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Auditory-Evoked Potentials and Selective Attention: Different Ways of Information Processing in Cannabis Users and Controls

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Key Words

Auditory-evoked potentials · Cannabis · Selective attention · Event-related potentials EEG · Age of onset · Cumulative toxicity

Abstract

The present study tested the hypothesis that chronic cannabis use leads to persistent attentional dysfunctions and that age of onset of cannabis use is a potential predictor of impaired test performance and information processing. Brain event-related potentials (ERPs) during a complex auditory selective attention task were recorded from 21 cannabis users divided into two groups according to age of onset and from 13 controls comparable with respect to age, IQ and educational background. Participants were instructed to detect target tones of a particular location, pitch and duration from a total sample of random frequencies. The study reveals that the latency of the greatest negative peak of ERPs (200 and 300 ms) to target tones was shorter in controls, while there was no clear difference between target and non-target within cannabis users. In addition, users displayed a reduced P_3 to target tones. This was more pronounced in early-onset cannabis users. These data suggest that chronic cannabis use relates to different types of information processing under conditions of selective attention. There is some evidence that users employed different strategies of attention allocation. The results are discussed with respect to possible underlying mechanisms and clinical implications.

Introduction

Cannabis is the most widely consumed non-legal substance, especially by young people. For this reason, many studies investigated possible harzardous influences of cannabis on physical or mental health. The wide scope of previous studies indicated impairments in attention, memory and time perception during acute intoxication [for review see ref. 1]. However, concerning potential long-term effects of chronic use of cannabis, there is still a large controversy with respect to both biochemical and behavioural aspects [2–9]. The findings of Pope et al. [6] and Fried et al. [8] suggest that cognitive impairments in long-term cannabis users appear to be reversible after abstinence or cessation of use. In contrast, results of Solowij et al. [7] and Bolla et al. [9] indicate long-lasting decrements in cognitive functioning. Recent studies suggest that Δ^9-tetrahydrocannabinol (THC) might cause a persis-

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tent dysfunction in prefrontal cortical systems which play an important role in the modulation of attention and working memory [10–13]. Struve et al. [13] found altered EEG activity over the bilateral frontal and prefrontal cortex in chronic cannabis users. Animal studies have shown that repeated administration of THC to rats leads to persistent and anatomically selective reduction in prefrontal cortical dopamine metabolism [14]. There are reports demonstrating that effects of cannabinoids on information processing in humans may depend on the age of onset [15–17]. A significant impairment in neuropsychological tests in early-onset (EO) users (onset before the age of 17) compared with late-onset (LO) users and controls (who differed only slightly from each other on these tests) could be demonstrated by Pope et al. [17].

Solowij et al. [4, 5, 18] investigated persistent attentional impairment in cannabis users via event-related potentials (ERPs) during a complex auditory selective attention task. In summary, in all of the three studies, an enhanced processing negativity to irrelevant stimuli (tones) and a reduced processing negativity to relevant stimuli could be demonstrated for cannabis users in contrast to controls. This was hypothesized to reflect an impaired ability to focus attention and to filter out irrelevant information. Regarding the amplitude of P_3, the authors inferred a dysfunction in the allocation of attentional resources and strategies of stimulus evaluation. Following Hansen and Hillyard [19, 20], we used a complex multidimensional auditory selective attention task, containing tones that vary on the dimensions of location, pitch and duration, in which duration discrimination was most difficult followed by pitch discrimination to answer the following questions.

(1) Do cannabis users reveal different information processing regarding N_2 (measured between 200 and 300 ms) and P_3 (measured between 300 and 400 ms) to target tones and non-target tones that differ either in the dimension of duration or pitch or location or in all dimensions during a complex auditory selective attention task?

(2) If so, are these differences related to the age of onset of users?

Materials and Method

Subjects

Participants were recruited by written announcements attached to different places around the city of Aachen, Germany, and by word of mouth. Prior to final enrolment, inclusion criteria were screened by a telephone interview. All subjects were healthy volunteers. They were free of any past or present psychiatric disease or head injury. Modest alcohol consumption was accepted (≤ 5 beers per week). No participant regularly consumed alcoholic drinks other than beer and wine. Individuals with previous or present abuse of other drugs than cannabis (with the exception of nicotine and caffeine) were rejected. The inclusion criteria for the user group was a minimum of 2 years of regular use of cannabis which was defined as using cannabis at least twice a week for 2 years and no acute intoxication at the time of testing. Participants were instructed to abstain from cannabis and alcohol for at least 24 h prior to testing. All participants agreed to provide one blood and one urine sample on each of the two test sessions. The final sample consisted of 15 male and 6 female cannabis users and 13 controls. The sample was divided into EO (<16 years; $n = 10$) and LO (≥ 16 years; $n = 11$) users and controls. As depicted in table 1, major differences in demographic variables between users and controls were not observed, whereas comparisons between the two user groups yielded significant differences with respect to user history.

