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ORIGINAL PAPER

Auditory mismatch negativity deficits in long-term heavy cannabis users

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Abstract Mismatch negativity (MMN) is an auditory event-related potential indicating auditory sensory memory and information processing. The present study tested the hypothesis that chronic cannabis use is associated with deficient MMN generation. MMN was investigated in age- and gender-matched chronic cannabis users ($n = 30$) and nonuser controls ($n = 30$). The cannabis users were divided into two groups according to duration and quantity of cannabis consumption. The MMNs resulting from a pseudorandomized sequence of 2 × 900 auditory stimuli were recorded by 32-channel EEG. The standard stimuli were 1,000 Hz, 80 dB SPL and 90 ms duration. The deviant stimuli differed in duration (50 ms) or frequency (1,200 Hz). There were no significant differences in MMN values between cannabis users and nonuser controls in both deviance conditions. With regard to subgroups, reduced amplitudes of frequency MMN at frontal electrodes were found in long-term (≥8 years of use) and heavy (≥15 joints/week) users compared to short-term and light users. The results indicate that chronic cannabis use may cause a specific impairment of auditory information processing. In particular, duration and quantity of cannabis use could be identified as important factors of deficient MMN generation.

Keywords Cannabis · Long-term effects · Cognitive deficits · Event-related potentials · Mismatch negativity

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Introduction

Cannabis sativa is the most widely used illicit drug in the Western world. Co-occurrence of cannabis abuse with other psychiatric disorders has been well described, particularly with schizophrenia [6, 10]. Δ^9-Tetrahydrocannabinol (Δ^9-THC) has been identified as the primary psychoactive constituent of the *C. sativa* plant [9]. Δ^9-THC produces characteristic behavioral, cognitive and psychomotor effects due to its partial agonistic activity at the central cannabinoid (CB_1) receptor. More than 60 additional cannabinoids have been detected [7]. Cannabidiol (CBD) is the second most abundant constituent of *C. sativa* that, in contrast to Δ^9-THC, has no psychoactive properties. Several studies found that CBD may reduce several psychoactive effects of Δ^9-THC. Therefore, neuroprotective and antipsychotic activity of CBD has been suggested [22, 34, 52].

Numerous studies have reported on the chronic effects of cannabis use on cognitive performance using neurophysiological and neuropsychological assessments. In particular, specific impairments of attention, memory and executive functions have been observed in chronic cannabis users even when they were not acutely intoxicated [19, 40], as well as in children prenatally exposed to cannabis [27]. Certain deficits in neurocognitive function have also been described in schizophrenic patients with comorbid substance abuse (primarily cannabis) compared to nonusing schizophrenic controls [48], whereas other studies found no or even better cognitive performances in dual diagnosis schizophrenia [31]. Brain imaging studies of cannabis users have demonstrated altered morphology, function, blood flow and metabolism in prefrontal, hippocampal and cerebellar regions [20, 29, 51], whereas there were no differences in brain morphology in schizophrenic patients with predominantly comorbid cannabis abuse

compared to nonusing patients [49]. Interestingly, cognitive impairments appear to increase with duration and frequency of cannabis use suggesting persistent deficits as a result of long-term changes due to a neurotoxic effect of long-term cannabis exposure [2, 43]. These observations are consistent with the finding of high CB_1 receptor densities in the cerebral cortex, especially in frontal regions, the hippocampus and the cerebellum [13]. These brain regions have been found to be critically involved in cognitive processes, such as attention, memory and executive functions. However, only a small number of event-related potential studies in cannabis users have been carried out so far [17, 41, 42].

