants performed a visual selective attention task and concomitant ERPs were recorded. Results: Accuracy decreased linearly and reaction times increased linearly with THC dose. However, performance measures and most of the ERP components related specifically to selective attention did not show significant dose effects. Only in relatively light cannabis users the Occipital Selection Negativity decreased linearly with dose. Furthermore, ERP components reflecting perceptual processing, as well as the P300 component, decreased in amplitude after THC exposure. Only the former effect showed a linear dose–response relation. Conclusions: The decrements in performance and ERP amplitudes induced by exposure to cannabis with high THC content resulted from a non-selective decrease in attentional or processing resources. Significance: Performance requiring attentional resources, such as vehicle control, may be compromised several hours after smoking cannabis cigarettes containing high doses of THC, as presently available in Europe and Northern America.

1. Introduction

Cannabis, also known as marijuana, is the plant material of the *Cannabis sativa* L. It is one of the most commonly used recreational drugs in the Western world. The main reasons for its abuse are its reinforcing (Justinova et al., 2005), relaxing, euphoric and psychedelic effects. Cannabis exerts its psychoactive effects mainly through Δ^9-tetrahydrocannabinol (THC). THC is an agonist of Cannabinoid type 1 (CB1) receptors. These receptors are vastly present all over the cortex (Herkenham et al., 1990; Eggan and Lewis, 2007). They typically reside on presynaptic neurons and are inhibited by retrograde transmission of endogenous cannabinoids (Wilson and Nicoll, 2001).

Numerous studies have shown that acute exposure to cannabinoids has detrimental effects on cognitive functioning, including psychomotor and memory performance (for reviews, see Ameri, 1999; Lichtman et al., 2002; Iversen, 2003; Ramaekers et al., 2004; Lundqvist, 2005; Ranganathan and D'Souza, 2006). Acute exposure to THC and cannabis also affects selective attention (Hooker and Jones, 1987; for a review Pope et al., 1995; more recently Curran et al., 2002) and executive functions such as planning, psychomotor inhibition and performance monitoring (Ramaekers et al., 2006).

In recent years the average THC content of (sinsemilla or "skunk") cannabis cigarettes has increased to about 50 mg in Western Europe (61 mg cf. Niesink et al., 2004; 42 mg cf. Potter et al., 2008) and to 63 mg in the United States of America (El Sohly, 2004). In contrast acute effects in laboratory tests have been studied up to doses of about 40 mg THC (Hart et al., 2001; Ramaekers et al., 2006). The present study assessed the effects of exposure to cannabis cigarettes containing doses up to 69.4 mg THC in regular non-daily cannabis users. Intermediate doses studied were 29.3 and 49.1 mg, next to placebo. The present article focuses on the effects of these doses on non-spatial visual attention and concurrent ERP recordings. Elsewhere we reported that these high doses of THC are detrimental to processing speed and accuracy on a number of psychomotor tasks (Hunault et al., 2009) that were dependent on sustained attention, working memory and motor control.

Six ERP components were recorded at various latencies and scalp positions in the present non-spatial visual attention task. These included manifestations of 1) perception of the stimulus features that defined relevant and irrelevant stimuli (the exogenous Spatial-

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Frequency-Dependent potential at about 80 ms, SFD80; Kenemans et al., 2000), 2) initial selection (Frontal Selection Positivity, or FSP), 3) subsequent selective processing (Occipital Selection Negativity, OSN) and 4) integration of relevant stimulus features (N2b), 5) stimulus classification (P300; Kenemans et al., 1993, 2002) and 6) a direct ERP index of central motor processes, i.e., the lateralization of brain potentials recorded above the motor cortex (Lateralized Readiness Potential, LRP, as in Kenemans et al., 1995). Possible effects of THC on the LRP onset-latency were compared with those on reaction times to distinguish whether the locus of effects was premotor or motor (Ilan et al., 2004, 2005; Hunault et al., 2009). Previously, specific ERP components in this task have shown modulations with acute caffeine consumption (Kenemans and Lorist, 1995) and alcohol dependence (Bijl et al., 2005).

Previous cannabis studies revealed a general decrease in ERP components evoked between 100 and 700 ms during working memory (including P300) and episodic memory tasks using cigarettes containing ~3.5%, or ~30 mg THC (Ilan et al., 2004, 2005). It was concluded that cannabis acutely diminished transient attention devoted to stimulus processing (as reflected in the N200 component of the ERP), as well as memory encoding and retrieval (as reflected in the ERP slow wave). In line with these results (at ~30 mg THC doses) and the observed behavioral results at higher doses (Hunault et al., 2009) we expected that amplitudes of several ERP components would decrease monotonically with doses up to 69 mg THC.

Chronic use of psychoactive substances can lead to alterations in neurotransmitter systems that either lead to between-subject main effects or interact with acute dose effects (Polich and Criado, 2006). With regard to cannabis such interactions between chronic and acute drug intake have been reported for attention and its ERP manifestations (Polich and Criado, 2006) as well as for other cognitive functions (Ehrenreich et al., 1999; Pope et al., 2003). Therefore we tested whether or not the amount of cannabis, nicotine and alcohol that the participants used recreationally, as well as their age of onset of cannabis use, influenced the acute dose effects.

2. Experimental procedures

2.1. Participants

Twenty-four male volunteers (age 18–33) participated in this study. They were recruited through advertisements in local newspapers. The participants were selected on the basis of their self-reported average cannabis use, which was between 2 and 18 cannabis cigarettes per month (median 8; median duration of cannabis use 6.5 years, range 2–18). All participants declared that they didn't use other drugs of abuse, except alcohol. See Table 1 for further details on the demographics and drug use of the participants.