Measurements for Comparability of Groups

General intellectual ability was assessed by the Full Scale IQ Index based on the Hamburg-Wechsler intelligence test for adults (revised version) subscales (information, picture completion, block design and similarities) [21]. In order to estimate the degree of acute intoxication, THC and THCOH levels were determined and accumulated. The body mass index (BMI = relation height to weight) was calculated for users because of the complex pharmacokinetics of cannabinoids with storage of psychoactive metabolites in fatty tissue. Cumulative toxicity was extrapolated, based on past and present habits of consumption in individual users. Therefore, subjects had to estimate the average number of days of consumption and amount of consumption per week separately for each 6-month period over the total years of use. Cumulative toxicity was independent of age of onset of cannabis use.

Stimuli

Stimuli consisted of sequences of tones (80 dB) delivered randomly to the left and right ear via headphones (ABR Tubephone ER-3, Etymõtic Research). Half of the tones presented to each ear were 1,047 Hz, half of them 1,319 Hz. Within each frequency, one half of the tones were of a duration of 52 ms, whereas the duration of the other half was 102 ms, both with a 10-ms rise and fall time. The stimuli were presented as 5 random sequences. Each consisted of 200 stimuli with random interstimulus intervals between 1.25 and 1.75 s. Frequency of occurrence was 12.5% for each of the 8 stimuli so that 12.5% were defined as target and 87.5% as non-target tones. All aspects of stimulus generation, delivery, randomisation and storage of response markers were controlled by a computer (Neuroscan STIM 3.0 Software; Neuroscan STIM Audio System P/N 1105). Based on a procedure by Hansen and Hillyard [19], stimuli were classified according to whether they matched (+) or did not match (–) the target on each of the dimensions location (L), pitch (P) and duration (D). The target stimulus (L+P+D+) was always the tone presented to the right ear with a high pitch (1,319 Hz) and long duration (102 ms). Responses to classify the stimuli as target or non-target tones were made via pressing a touch pad (Neuroscan P/N 1141).

ERP Recording

Recordings were obtained from 12 EEG channels (Fp_1, Fp_Z, Fp_2, F_3, F_Z, F_4, C_3, C_Z, C_4, P_3, P_Z, P_4) using an electrode cap (Electro-cap International) and tin electrodes. The right earlobe (A_2) was used as a

Table 1. Participants' characteristics and habits of consumption in cannabis users

Characteristics	EO (< 16 years; n = 10)	LO (≥ 16 years; n = 11)	Controls (n = 13)
Present age, years	22.2 ± 3.4	24.6 ± 3.0	23.1 ± 2.6
Age of onset, years	15.1 ± 0.61	19.4 ± 2.1	–
IQ (Full Scale IQ Index of HAWIE-R)	123.5 ± 10.8	132.9 ± 12.8	127.8 ± 12.2
Female/male	5/5	1/10	6/7
Regular use, years	7.1 ± 3.4	5.2 ± 2.4	–
Estimated life dose, g	1,136.7 ± 612.4	1,276.6 ± 1,390.5*	–
Weekly frequency of use in the last month prior to testing day per week	5 ± 2.1	2.3 ± 1.9 **	–
THC + THCOH, ng/ml plasma	2.11 ± 3.44	0.53 ± 1.1	–
BMI	23.24 ± 2.5	24.57 ± 6.7	–

Figures are means ± SE. Difference from EO group: * $p < 0.05$; ** $p < 0.01$, according to t tests. HAWIE-R = Hamburg-Wechsler intelligence test for adults, revised version.

reference. Impedance between each channel and reference was kept below 2 kΩ. Data were recorded using a bandpass filter of 0.1–100 Hz, without notch filter and stored as 1,024-ms lasting epochs started at stimulus onset. Thus, no recording of pre-stimulus activity took place. The ground electrode was located on the left forearm. Data were recorded digitally with a rate of 1 point/ms without further filtering or online artefact rejection.