The auditory mismatch negativity (MMN) is a negative component of the auditory event-related brain potential (ERP) which is elicited by any discriminable change of a repetitive sound [23]. It occurs with a latency of 100–200 ms after the presentation of a tone stimulus that deviates in one of its acoustic dimensions (e.g., frequency, intensity, duration and location) from a sequence of frequently repeated standard stimuli. The use of the MMN as an objective measure of auditory function is based on the independence of the MMN elicitation from attention reflecting a predominantly automatic and preattentive process [26]. However, some studies have also reported that under exceptional circumstances MMN generation can be modulated by attention [44, 50]. The glutamatergic *N*-methyl-D-aspartate (NMDA) receptor seems to play a central role in MMN generation. Animal and human experimental studies demonstrated that NMDA receptor antagonists dose-dependently blocked the MMN response recorded in the primary auditory cortex [12, 15, 46]. There is, however, also evidence for an additional frontal contribution to the MMN [24]. Näätänen and Michie [25] suggested that the sensory-specific cortex pre-perceptually detects stimulus change, whereas the subsequent frontal activation might be associated with involuntary attention switch to stimulus change by comparing the deviant stimulus to the sensory memory trace of the standard stimulus [32]. Deficits in MMN generation are a robust feature in schizophrenia indicating impaired functioning of automatic information processing and auditory sensory memory that also extends to early stages in cortical information processing [14, 45].

The specific aim of this study was to determine the effects of chronic cannabis use on MMN generation. Based on the assumed relationship between cannabis, the endogenous cannabinoid system and cognitive dysfunctions found in schizophrenic patients [4, 8], it was hypothesized that (1) chronic cannabis users reveal smaller MMN amplitudes and prolonged MMN latencies compared to nonuser controls, and (2) duration and quantity of cannabis use are related to MMN amplitudes and latencies.

Materials and methods

Subjects

Thirty chronic cannabis users and 30 nonuser controls were included in this study. All subjects were full-time students at the Ruhr-University Bochum, Germany. The minimum requirement for participation as a cannabis user was regular use of at least three times per week for a period of at least 2 years. Detailed drug histories were assessed, and for all users cannabis abuse could be diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, (DSM-IV) criteria [1]. The cannabis user group had used cannabis for a mean of 6.9 years (range 2–13 years) at a mean quantity of 15.6 joints/week (range 3–32 joints/week). The cannabis user group was split at the median on both quantity (light <15 joints/week vs. heavy ≥ 15 joints/week) and duration (short-term <8 years vs. long-term ≥ 8 years) of cannabis use. No meaningful division of groups could be achieved on the basis of age at onset of cannabis use. All cannabis users were cigarette smokers with a mean duration of nicotine consumption of 5.6 years and a mean quantity of 8.6 cigarettes/day, whereas in the nonuser control group, 9 of 30 subjects were cigarette smokers with a mean duration of nicotine consumption of 6.2 years and a mean quantity of 9.9 cigarettes/day. The demographic characteristics of the entire sample and the mean levels of cannabis use for each group are provided in Table 1.

The group of nonuser controls was matched for age and gender ($p > 0.1$). The control subjects had never used cannabis in the past according to their statement in the questionnaire. Both cannabis users and controls had normal hearing and had no history of any psychiatric or neurological disorders, or use of any other drugs, as confirmed by a structured psychiatric interview (MINI) [38]. All subjects were right-handed, as assessed by the Edinburgh Handedness Questionnaire [28]. Cannabis users were instructed to abstain from cannabis for at least 24 h prior to testing in order to minimize acute cannabis effects. No cannabis withdrawal was seen nor reported. For both cannabis users and controls, alcohol consumption was not allowed for at least 24 h prior to testing. Moreover, the urine of all subjects was tested for amphetamines and ecstasy, benzodiazepines, cannabinoids, cocaine, methadone and opiates before the test session in order to ensure that they had not consumed any illegal drug prior to testing, and to verify the use of cannabis in the user group. All subjects did not take any medication before the onset of the study. The study was approved by the Ethics Committee of the Medical Faculty of the Ruhr-University Bochum and carried out in accordance with the Declaration of Helsinki. After complete description of the study, all subjects gave

Table 1 Demographic characteristics of the study sample (in means ± SD)