Table 1
Participants' demographic and drug use characteristics.

	Mean (SD)		
	Total	Lower half	Upper half
Age (years)	24 (4)	21 (2); $n=11$	27 (4); $n=12$
Past year cannabis use (joints/month)	8 (4)	5 (2); $n=11$	12 (3); $n=12$
Age of onset of cannabis use (years)	16 (2)	15 (1); $n=11$	18 (1); $n=12$
Past year nicotine use (cigarettes/day; $n=18$)	8 (6)	2 (2); $n=12$, incl. 5 non-smokers	12 (4); $n=11$
Past year alcohol use (glasses/week; $n=22$)	13 (9)	7 (3); $n=12$, incl. 1 non-drinking	19 (11); $n=10$
Employment status ($n=19$)	*N*		
Student	14/19		
Unemployed	1/19		
Employed	4/19		

Participants were excluded if they had a history of psychiatric diseases or (had) suffered from respiratory diseases, liver conditions or cardiovascular problems, according to a medical health questionnaire filled out by the participants. Chronic use of medication(s) was another reason for exclusion. No use of any medication use was reported by the participants from 15 days before until the end of the study. Furthermore, DrugControl® urinary tests for the presence of amphetamines, barbiturates, benzodiazepines, cocaine metabolite, methaqualone, opiates, MDMA (ecstasy), MDA (3,4-methylenedioxyamphetamin) and THC (cut-off level 50 ng/ml THC-COOH) were negative. Finally, excessive alcohol consumption, as indicated by abnormal values of several liver enzymes — i.e., gamma-glutamyltransferase (GGT), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) — also led to exclusion. Furthermore, participants stayed in the hospital on the night preceding testing. This ensured that the subjects refrained from alcohol and drug intake for at least 10 h prior to the study.

The current data were recorded from a study conducted at the RIVM (the Dutch National Institute for Public Health and the Environment), in which participants performed numerous psychological tests assessing reaction time, memory and selective attention (Hunault et al., 2009). The study protocol was approved by the ethical committee of the University Medical Centre, Utrecht. Each participant was informed about the possible risks and signed an informed consent form. The study was conducted following the guidelines for Good Clinical Practice.

During analysis, it was decided to exclude one participant due to anomalous data (trouble staying awake leading to extremely high error rates and barely discernable ERPs).

2.2. Design and procedures

2.2.1. Design

The experiment was set up as a placebo-controlled randomized 4-way crossover design. Between each of the four test days, with different THC doses, a wash-out period of at least seven days was observed (see below). Groups characterized by low versus high values on age, age of first cannabis use and average use of cannabis, alcohol and nicotine, respectively, were formed post-hoc by a split half on these variables (Table 1).

2.2.2. Cannabis

Participants smoked one of four cannabis cigarettes, referred to as joints, on each test day, under non-fasting conditions. The four joints differed in THC content. The lowest dose contained 29.3 mg THC, the medium dose 49.2 mg THC and the highest dose 69.4 mg THC. A cannabis batch containing less than 0.003% THC, supplied by the National Institute on Drug Abuse (Bethesda, MD, USA), was used for placebo joints. The joints consisted of a conically shaped shell made of cigarette paper. The shell was filled with 300 mg cannabis and 700 mg tobacco. Such a mixture seems most commonly smoked in Western Europe (cf. Amos et al., 2004). The smoking procedure was standardized by means of computer generated instructions, based on a pilot study conducted two months before the study, and aimed to mimic the recreational cannabis use of the participants, (3 s for getting ready, 2 s for inhalation, 3 s for holding breath, and 32 s for normal breathing and relaxation). The whole joint was smoked in about 22 min. Blood-serum concentrations of THC, its metabolites 11-OH-THC and THC-COOH and subjective rating of cannabinoid effects (subjective "high", indicated on a 100 mm visual analog scale) were sampled at 14 time intervals. These included one prior to smoking (to test abstinence in the period immediately prior to the study and between sessions) and one at 2 h after onset of smoking, i.e. when the visual selective attention task was performed (see Hunault et al., 2008, for a more complete presentation of those data).

In two participants THC level was larger than the detection limit before THC intake (at $t=0$) on 3 or 4 test days. The same was true for 13% of the assessments in the remaining participants. Therefore all statistical analyses have been repeated after 1) elimination of those two participants and 2) replacement of the suspicious data by regression estimates. Because these analyses produced identical statistical results, only the main analyses, including 23 participants will be presented below.

2.2.3. Task

On each test day participants performed a visual selective attention task, at 2 h post THC exposure, during the elimination phase of the drug (THC serum levels peaked within 15 min). During the task they had to respond to one of four different visual stimuli by pressing a button, while ignoring the other three. The visual stimuli consisted of square-wave gratings, varying in fundamental spatial frequency (high or low, 0.6 and 4.8 cycles/° of visual angle, respectively) and orientation (horizontal or vertical), as shown in Fig. 1. The gratings subtended 6.67° of visual angle and were presented in the center of a computer screen, against a gray background. Each grating was presented for 50 ms. Stimulus onset asynchrony varied between 750 and 950 ms and during this interval a fixation cross was presented. A full experiment contained eight experimental blocks, each consisting of pseudorandom series of 32 presentations of each of the four gratings. Each block was accompanied by a written instruction to push a button in reaction to only a certain grating stimulus (e.g. wide, horizontal bars), and to ignore the others. The instruction also indicated which index finger should be used to respond (either right or left). Each combination was used as a target stimulus twice, requiring a right-hand response in one block and a left-hand response in the other. A practice block containing 12 trials preceded each block. Response speed was emphasized as being more important than accuracy.