Procedure

Subjects participated in two 2½-hour test sessions. During the first session, all participants were screened with respect to exclusion and inclusion criteria (see above).

In order to confirm the inclusion criteria and to control the validity of the subjects' verbal reports in the interview, subjects were administered the Minnesota Multiphasic Personality Inventory [22] to exclude individuals with depression or psychopathological conditions. On both sessions, blood and urine samples were taken from each participant for (a) analysis of possible blood alcohol content, (b) screening for drugs of abuse in urine samples, and in the cannabis user group also for (c) determination of blood concentrations of Δ^9-THC and its major metabolites 11-hydroxy-Δ^9-THC (11-OH-Δ^9-THC, THCOH) and 11- or 9-carboxy-Δ^9-THC (11- or 9-COOH-Δ^9-THC, THCCOOH), by gas chromatography/mass spectrometry and (d) measurement of total THC metabolites in urine by fluorescent polarization immunoassay. At the second session, which took place within 1 month in most cases, the ERP data were recorded from the remaining subjects.

After arrival at the laboratory, the electrodes were attached and participants took place in a darkened, quiet room adjacent to the laboratory. They were trained on the selective attention task until they achieved the criterion level of performance of 75% hits to target tone (right ear, 1,319 Hz, 102 ms). They were instructed to attend to this tone and to respond as rapidly as possible by pressing a response button mounted on the arm of the chair and to respond to all other tones by pressing another button. All subjects completed the trials with their right hand.

Data Analysis

If participants pressed the correct button to classify a stimulus as target or non-target tones within a 1,024-ms response window after stimulus onset, this reaction was classified as correct (hit). ERP epochs linked to wrong responses of a subject or artefacts were rejected from further analyses. The Fp_1, Fp_Z and Fp_2 channels were used for offline artefact rejection caused by eye movements. Artefact rejection was made by visual inspection of every single sweep. Separate averages of the artefact-free epochs were created for each of the 8 tones per person. Subsequently, each of the 8 average value curves, which consisted of 80–90 epochs, was baseline corrected (0–20 ms). Afterwards, these curves were bandpass filtered from 0.1 to 30 Hz.

Subsequently described analyses were based on the ERPs to target tones (L+P+D+), tones that matched target not in duration (termed as L+P+D–), tones that matched target not in pitch (termed as L+P–D+), tones that matched target not in location (termed as L–P+D+) and tones that matched target in no attribute (termed as L–P–D–). In order to assess possible differences in processes of selective attention, groups were compared with respect to amplitude and latency of N_2 peak (200–300 ms) and P_3 peak (300–400 ms) to these 5 tones. Moreover, difference values were calculated by subtracting amplitude and latency of ERPs to each of the 4 non-target tones from amplitude and latency of ERP to target tones (e.g. N_2 peak in ERP to L+P+D– minus N_2 peak in ERP to L+P+D+).

Group differences between cannabis users and controls according to amplitude and latency of N_2 peak and P_3 peak as well as to difference scores in amplitudes and latencies of N_2 peak and P_3 peak were tested by analyses of variance with group as between-subject factors (cannabis users, controls) and stimulus type (target, L+P+D–, L+P–D+, L–P–D–), electrode position (N_2: frontal vs. central; P_3: central vs. parietal) and hemisphere (left, middle or right) as 3 within-subject factors. Since the Levene-2V test revealed significant differences in distribution of variances at 3 of 24 amplitude and latency difference values (C_3 and C_Z), all data were also tested via non-parametric methods (Mann-Whitney U test).

For comparison between groups of cannabis users, analyses of variance were accomplished with group as between-subject factor

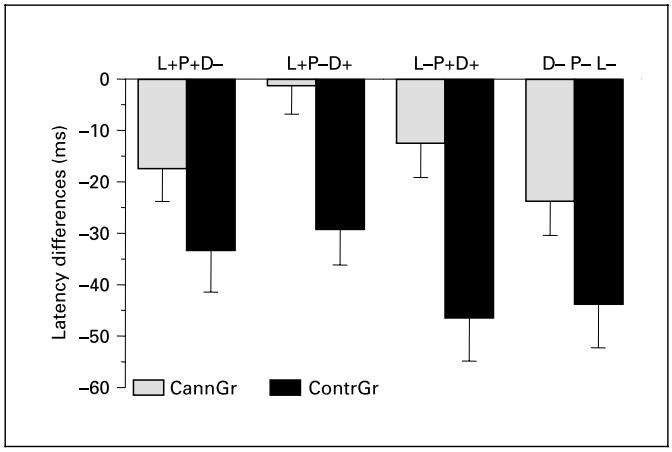

Fig. 1. Means and standard errors of means (SEM) of latency differences between target and non-target stimuli (L+P+D–, L+P–D+, L–P+D+, L–P–D–) averaged across all electrode positions for the cannabis (CannGr) and control group (ContrGr).