	All users ($n = 30$)	Long-term users ($n = 15$)	Short-term users ($n = 15$)	Heavy users ($n = 16$)	Light users ($n = 14$)	Controls ($n = 30$)
Age (years)[a]	23.0 (2.2)	24.2 (1.9)**	21.7 (1.8)	23.3 (2.1)	22.6 (2.3)	23.9 (2.3)
Sex (male/female)[b]	17/13	9/6	8/7	8/8	9/5	15/15
Education (years)[a]	14.9 (1.6)**	15.4 (1.7)	14.5 (1.4)	14.7 (1.8)	15.2 (1.4)	16.6 (2.5)
Cannabis use						
Quantity (joints/week)[a]	15.6 (8.8)	18.6 (8.1)	12.6 (8.7)	22.4 (5.4)***	7.8 (3.9)	0
Duration (years)[a]	6.9 (3.0)	9.5 (1.5)***	4.4 (1.8)	8.2 (2.6)*	5.5 (3.0)	0
Abstinence (days)[a]	2.5 (2.2)	1.7 (0.7)	3.3 (2.9)	1.6 (0.7)*	3.4 (2.9)	0
Nicotine use						
Smokers (yes/no)[c]	30/0***	15/0	15/0	16/0	14/0	9/21
Quantity (cig./day)[a]	8.6 (8.5)	11.3 (8.6)	5.9 (7.8)	9.1 (8.4)	8.1 (9.0)	9.9 (5.0)
Duration (years)[a]	5.6 (4.9)	8.2 (4.7)**	3.1 (3.6)	6.8 (5.0)	4.3 (4.6)	6.2 (3.6)
Alcohol use						
Quantity (drinks/week)[a]	4.1 (5.7)*	5.0 (7.9)	3.2 (1.8)	4.4 (7.8)	3.7 (1.8)	1.9 (1.8)

Long-term users ≥8 years, short-term users <8 years, heavy users ≥15 joints/week, light users <15 joints/week

[a] Mann–Whitney test: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (users vs. controls; long-term vs. short-term; heavy vs. light)

[b] χ^2 test test: $p > 0.1$

[c] χ^2 test test: $p < 0.001$

their written informed consent. Subjects received monetary compensation (20 Euros) for participating in the study.

Auditory stimulation

The subjects were presented with a pseudorandomized sequence of 2 × 900 tone stimuli to elicit auditory evoked MMN (Presentation 11.3®, Neurobehavioral Systems Inc., Albany, CA, USA). Standard tones (80%) had a frequency of 1,000 Hz and a duration of 90 ms (including 10 ms rise/fall time). Duration deviants (10%) were of the same frequency but at a shorter stimulus duration (50 ms), and frequency deviants (10%) were of the same duration but at a higher stimulus frequency (1,200 Hz). All the stimuli were pure sinusoidal tones with 80 dB SPL. The tones were presented via headphones (Sony MDR-XD400) to both ears with no two deviants following in a row at a mean interstimulus interval of 450 ms (±30 ms).

Event-related potential recording

Recording took place in a sound-attenuated and electromagnetically shielded room adjacent to the recording apparatus (BrainVision BrainAmp® MR, Brain Products GmbH, Munich, Germany). Subjects were seated in a slightly reclined chair with a headrest. During the entire test session, all subjects were instructed to avoid body and eye movements, and to watch a picture on the wall. The ERPs recorded by 32 Ag–AgCl electrodes referred to FCz, using an electrode cap (EasyCap®, EasyCap GmbH, Herrsching, Germany). The electrodes were placed according to the International 10/20 System. FpFz served as ground electrode. Eye movements were monitored using an electrode located 1 cm below the left outer canthus. Impedances were kept below 5 kΩ. For the analyses of the auditory ERPs (BrainVision Analyzer®, Brain Products GmbH, Munich, Germany), epochs of 560 ms duration including a 100 ms pre-stimulus baseline were constructed. Epochs with amplitudes that exceeded ±100 μV at any electrode were excluded from further averaging. Following artifact rejection, epochs were averaged off-line for each subject and were digitally filtered with a high-pass filter of 1.0 Hz (24 dB/oct) and a low-pass filter of 20 Hz (24 dB/oct). The MMNs were measured in the difference waves obtained by subtracting the ERPs to the standards from the ERPs to the deviants per subject. The MMN amplitude was defined as the largest negative deflection occurring during the 130- to 250-ms latency range after stimulus onset. Thereafter, MMNs were determined semi-automatically with a visual control at the electrode positions Fp1, Fp2, Fz, F3, F4, Cz, C3, C4, T7 and T8.