2.2.4. EEG measurement

EEG was recorded from six midline (AFz, Fz, Cz, Pz, POz, and Oz) and two lateral electrodes (C3 and C4) using an electrocap. The right mastoid was used as a reference and a ground electrode was attached to the forehead. Electrodes placed above and below the right eye and at the outer canthi of both eyes were used to measure the vertical and horizontal EOG, respectively. Impedances were kept below 5 kΩ. Signals were amplified using Ampligraph amplifiers with an online 100 Hz low-pass filter and were sampled at a rate of 250 Hz using Neuroscan Acquire software.

2.2.5. Procedure

The evening before the first test day, participants familiarized themselves with a shortened test version of the task to mitigate initial learning effects. On all test days, the participants were seated in a chair in front of the computer screen. EOG electrodes and the electrocap were then applied. Background EEG was measured for 4 min and the experimental blocks were presented. Block order was randomized across participants, with the restriction that each target configuration (frequency × orientation) was presented twice in a row, once for each target hand. After four experimental blocks, there was a short break. For each participant, block order was identical on all four test days.

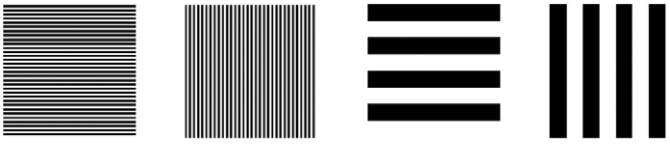

Fig. 1. Visual stimuli (square-wave gratings) used in the present study. In an experimental block where the first grating is the target grating, the subsequent non-targets are frequency-relevant, orientation-relevant and irrelevant respectively, which is defined by the features they share with the target.

2.3. Data analysis

2.3.1. ERP

The raw EEG signals were analyzed using BrainVision Analyzer software. Offline filtering was applied (30 Hz low-pass, 12 dB/oct. and high-pass, time constant of 1 s at 24 dB/oct). The data were epoched from 100 ms pre-stimulus to 750 ms post-stimulus. Subsequently, epochs containing artifacts larger than100 μV were removed and the data were corrected for ocular artifacts (Gratton et al., 1983). Next, average ERPs were computed for each of the four combinations of the relevance of spatial frequency and orientation with respect to the target for that particular experimental block. Only correct responses were included. Behavioral responses earlier than 100 ms and later than 750 ms post-stimulus were considered invalid and these epochs were not included in any average ERP. Subsequently all averages were baseline corrected by subtracting the average amplitude in the pre-stimulus baseline-interval from every data-point. The ERP manifestation of sensory processing, the so-called SFD80, was derived by averaging ERPs for all low- and high frequency gratings separately, regardless of stimulus relevance (i.e. target or non-target). The latter was then subtracted from the former to obtain the potential related to the differential processing of the spatial frequencies. For statistical analysis the mean activity between 90 and 110 ms post-stimulus (including the peak) at Oz was extracted. Next, the selection potentials (FSP, OSN and N2b) were derived by subtracting the ERP to irrelevant non-targets from the ERP to frequency-relevant non-targets (Fig. 1; see Kenemans et al., 1993). This subtraction reveals the electrical brain potentials that are related to the selective processing of the relevant spatial frequency relative to stimuli of irrelevant frequency. Previous studies have shown that frequency information is analyzed faster than the orientation for the stimuli used in this experiment (Kenemans et al., 1993). For statistical analysis components were defined by relating the attention effects observed in the present study to published data from comparable studies (Kenemans et al., 1995; Bijl et al., 2005). FSP was defined as the mean activity at Fz between 120 and 200 ms, OSN as the mean activity at Oz between 200 and 250 ms and N2b as the mean activity at Fz between 275 and 325 ms. P300 was defined as the mean activity at Pz between 400 and 500 ms post-stimulus evoked by the target. The P300 was derived after subtracting the ERP to the orientation-relevant non-target from the ERP to the target (see Fig. 1). This subtraction reveals the extra processing of target stimuli relative to non-target stimuli with the same orientation (cf. Kenemans and Lorist, 1995; Bijl et al., 2005). To quantify motor preparation Lateralized Readiness Potentials (LRPs) were calculated by subtracting activity at electrode C4 from that at C3 and C3 from C4 for all correct right- and left-hand responses respectively (Coles et al., 1988). These were then averaged time-locked both to stimulus and response onset. Average amplitudes between 325 and 375 ms and average amplitude in the 50 ms preceding response onset were analyzed statistically for the stimulus-locked LRP and response-locked LRP respectively. To test whether THC exposure influenced pre-motor or motor stages of information processing, LRP onsets were calculated for both stimulus and response-locked LRPs. Onsets were determined by a regression method after Jackknife averaging (Miller et al., 1998) as recommended by Mordkoff and Gianaros (2000).

2.3.2. Statistical analysis

The vast majority of the data did not deviate from normality according to Kolmogorov–Smirnov tests. The exceptions involved to-be-expected floor effects for THC, and 'high' under placebo and response errors on three (out of 16) stimulus × drug combinations. Therefore, all data were analyzed by parametric tests. The blood serum, behavioral and ERP measures were analyzed by a repeated-measures MANOVA with a dose factor comprising four levels (placebo, low, medium and high). To further characterize possible

drug effects, post-hoc polynomial contrasts were analyzed. The analysis of accuracy also included stimulus type (Target, Spatial Frequency relevant non-target, Orientation-relevant non-target and irrelevant non-target) as within-subject factor. Finally, to assess the effects of age, age of first cannabis use and average use of cannabis, alcohol and nicotine the analyses were repeated with the Low and High split halve group on each of these variables as between-subject factors (see Table 1). Because age and the use of alcohol and nicotine did not affect the results, only effects related to cannabis use will be reported below.