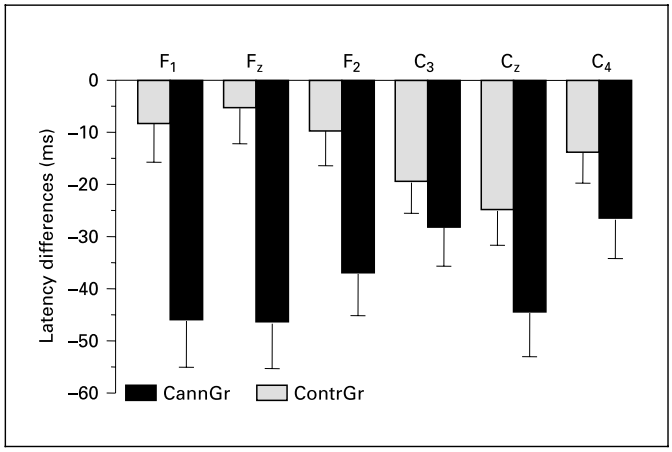

Fig. 2. Means and standard errors of means (SEM) of latency differences between target and non-target stimuli for electrode positions averaged across all non-target tones for the cannabis (CannGr) and control group (ContrGr).

(EO, LO, controls) and the same within-subject factors as described above. Moreover, localisation of significances was achieved by use of post hoc Scheffé tests for multiple comparisons. Afterwards, analyses of covariance were performed with group as the between-subject factor (EO, LO, controls) and the same within-subject factors as mentioned above using cumulative toxicity and THC+THC level as covariates. Results were considered significant if $p < 0.05$.

Results

Comparability of Groups

As can be seen in table 1, general intellectual ability was comparable between all groups which consisted mainly (70%) of students. Subjects in all groups were of comparable age and educational background and all of them were right-handed. Significant differences between users with EO and LO of cannabis use were found for the frequency of use within the last month which was higher in EO, whereas estimated life time toxicity ($p < 0.02$) was higher in LO. THC and THCOH levels indicated a very low level of acute intoxication which was not different between EO and LO. Moreover, duration of use and BMI scores did not differ according to age of onset.

Comparison between Cannabis User Group and Non-User Group

Concerning the amplitude of the N_2, analysis of variance indicated no significant differences between cannabis users and the control group with respect to absolute amplitudes ($F < 1$) or the difference values [amplitude to target minus amplitude to each of the 4 non-target tones (L+P+D–, L+P–D+, L–P+D+, L–P–D–); $F < 1$].

While no significant main effect for group ($F < 1$) could be detected for absolute latency, a significant interaction between group and stimulus type was observed ($F_{4, 29} = 3.627$, $p = 0.016$), indicating that cannabis users exhibited significantly reduced latencies to L– and – in tendency – increased ones to the target tone.

With respect to the latency of the N_2, the difference values to target minus those to non-target tones revealed a highly significant main effect for group ($F_{1, 32} = 9.222$, $p = 0.005$; fig. 1).

As indicated in figure 1, the mean latency difference between target tone and each of the 4 non-target tones was lower (–13.82 vs. –38.29 ms) in the cannabis group than in the control group. Moreover, the interaction between group and electrode position yielded a significant effect ($F_{1, 32} = 7.312$, $p = 0.011$) with users displaying smaller latency differences at all frontal positions compared with controls, whereas the interaction between group and electrode position failed significance ($F_{2, 31} = 3.030$, $p = 0.063$; fig. 2). Latency differences according to tones averaged across all electrodes revealed significant differences between users and controls concerning L+P–D+ ($F_{1, 32} = 10.009$, $p = 0.003$), L–P+D+ ($F_{1, 32} = 10.191$, $p = 0.003$) and in tendency for L–P–D– ($F_{1, 32} = 3.590$, $p = 0.067$) with users exhibiting smaller latency differences.