Statistical analysis

Statistical calculations were based on nonparametric tests. Group differences of the MMN amplitudes and latencies as well as the demographic parameters were assessed by the Mann–Whitney test and the χ^2 test. Values were expressed by mean ± standard deviation (SD). The covariates' duration and quantity of nicotine consumption were added

to the analysis by using univariate analysis of covariance (ANCOVA). Partial correlation coefficients were calculated to determine relationships between duration and quantity of cannabis use, covariates such as duration and quantity of nicotine consumption, and the electrophysiological variables. Statistical significance was taken as $p \leq 0.05$. A $p \leq 0.10$ was regarded as statistical tendency. All statistical analyses were carried out by using the statistical analysis software package SPSS 17.0® (Munich, Germany).

Results

Study subjects

Demographic characteristics are presented in Table 1. There were no significant differences in age and gender between the user group and the control group, but in the user group there were more smokers than in the control group ($p < 0.001$). Cannabis users consumed more alcohol per week ($p < 0.05$) and had less years of education than nonuser controls ($p < 0.01$). Long-term users were older than short-term users ($p < 0.01$). The time since last use of cannabis was shorter in heavy users compared to light users. However, alcohol consumption and years of education did not differ between groups based on duration and quantity of use ($p > 0.1$).

Mismatch negativity

Grand average difference waveforms at Fz and Cz for the user and control group are presented in Fig. 1. Initial comparisons found reduced MMN amplitudes for the electrode Cz ($Z = -2.011$, $p = 0.044$) in the frequency but not in the duration deviance condition in chronic cannabis users compared to nonuser controls. Moreover, there was a statistical trend towards reduced frequency MMN amplitudes for the electrodes C3 ($Z = -1.656$, $p = 0.098$) and C4 ($Z = -1.892$, $p = 0.058$). MMN amplitudes at frontal and temporal electrode positions were not significantly altered. No significant differences in MMN latencies between users and controls neither in the frequency nor in the duration deviance condition have been observed.

With regard to subgroups of cannabis users, we found significantly reduced amplitudes of frequency MMN in long-term users (≥8 years of use) compared to short-term users at frontal electrode positions (Fz: $Z = -2.468$, $p = 0.014$; F4: $Z = -2.592$, $p = 0.010$). Moreover, amplitudes of the frequency MMN were smaller in heavy users (≥15 joints/week) compared to light users at electrode positions Fz ($Z = -2.245$, $p = 0.025$) and C4 ($Z = -1.995$, $p = 0.047$). MMN latencies were not significantly altered in any subgroup.

Because of the potential contribution of nicotine use to MMN values, user and control groups as well as the user subgroups were corrected for the covariates duration and quantity of nicotine consumption, respectively. After correction for nicotine use, there were no significant differences between the cannabis user group and the control group in any of the MMN measures (Fig. 2). However, MMN amplitudes in the frequency deviance condition were significantly smaller at electrode F4 ($F = 4.659$, $p = 0.040$) with a trend at Fz ($F = 4.028$, $p = 0.055$) in long-term users compared to short-term users when correcting for duration of nicotine use (Fig. 3). Moreover, frequency MMN amplitudes remained significantly reduced in heavy users compared to light users at electrode position