3. Results

3.1. Blood serum THC and subjective "high"

Serum THC concentrations at the start of the selective attention task were dose-dependent (see Table 1; $F(3,16)=9.28$, $p<0.005$; incomplete data for 4 participants). THC concentrations showed significant linear ($F(1,18)=26.71$, $p<0.0005$) and quadratic trends ($F(1,18)=8.57$, $p<0.01$), reflecting significant increases from placebo up to medium dose, but no significant increase between medium and high dose. Subjective "high" was dose dependent as well (Table 1; $F(3,20)=19.59$, $p<0.0005$) and showed a linear increase ($F(1,22)=52.29$, $p<0.0005$).

3.2. Behavioral data

Table 1 shows participants' performance, in terms of speed and accuracy. A significant effect of dose on mean reaction time (MRT; $F(3,20)=7.68$, $p<0.0005$) and its standard deviation was found (SDRT; $F(3,20)=4.65$, $p<0.013$), with both MRT and SDRT being lowest in the placebo condition and highest in the high dose condition. Both measures revealed a significant linear dose-related effect, in the absence of higher-order effects (within-subjects linear trend: $F(1,22)=24.10$, $p<0.0005$ and $F(1,22)=13.56$, $p<0.001$, respectively).

For accuracy a significant main dose effect was found ($F(3,20)=3.35$, $p<0.05$), again sustained by a linear relationship, in the absence of higher-order effects ($F(1,22)=10.6$, $p<0.005$). The stimulus-type factor also had a significant main effect on accuracy ($F(3,20)=30.64$, $p<0.0005$). The lowest accuracy rates were observed for the frequency-relevant stimuli, both targets and non-targets. No dose × stimulus-type interaction was found ($F(3,20)<1$, n.s).

3.3. ERP data

Fig. 2 shows the grand average SFD80 potential at electrode Oz, for each of the four THC doses. The SFD80 is related to perception of high versus low spatial frequency gratings. It revealed a significant dose effect ($F(3,20)=5.07$, $p<0.0005$). Increasing doses were linearly related to decreasing SFD80 amplitudes ($F(1,22)=15.104$, $p<0.001$). Visual inspection of the ERPs prior to subtraction showed that the effect was especially clear for the large negative peak evoked by high frequencies and that it did not involve latency shifts. Finally, SFD80 was smaller in the high use group ($F(1,21)=4.29$, $p=0.05$).

The selection potentials, FSP, OSN and N2b (see Fig. 3) did not show any statistically significant dose-related differences (all $F(2,23)\leq 1$, n.s.). However, the between group analysis showed that OSN (at electrode Oz) did decrease linearly with cannabis dose in the low cannabis use group ($F(1,10)=6.97$, $p<0.05$), but not in the high use group (Fig. 4, $F<1$, n.s.; group × dose effect, $F(3,17)=3.10$, $p=0.05$). Furthermore, FSP amplitude (at electrode Fz) was smaller in the high use group ($F(1,19)=11.71$, $p<0.01$) and OSN amplitude was smaller in the group that started using cannabis at an early age ($F(1,19)=4.44$, $p<0.05$).

Fig. 5 shows the P300 component in the grand average ERP (at electrode Pz). There was a significant main dose effect on P300 amplitude ($F(3,20)=9.62$, $p<0.0005$). The largest amplitudes were recorded during the placebo condition. The linear as well as the quadratic polynomial contrast was significant ($F(1,22)=29.91$, $p<0.0005$ and $F(1,22)=4.95$, $p<0.037$, respectively). This was reflected in the absence of differences between the three dose conditions, while each dose condition differed from placebo. Visual inspection of the ERPs prior to subtraction showed that the effect was indeed produced by an amplitude decrement in the target ERP, without latency shifts.

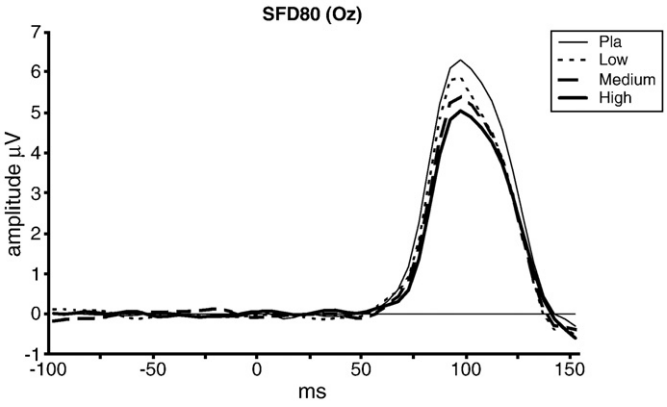

Fig. 2. Grand average ($n=23$) differential brain responses for ERPs evoked by the low frequency gratings minus those evoked by high frequency gratings at electrode Oz, showing the SFD80 just prior to 100 ms. Gratings were presented at 0 ms. The different lines indicate ERP under different THC doses.