With respect to the P_3 amplitude of the target tone, cannabis users displayed an overall lower amplitude which, however, reaches statistical significance only at P_4

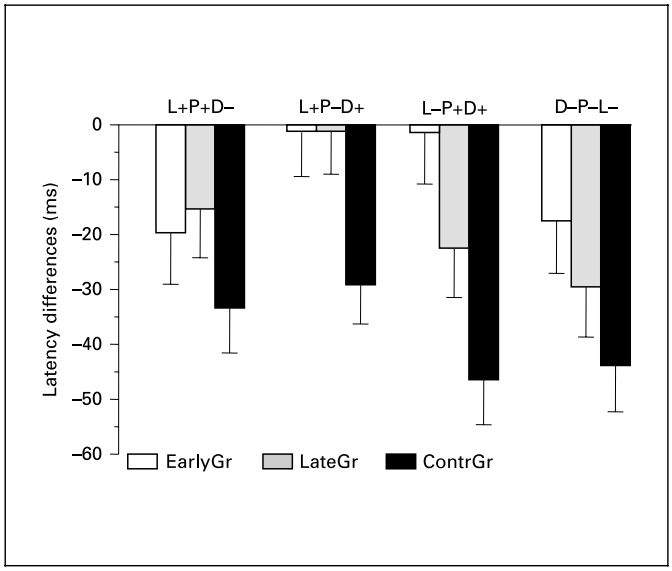

Fig. 3. Means and standard errors of means (SEM) of latency differences between target and non-target stimuli (L+P+D–, L+P–D+, L–P+D+, L–P–D–) averaged across all electrode positions for the EO and LO user group and control group. EarlyGr = EO user group; LateGr = LO user group; ContrGr = control group.

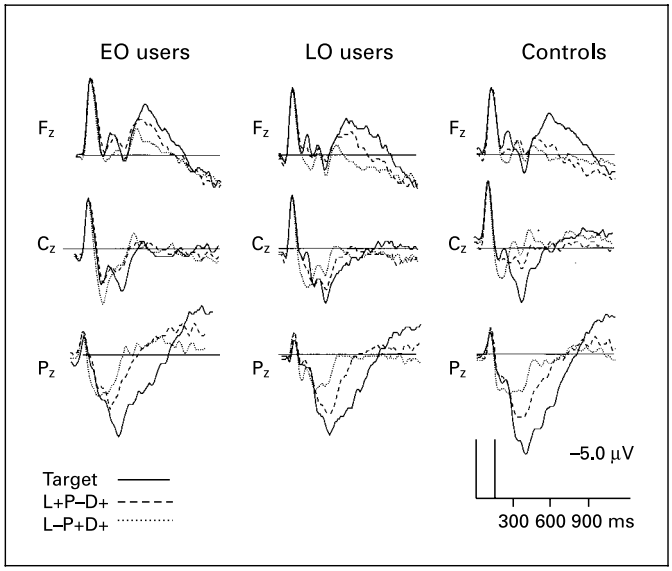

Fig. 4. Grand average ERPs to target and two non-target stimuli at frontal, central and parietal electrode positions.

(t_{32} = –2.55, p = 0.02). Analysis of variance revealed no significant main effect for group ($F_{1, 32}$ = 1.219, p > 2) but a significant interaction between group · electrode position ($F_{2, 31}$ = 6.531, p = 0.004) with users exhibiting a reduced amplitude at central and right hemisphere positions. No differences between cannabis users and controls were found for latency of this positive peak. Since P_3 is a slow wave and this interval may be too short, we additionally analysed the area of the positive waves from 300 to 700 ms to target tones. However, no significant differences were found.

Because of small and unequal sample sizes and heterogeneity of variances in some amplitude and latency differences, non-parametric Mann-Whitney U tests were also computed to investigate differences between the cannabis group and the control group. The results confirmed the former findings of the analyses of variance.

Age of Onset

Regarding the latency differences of the N_2 peak (ERP to target minus ERP to each non-target tone), analysis of variance exhibited a significant main effect of the factor group ($F_{2, 31}$ = 4.796, p = 0.015; fig. 3).

Post hoc tests (Scheffé) revealed a significant difference between the EO user group and the control group (averaged distance = 28.23, p = 0.023; fig. 3). Neither cumulative toxicity ($F_{1, 29}$ = 0.157, p = 0.291) nor THC+THCOH level ($F_{1, 29}$ = 0.424, p = 0.520) exerted a significant main effect on latency differences, whereas significant differences between groups remain significant ($F_{2, 29}$ = 5,476, p = 0.010). Although difficult to measure, inspection of the individual waveform revealed that 2 subjects (1 EO and 1 control) did not show the N_2 to target tones except for 5 EO users who showed a clear identifiable N_2 wave to L–P+D+, whereas it was apparent in 8 LO users and 11 controls. Furthermore, concerning ERPs to L+P–D+, the peak of the second wave was later than 300 ms in 4 EO and 2 LO users, and 4 controls (fig. 4).