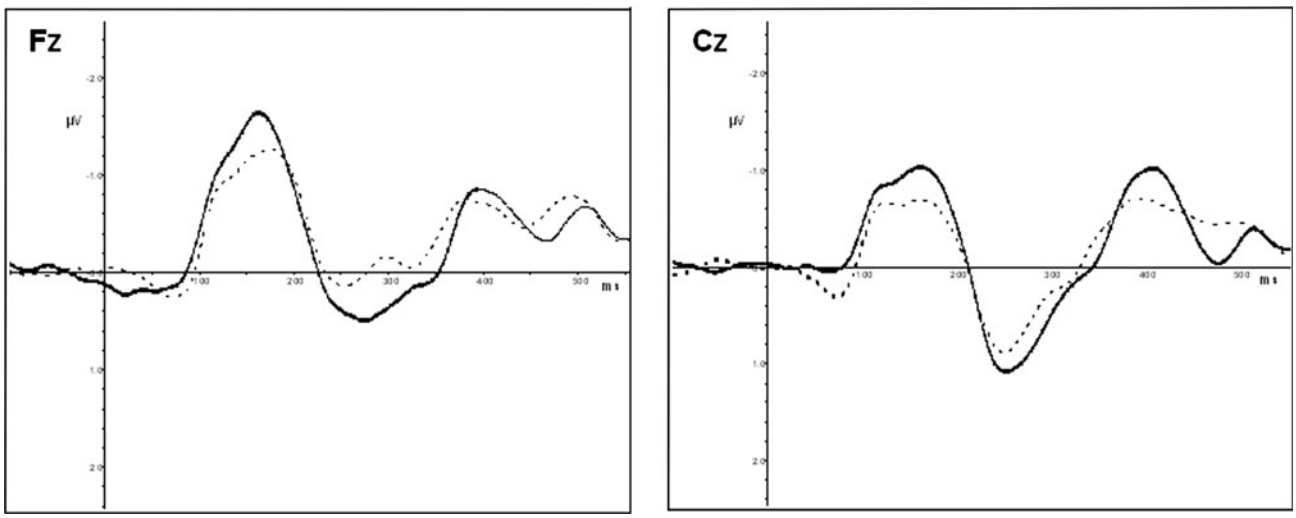

Fig. 1 Grand average waveforms at electrode positions Fz and Cz for the frequency deviance condition in cannabis users (*dotted line*) and nonuser controls (*solid line*)

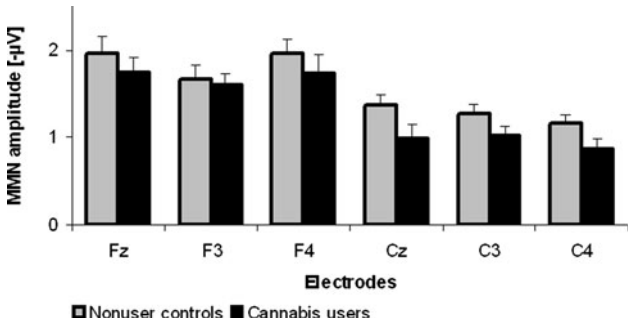

Fig. 2 Mismatch negativity amplitudes of chronic cannabis users compared to nonuser controls in the frequency deviance condition (in means ± SEM)

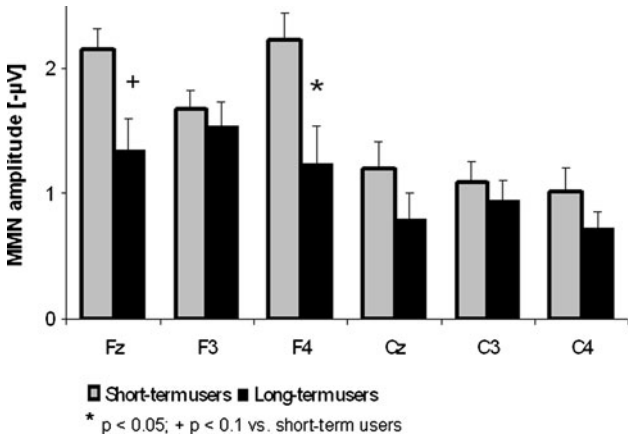

Fig. 3 Mismatch negativity amplitudes of short-term users compared to long-term users (in means ± SEM)

Fz ($F = 6.148$, $p = 0.020$) even after correction for quantity of nicotine use (Fig. 4).

Correlation of mismatch negativity with demographic variables

Duration of cannabis consumption was negatively correlated with MMN amplitudes in the frequency deviance condition at electrodes Fz ($r = -0.501$, $p = 0.005$) and F4 ($r = -0.499$, $p = 0.005$) showing smaller amplitudes with longer duration of use. Quantity of use, age at onset of use and duration of abstinence did not correlate with MMN to frequency or duration deviants. However, these results did not survive statistical significance when correcting for duration of nicotine use (Fz: $r = -0.326$, $p = 0.084$; F4: $r = -0.363$, $p = 0.053$).