3.4. LRP data

The stimulus-locked LRP did not show any dose effects on either onset (all JackKnife $t(22)<0.42$, n.s.) or amplitude ($F(3,20)=1,44$, n.s.). As shown in Fig. 6, no substantial differences could be detected prior to the response in the response-locked LRP waveforms either. This was confirmed by the statistical analyses (onset, all JackKnife $t(22)<0.90$, n.s.; amplitude $F(3,20)<1$, n.s.). However, there appeared to be a substantial, dose-dependent effect around 40 ms post-response, characterized by gradually decreasing amplitudes with increasing dose. These differences were statistically significant: $F(3,20)=8.70$, $p<0.001$. The decrease in amplitude as a function of THC dose had a significant linear component (polynomial contrast $F(1,22)=16.32$, $p<0.001$), whereas higher-order polynomial terms were not significant. Visual inspection of the ERPs at the contralateral electrode (C3 or C4) following left- and right-hand responses, respectively, confirmed that the amplitude decrement was present about equally for both pairs of response side and contralateral recording side, and did not involve THC-induced latency shifts.

4. Discussion

The aim of the present study was to reveal acute THC-effects on non-spatial visual selective attention and concomitant ERPs 2 h after exposure to cannabis with THC doses up to two times higher than those used in previous studies. Response speed and its standard deviation increased and accuracy decreased with doses ranging from 29.3 to 69.4 mg. Both effects were linear. With regard to the ERPs recorded during this task, reduced amplitudes were observed for the occipital SDF80 (a manifestation of sensory processing), the P300 (a manifestation of target classification) and a central post-motor potential. For SFD80 and post-motor potential these decreases were linear within the tested dose-range. Finally, the OSN (reflecting a selective processing stage) decreased linearly in amplitude with increasing dose in low but not high cannabis users within the present sample (median split). No significant amplitude effects were observed for other ERPs related to selective attentional processing of relevant

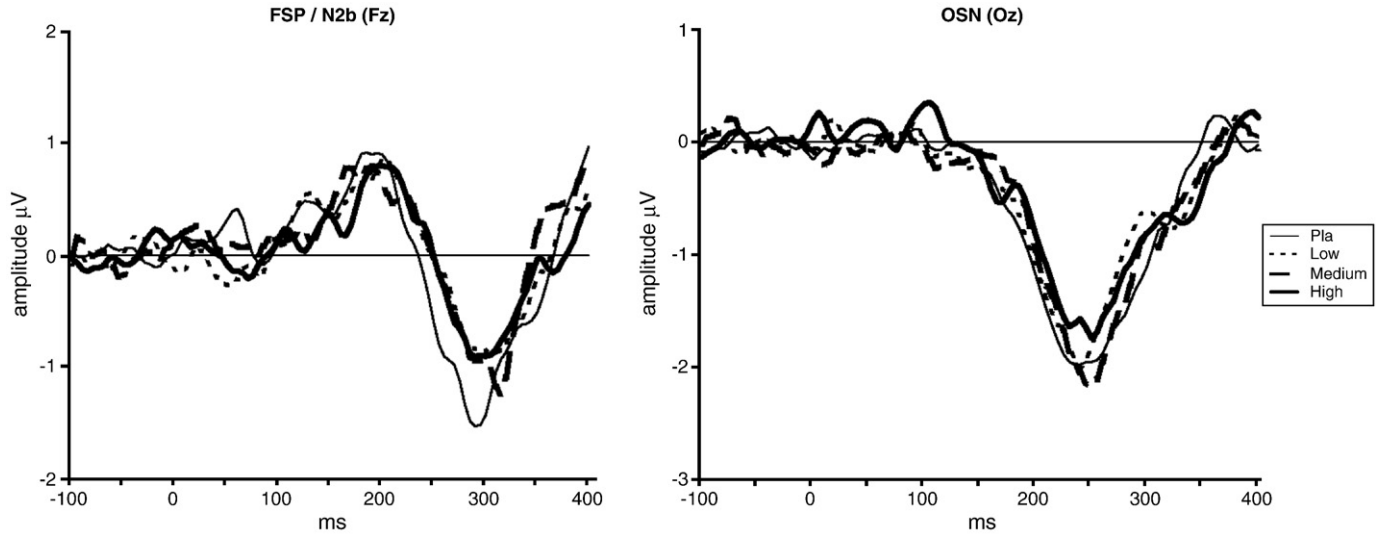

Fig. 3. Grand average ERPs showing the differential selection potentials (frequency-relevant non-target minus irrelevant non-target) FSP, OSN and N2b at electrodes Fz and Oz.

stimulus features, such as initial selection (manifested by the FSP) and integration of relevant stimulus features (N2b).

The current study showed a general effect on reaction time and accuracy, cf. previous results with other psychomotor tasks using cannabis with lower doses of THC (e.g., Ilan et al., 2004, 2005). When the THC dose increased, participants' reaction speed slowed down and showed more variance, the latter suggesting increased lapses of attention. The amount of errors also increased. However, THC did not have a discriminatory effect on accuracy for the different stimulus categories. It was therefore impossible to attribute the reduced accuracy to impairments in the selective processing of the visual stimuli. It should be noted that the error data were not distributed normally. Therefore this conclusion might be less reliable. However, the pattern of results (Table 2) does not suggest an interaction either.

In line with these behavioral data, most ERP correlates of selective processing were not significantly affected by exposure to cannabis. Neither the FSP, nor N2b was affected by THC. This null-result seems at variance with the reduction of ERP amplitudes in the same latency range reported previously at lower doses of THC (Ilan et al., 2004, 2005). However, these authors did not consider differential but absolute ERP amplitudes and used quite different (memory) tasks. There is general consensus that memory processes are affected by THC (e.g., Ameri, 1999). In fact the light cannabis users in our sample did show a linear dose-related decrease in OSN amplitude. In contrast, the more heavy recreational cannabis users in our sample showed no appreciable dose-related OSN modulation. This absence might be related to a blunted cannabis response in heavy users that has been reported for behavioral measures (D'Souza et al., 2008). A blunted response in a subset of participants probably obscured the main dose effect from reaching statistical significance.