Discussion

The results of the present study are suitable to contribute to the controversies and open questions concerning cognitive impairment after long-term use of cannabis as listed by Parrot [23]. There is evidence for different patterns of information processing between cannabis users and controls. While controls displayed a shorter latency of the negative peak to target tones compared with all of the 4 non-target tones, this clear difference was absent in

users. Taking this together with the reduced P_3 amplitude, users seemed to allocate attentional processes differently from controls.

This is in line with previous studies reporting differences in attentional processes [7, 9–13], although most of them did not apply the same approach and methodology as the present experiment. According to the resource allocation theory, a reduced P_3 amplitude could reflect a higher load of mental working capacity [24–26], perhaps resulting from users actually attending to tones which were presented to the wrong ear and therefore irrelevant for accomplishing the task. Interestingly, users did not differ in latency differences with respect to those tones that differed in duration from target tones, which was most difficult to discriminate. This finding supports the hypothesis that users were not generally impaired in allocating attention. On the other hand, all users experienced the testing as more stressful and the discrimination task as more difficult than controls which, again, supports the hypothesis that users possibly use a less effective strategy which might be apparent in more complex or long-lasting tasks.

In line with previous research [8, 16], differences between users and controls were related to age of onset. Moreover, these results were not due to acute intoxication of users or cumulative toxicity.

Nevertheless, several limitations of our study should be considered. (1) When discussing the results of the present study, one has to comment on some sample characteristics. On the one hand, 'pure' cannabis users without any other 'drug history' are very rare. This rigid exclusion criterion limited sample size. On the other hand, one has to assume that voluntariness of participation may result in selective samples probably composed of interested and therefore, more intelligent subjects. Since an 'amotivational syndrome' has frequently been associated with the use of cannabis [1], one has to cope with the fact that characteristics of users in the present study may not be extrapolated to the general population of users. One of these characteristics is the IQ, which may be an important mediator especially in the user group. Subjects with a lower IQ suffer more from cannabis use than persons with a high IQ in terms of lower memory performance and greater deviation in ERPs [3, 18]. Possibly, persons with a high IQ were able to compensate subtle cognitive impairments and, as a consequence, perform better in neurophysiological tests. (2) No audiometry was conducted prior to testing which could have a crucial impact on the interpretation of the ERP data. (3) Due to varying potencies of cannabis plants, variable methods of smoking and inhalation, and uncertain bioavailability of THC from smoked cannabis, the measurement of cumulative toxicity by estimation of the total amount consumed is probably little reliable. (4) It must be kept in mind that EO users had (non-significantly) more years of regular use and importantly, a significantly more frequent consumption during the month prior to testing. Although THC+THCOH levels did not have a significant effect on the ERP differences, one cannot completely rule out that differences were due to a 'residual drug' effect on attention. (5) A more detailed analysis of ERP data would have been more appropriated in order to investigate N_2 and P_3. This could have been achieved by using mean amplitudes and considering wider ranges of the ERPs. Overall, interpretation of results is difficult because in some subjects, both components did not peak within the considered intervals (200–300 and 300–400 ms). (6) Using the present study design, one cannot rule out differences between the groups investigated prior to the onset of cannabis consumption. Full longitudinal studies are needed to rule out this possible alternative hypothesis. This means, that certain characteristics of a person may lead to different kinds of application, different duration of use or different ages of onset. One cannot rule out that cannabis use may serve as a kind of 'self-medication' started after the experience of some kinds of deprivation. Interestingly, heterogeneity (as can be seen by higher variances) is higher in the LO group, indicating different triggers as compared with the more homogenous EO users. These considerations should be carefully taken into account when comparing heavy/long-term with moderate/short-term users as frequently done in the literature [2, 18].

In summary, the present study clearly points out that cannabis users do differ with respect to attentional processes from control subjects. Moreover, age of onset could be identified as an important mediator. A further important result is that the prefrontal cortex (see most striking effects for frontal electrodes) characterized by dense cannabinoid receptors play a crucial role in information processing and attention allocation [2, 12, 27]. Combining ERP and brain imaging research will be a promising way to investigate neuroanatomic and neurofunctional differences associated with cannabis use.

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