In the cannabis user group, duration of nicotine consumption was negatively correlated with MMN amplitudes to frequency deviants at Fz ($r = -0.399$, $p = 0.029$), Cz ($r = -0.579$, $p = 0.001$) and C4 ($r = -0.420$, $r = 0.021$), whereas quantity of nicotine consumption was negatively correlated with frequency MMN amplitudes at Cz

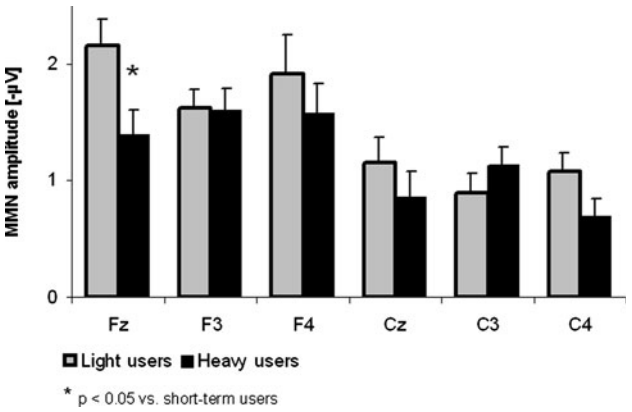

Fig. 4 Mismatch negativity amplitudes of light users compared to heavy users (in means ± SEM)

($r = 0.503$, $p = 0.005$) and C4 ($r = -0.401$, $p = 0.028$). For nonuser controls with cigarette abuse, neither duration nor quantity of nicotine consumption was correlated with MMN parameters in both deviance conditions. In addition, there was no influence of covariates such as age, gender, education or quantity of alcohol consumption on MMN amplitude values in both groups. Covariates such as age, gender, education or quantity of alcohol consumption had no influence on MMN amplitude values in both groups.

Discussion

This is the first study on MMN impairments among long-term heavy cannabis users. Interestingly, there were no significant differences in MMN values between cannabis users and nonuser controls in both deviance conditions. Duration of cannabis use failed to correlate with MMN amplitudes to frequency deviants by a small margin. Moreover, there was no correlation between the quantity of cannabis use and MMN values. With regard to subgroups, a significant reduction of frequency MMN was found in long-term users as well as in heavy users compared to short-term users and light users, respectively, at frontal electrodes. In contrast to the frequency deviance condition, there were no significant differences in MMN values to duration deviants. Additionally, the MMN latencies were not significantly altered in cannabis users compared to controls, which was not very surprising since the MMN latency is a less reliable finding in schizophrenia research [45].

Our data indicate that long-term heavy cannabis use may affect auditory sensory memory and information processing. Similar deficits were seen in schizophrenic patients [45], but also in patients with autism as well as with Alzheimer's and Parkinson's disease [18, 30]. It can be suggested that this effect might be due to cell toxicity or

disruption of neurotransmitter coordination produced by long-term heavy cannabis exposure [5, 36, 37]. In this context, Δ^9-THC as the principal psychoactive exocannabinoid may play a crucial role in cognitive dysfunction through activation of presynaptic CB_1 receptors in the hippocampus and the prefrontal cortex. Cannabinoids are lipophilic substances that accumulate in fatty tissues and thus probably in the brain [33]. While all subjects were required to abstain from cannabis for at least 24 h before testing, the long-term users as well as the heavy users may have considerably higher cannabinoid levels continuously present in the body, which may continue to affect their cognitive performance even when they are not acutely intoxicated.

The results of this work are in accordance with previous event-related potential studies that investigated the effects of chronic cannabis use on selective attention. In this context, it is of note that attentional deficits in schizophrenia, as indexed by reductions of processing negativity (PN) and P300 amplitude, may, at least in part, be due to impairments in preattentive mechanisms [39]. The minimum abstinence period for the following studies was 24 h prior to testing. Cannabis users showed a significant increase of frontal PN to irrelevant stimuli compared to nonuser controls indicating that long-term cannabis use may impair the ability to focus attention and filter out irrelevant information [41]. Interestingly, these deficits were strongly correlated with duration but not with frequency of cannabis use. Moreover, cannabis users revealed significantly reduced P300 amplitudes and/or prolonged P300 latencies compared to controls reflecting dysfunctional allocation of attentional resources and prolonged stimulus evaluation time [17, 41, 42]. However, the attribution of cannabis-associated attentional deficits to persisting acute effects, residues of cannabinoids in the brain, withdrawal phenomena or lasting changes due to a neurotoxic effect of long-term cannabis exposure requires further investigation.