The only task-related ERP component that did show a clear main effect of THC dose was the P300. This component was decreased in previous acute cannabis studies (Ilan et al., 2004; Roser et al., 2008) as well as in the majority of reports on chronic cannabis intake (Solowij et al., 1991; but see Patrick and Berthot, 1995, for an exception; Kempel et al., 2003; Yoon et al., 2006). The P300 has been interpreted as a manifestation of the amount of attentional resources devoted to stimulus categorization (Kok, 2001). The latter also implies updating and maintaining the memory representation of context, e.g., task instructions (Polich, 2007). Note that in the present task the most

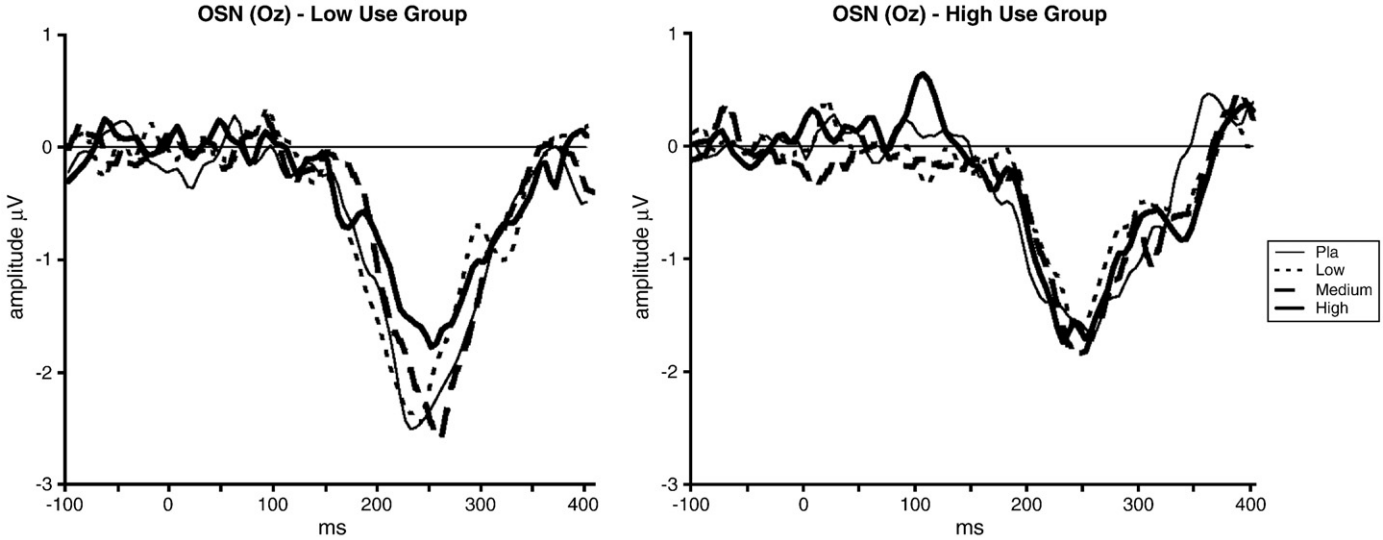

Fig. 4. Grand average ERPs showing the OSN at electrode Oz for low (left panel; $n = 11$) and high use subgroups (right panel; $n = 12$). Only the low use group showed a significant THC effect.

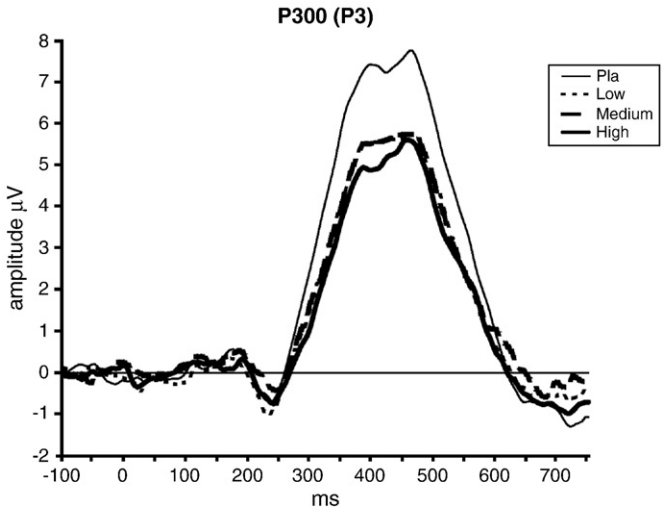

Fig. 5. Grand average ERPs showing the differential P300 effect (target minus orientation-relevant non-target) under different THC doses at electrode Pz.

important task-related categorization presumably involved target versus non-target discrimination. From that perspective the decrease in P300 might be related to the decrease in the reaction time for targets and its standard deviation. The latter has been interpreted as a manifestation of lapses of attention, which suggests that lapses of attention increase with THC dose. So, following Ilan et al. (2004) and Roser et al. (2008), it is concluded that acute cannabis and/or THC intake interferes with attention devoted to stimulus processing, or more specifically, stimulus categorization and context updating. It should be noted that this decrease in P300 amplitude is not specific to cannabis or THC intake. In contrast, it is rare to observe psychiatric or neurological conditions with an impact on cognition that do not affect P300 amplitude and/or latency (Polich and Herbst, 2000).

The P300 did not show a linear dose–effect relation, in contrast to THC serum levels, and behavioral measures. This would imply that either the effect was not receptor-specific, or it constituted a floor-effect. In line with the interpretation that P300 reflects context updating (Donchin, 1981) a loose relationship between the actual performance on a given trial and P300 amplitude might be expected. The observed difference in dose–response relations for P300 (non-linear) and behavior (linear) might be a reflection of such loose relationship.

P300 latency did not seem to be affected by THC intake. This replicates a study by Roser et al. (2008) who tested for a P300 latency effect and did not find it. Studies on chronic effects of cannabis also

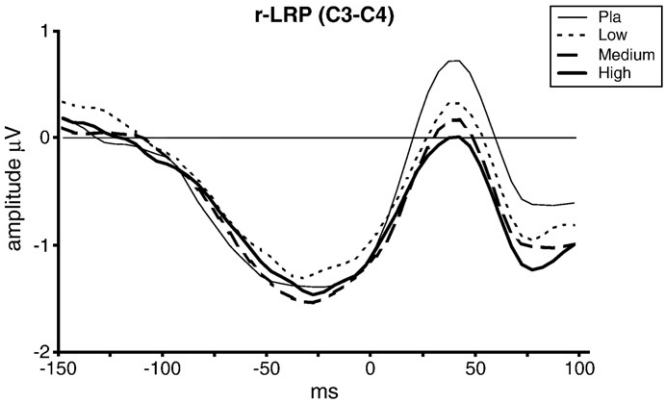

Fig. 6. Grand average response-locked LRP showing the lateralization of brain responses at central electrodes in a time-window surrounding the motor response (at 0 ms). The different lines indicate the LRP under different THC doses.

failed to observe a latency effect (Patrick et al., 1995; Kempel et al., 2003), although not unequivocally (Solowij et al., 1995).

Furthermore, two dose-related effects of THC on brain correlates of sensory processing were observed in the present study. Firstly, the differential bottom–up sensory processing of spatial frequencies decreased linearly with THC dose. This component reflects the sum of the amplitudes in two areas of occipital cortex that are sensitive to high and low spatial frequencies, respectively (Kenemans et al., 2000). A similar decrement in ERPs related to visual sensory processing has been reported for both acute (Ilan et al., 2004) and chronic cannabis use (Patrick et al., 1997). The present study extends the previous findings. It involved an ERP component (SFD80) that is not affected by attentional processes (Kenemans et al., 2002). This could not be excluded for the N100 that was found to be modulated in the previous studies (Heinze et al., 1994; Mangun, 1995). Moreover, the present study showed that the dose–response relationship was linear up to 69 mg THC.

Secondly, response-locked potentials at lateral electrodes located over the motor cortex (C3 and C4), revealed an interesting dose effect. Whereas the pre-movement LRP did not vary reliably in amplitude and onset with different doses, the relative positivity around 40 ms post-response did. This peak was most pronounced in the placebo condition and its amplitude decreased in a linear fashion with increasing dose. This potential is reminiscent of the so-called reafferent potential, that follows both active and passive movements within 100 ms of movement onset (Shibasaki et al., 1980). The reafferent potential originates from the somatosensory area and is larger over the hemisphere contralateral to the movement side (Bötzel et al., 1997; Kristeva-Feige et al., 1997). Because of its contralateral dominance it presumably did show up in the LRP traces in the first place. By interpreting the post-movement LRP effect as reafferent and thus somatosensory, it relates to studies that have demonstrated subjectively disordered external and body-perception after administration of THC (D'Souza et al., 2004). Together with the SFD80 effect it suggested that cannabis inhibits sensory processes in general. Early reports on cannabis frequently mentioned the perceptual altering properties of cannabis. These reports go back to JJ Moreau de Tours, 1845 (cited by D'Souza et al., 2004), and include toxicological accounts of the effects of cannabis (such as Ameri, 1999) as well as DSM-IV and ICD-10. These reports are supported by subjective ratings of perceptual alterations (D'Souza et al., 2004; Zuurman et al., 2008). In contrast there is little support for perceptual alterations from studies that record objective correlates of basic perceptual functioning, except for a few studies on binocular depth inversion (Leweke et al., 1999, 2000; Koethe et al., 2006). However, binocular depth inversion is interpreted as reflecting the influence of top–down conceptual knowledge in visual perception. The latter influence is diminished by synthetic THC analogs, but not by cannabidiol (Leweke et al., 2000). Another indication that (chronic) cannabis use influences basic perceptual processing comes from a study that showed that 18 Hz steady state visual evoked potentials were decreased in female cannabis users (Skosnik et al., 2006). Together with the present results, and those by Ilan et al. (2004), this suggests that ERP recordings are among the more reliable indicators of modulations of perception by cannabis and THC.

A pharmacological basis for decreases in sensory/perceptual ERP components, could be the moderate presence of CB1 receptors throughout the cerebral cortex (Herkenham et al., 1990). Although not particularly dense in primary sensory cortices, these areas show a distinct laminar distribution of CB1 receptors (Eggan and Lewis, 2007). This distinct distribution might hypothetically account for distinct effects of cannabis on ERPs generated from these cortices (such as SFD80 and post-motor potential) and not others (most selection potentials). In general, THC binding to CB1 receptors produced non-task related decrease of regional cerebral blood flow in occipital, temporal, parietal and frontal cortex, suggesting deactivation of these cortices (O'Leary et al., 2002). These deactivations might stem from the agonistic effects

Table 2
Mean (±SD) THC blood serum concentration, subjective "high" (on a 100 mm visual analog scale) reaction time (MRT) and the standard deviation of the reaction times (SDRT) for all four doses. Performance on the four response categories is defined as the percentage correct responses to target stimuli (Hit) and correct non-responses to either irrelevant stimuli and stimuli sharing only the spatial orientation or frequency with the target stimulus.