Chronic effects of cannabis on MMN generation have to be distinguished from those obtained by acute administration of cannabinoids. Juckel et al. [16] investigated the acute effects of pure Δ^9-THC and standardized cannabis extract containing Δ^9-THC and CBD on MMN parameters in healthy subjects. Unexpectedly, the authors found no effects of pure Δ^9-THC on MMN amplitude or latency. However, there was a significant increase of MMN amplitude under the standardized cannabis extract indicating higher cortical activation. This result has been attributed to the effects of CBD confirming the hypothesis that CBD may exhibit antipsychotic properties [22, 34, 52]. Based on the negative findings of Δ^9-THC, the data was reanalyzed with regard to several single nucleotide polymorphisms within the neuregulin 1, the dysbindin and the G72 gene that are thought to be susceptibility genes for schizophrenia [35]. In fact, Δ^9-THC revealed genotype-dependently reduced MMN amplitudes at frontal and central electrodes suggesting that variations within schizophrenia-related genes may alter the sensitivity to the effects of CB_1-agonistic cannabinoids on auditory sensory processing. The exact mechanisms underlying the contradictory results concerning the acute and chronic effects of cannabinoids on MMN generation remain unclear and cannot be derived from the current data. It can be hypothesized that functional and/or structural changes in the brain due to pharmacokinetic and pharmacodynamic diversities, chronic neurotoxic effects in long-term cannabis users as well as genetic factors may account for these differences.

In addition, duration and quantity of nicotine consumption in the cannabis user group was negatively correlated with MMN amplitudes to frequency deviants as well, whereas there was no correlation between nicotine consumption and MMN values in smoking nonuser controls. This finding was not very surprising since all cannabis users were cigarette smokers using cannabis simultaneously with nicotine. Regrettably, reports on the chronic effects of nicotine on MMN have been noticeably lacking in the literature. On the other hand, nicotine has been shown to enhance some of the effects of Δ^9-THC by alterations of the pharmacokinetic and pharmacodynamic characteristics of Δ^9-THC [21]. Nicotine may improve absorption and distribution of Δ^9-THC in the blood and brain, whereas several compounds in tobacco have been found to alter the two Δ^9-THC-degrading cytochrome P450 enzymes, CYP2C9 and CYP3A4 [47]. Moreover, nicotine may upregulate the density of CB_1 receptors in the brain and augment the levels of endocannabinoids in some brain regions. It therefore remains speculative whether these interactive effects between Δ^9-THC and nicotine may contribute to the MMN deficits observed in chronic cannabis users.

Several limitations of this study have to be considered. First, the data was collected from an only moderately large group of subjects ($n = 30$). Second, information on duration, quantity and period of abstinence of cannabis use as well as on the use of other illegal drugs in the past were obtained by self-report without external validation. However, previous studies have demonstrated that self-reports of use of cannabis and other drugs seem to be fairly reliable [3, 11]. Third, as there are no defined criteria for the differentiation between long- and short-term use or heavy and light use of cannabis, respectively, the cannabis user group was split at the median on both quantity and duration of use. However, this approach is a well-established method for the determination of quantity and duration of cannabis use and is widely used in cannabis research [42, 43].

And finally, a possible selection bias caused by the study requirements might have affected the results. It can be speculated whether chronic cannabis users with severe cognitive deficits might have been less likely to participate in the study. Therefore, an underrepresentation of severely impaired subjects within the study sample may be assumed. Consequently taken together, the results of this study have to be interpreted with caution.

In summary, the results of this study provide support for the hypothesis that chronic cannabis use may be associated with a specific impairment of auditory sensory memory and information processing as measured by the auditory MMN. In particular, duration and quantity of cannabis use could be identified as important factors of deficient MMN generation. These findings warrant further studies into the neuronal mechanisms that are involved in the long-term effects of cannabinoids on MMN generation.

Conflict of interest statement The authors declare that they have no potential conflicts of interest in the context of the subject of this article.

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