Dose	THC (μg/l)	"High" (mm)	MRT (ms)	SDRT (ms)	Hits (%)	Correct rejections (%)		
						Frequency-relevant	Orientation-relevant	Irrelevant
Placebo	0.9 (1.7)	0.0 (0)	367 (44)	72 (15)	97 (3.8)	96 (2.3)	100 (0.8)	100 (0.4)
Low	7.2 (5.3)	17 (20)	376 (48)	78 (19)	97 (2.7)	95 (3.5)	99 (1.0)	100 (0.7)
Medium	12 (8.5)	26 (23)	386 (46)	82 (19)	95 (6.2)	95 (2.7)	99 (0.8)	99 (0.7)
High	14 (11)	38 (27)	390 (50)	82 (18)	96 (5.1)	95 (2.7)	100 (0.7)	99 (1.1)

of THC on presynaptic CB1 synapses, which are of inhibitory nature (Wilson and Nicoll, 2001).

Finally, we observed several ERP modulations that were related to interindividual differences in cannabis use. The upper half of the sample in terms of average cannabis use displayed smaller SFD80 and FSP amplitudes. Furthermore, the participants who started using cannabis earlier in their lives showed smaller OSN amplitudes. For SFD80 and OSN these results are in line with acute effects and might reflect the accumulative effect of chronic cannabis intake. Alternatively, because SFD80 is affected by average use, this effect might also constitute a residual effect of recreational use of cannabis. In contrast, the chronic or residual effect on FSP was not complemented by an acute effect in the present study. Therefore it might stem from the accumulative effect of subliminal acute effects. However, the retrospective design of the study cannot exclude the presence of innate interindividual differences that influence both ERP amplitudes and the chances on earlier and/or heavier cannabis intake. This is especially true for the OSN, which showed a blunted acute cannabis response in the relatively heavier cannabis users. Such a blunted response in a non-desirable (side) effect of cannabis, here a decrease in cognitive functioning, might account for a larger chance of continued and more frequent use of cannabis (D'Souza et al., 2008).

The present study has several limitations. First, as the cannabis was smoked with tobacco, a mixture of effects of THC, other cannabinoids and nicotine (Pritchard et al., 2004) or their interactions could have generated the present results. However, each cigarette contained the same amount of tobacco and nicotine. In addition smoked nicotine has a half-life of 45 min. Therefore nicotine was estimated to have a negligible effect on the present results. With reference to other cannabinoids, cannabinol, constituted only 0.32 to 0.36% of the cannabis used in the present study. Other cannabinoids were present at even lower doses.

Second, at time of the ERP recordings the blood serum THC concentration had decreased to about 5% of its maximum (Hunault et al., 2008). Yet, subjective "high" scores and reaction times on a variety of psychomotor tasks show time courses with a far longer half-lives (~3 h) or even flat time curves (e.g., Ilan et al., 2004, 2005; Ramaekers et al., 2006; Zuurman et al., 2008). Given the dose-dependent results on serum THC levels, subjective "high", mean RT and several ERP components in the present study, the brain THC level should still have been effective and well above a floor concentration, possibly due to the very high lipophilicity of THC (cf. Pope et al., 1995; Grotenhermen, 2003). Alternatively, active metabolites such as 11-OH-THC have a longer half-life (Grotenhermen, 2003; Hunault et al., 2008). The serum concentration of the latter metabolite, and not of THC itself, has been shown to correlate with the mismatch negativity ERP component (Juckel et al., 2007).

Furthermore, the study included participants that smoked between 2 and 12 cannabis cigarettes per month. Recently, it has been argued that such findings should not be generalized to daily cannabis users (Nordstrom and Hart, 2006). The present light users were specifically included because this strikes the balance between inclusion of naive non-users, which would be unethical, and the effects of abstinence and residual cannabinoids that have been reported for heavy users (cf. Ramaekers et al., 2006). However, even within this sample we obtained evidence for blunted responses in the relatively heavy compared to the light cannabis users (cf. D'Souza et al., 2008). For a more precise interpretation of the observed group differences it would be worthwhile to test whether these differences persist after longer and more controlled abstinence (Pope et al., 2001).

Also, we failed to record the handedness of the participants. Yet, possible influences of handedness should have been mitigated because dependent measures were aggregated over response side and ERPs were recorded from midline electrodes.

Finally, one might argue that, although statistically significant the observed error rates were low, and the RT effects were moderate, and therefore visual attention load was too low for observing selective attention effects. However, this has not precluded that ERP effects have been observed before in the present task as well as in other tasks with comparably low attentional load according to absolute error rate and RT effects (Kenemans and Lorist, 1995; Ilan et al., 2004).

In sum, the present study has set out to study the effects of exposure to cannabis with high doses of THC on selective attention. Yet, the pattern of results did not show significant decrements in performance or ERP correlates of selective feature processing after THC exposure, except for the OSN in the low cannabis use subgroup. We rather observed non-selective decrements in performance and ERP components such as P300 amplitude, suggesting a decrement in general attentional or processing resources. This decrement might partly stem from an increase in the number of lapses of attention. Furthermore, ERP manifestations of bottom–up visual and somatosensory processing were decreased in relation with THC dose. The present findings are relevant for, e.g., driving capabilities several hours after smoking cannabis cigarettes containing high doses of THC, as presently available in Europe and Northern America, or acutely following cigarettes containing less THC.

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