Neurophysiological correlates of the pathway to the early stages of psychosis

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EFFECTS OF CANNABIS USE ON EVENT RELATED POTENTIALS IN SUBJECTS AT ULTRA HIGH RISK FOR PSYCHOSIS AND HEALTHY CONTROLS

Mirjam J. van Tricht, Emma C. Harmsen, Johannes H. Koelman, Lo J. Bour, Thérèse A. van Amelsvoort, Don H. Linszen, Lieuwe de Haan, Dorien H. Nieman

ABSTRACT

Cannabis use has consistently been associated with psychotic symptoms as well as cognitive impairments. Moreover, its use may provoke subclinical psychotic symptoms and is associated with neuropsychological dysfunctions in subjects at Ultra High Risk (UHR) for developing psychosis. However, to our knowledge, no data are yet available on the relationship between cannabis use, UHR symptoms and information processing as assessed with Event Related Potentials (ERP) in UHR subjects. This cross-sectional study therefore aimed to investigate N100, N200, P200 and P300 ERP components in 48 UHR subjects (19 cannabis users; UHR+C) and 50 healthy controls (21 cannabis users; HC+C). Results showed smaller P300 amplitudes in HC+C and UHR subjects compared to HC-C. Moreover, HC+C showed prolonged P300 and N200 latencies compared to HC-C and UHR-C. No significant ERP differences were found between UHR+C and UHR-C. Regarding the relationship between information processing and psychopathology, we found associations between ERP components and severity of UHR symptoms, findings being most pronounced for N100 latencies and P300 amplitudes and severity of general psychopathology and positive symptoms. We conclude that UHR subjects and healthy cannabis users demonstrate similar P300 amplitude reductions compared to non-using control subjects. In addition, the interrelation of cannabis use with prolonged ERP latencies may signify reduced information processing speed associated with cannabis use. Finally, our findings cautiously support the hypothesis that the clinical phenomena of the UHR state may be associated with abnormalities in stimulus processing.
1. INTRODUCTION

Cannabis is the most frequently used drug among adolescents (Hall & Babor, 2000) and its use has often been linked to schizophrenia and other psychotic disorders (Johns, 2001). One of the active components of cannabis, delta-9-tetrahydrocannabinol (Δ9-THC) can produce psychotic-like symptoms as well as cognitive impairments (D’Souza et al., 2005; Linszen & van Amelsvoort, 2007; van der Meer et al., 2012; Meijer et al., 2012). Currently, one of the dominant theoretic frameworks to explain the associations between cannabis use and psychosis, is the cannabinoid hypothesis. This hypothesis proposes that the dysregulation of the endocannabinoid system is an important factor in the aetiology of the disease (Dissanayake et al., 2012). Specifically, it is hypothesized that the endogenous cannabinoid system in the human brain is susceptible to the use of THC during adolescence and that cannabis intoxication changes this system (Dean et al., 2003; Zavitsanou et al., 2004). Indeed, an association between the pathogenesis of schizophrenia and malfunctioning of the cannabinoid system has been reported, suggesting overlapping biological mechanisms underlying cannabis intoxication and schizophrenia (Dean et al., 2003; Solowij & Michie, 2007).

Information processing deficits may be a fundamental factor of psychosis (Bhattacharyya et al., 2012; Kapur, 2003). Efficient information processing requires a variety of abilities, including adequate pre-attentive processing of novel stimuli and the ability to inhibit responses to irrelevant stimuli, but also intact higher order, cognitive processing. Abnormalities in stimulus detection and processing may underlie the “downstream” clinical and cognitive impairments as observed in schizophrenia patients (Rissling et al., 2012). More specifically, it is hypothesized that the clinical phenomena of schizophrenia at least in part result from dysfunctions in the coordination of neural activity at the earliest stages of sensory and cognitive information processing (Kirihara et al., 2009; Hermens et al., 2009; Turetsky et al., 2009) and contribute to the psychosocial disability observed in patients with schizophrenia (Rissling et al., 2012; Jahshan et al., 2012).

Several neurophysiological paradigms can be applied to assess information processing abilities. For example, with the aid of the oddball paradigm, Event Related Potentials (ERPs) following task relevant and task irrelevant stimuli can be determined. The P300 (P3) for instance, is a cognitive ERP component associated with attention and memory functions. Specifically, two subcomponents of the P3 can be distinguished (Squires et al., 1975). The P3a potential, which typically reaches its maximum at central-frontal scalp positions (Jahshan et al., 2012; Atkinson et al., 2012; Naatanen et al., 1979; Laurens et al., 2005), is thought to reflect initial automatic processing when a novel or distracting stimulus is detected. In contrast, the following parietal maximal P3b is believed to be a reflection of subsequent effortful attentional resources, associated with updating task-relevant information in memory (Polich, 2007).

During the past decades, a growing body of research has indicated that cannabis use may result in information processing impairments similar to those observed in schizophrenia patients (Juckel et al., 2007; Roser et al., 2008). For instance, both
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Schizophrenia patients and healthy cannabis users show reduced P3 amplitudes (D’Souza et al., 2012; Böcker et al., 2010; Kempel et al., 2003; Roser et al., 2008; Solowij et al., 1995) and prolonged latencies (Kempel et al., 2003; Solowij et al., 1995), indicating similar neurobiological consequences of cannabis use as of schizophrenia. Additionally, in patients with schizophrenia (Potts et al., 1998; Salisbury et al., 2010; Haenschel et al., 2007) as well as healthy cannabis users (Böcker et al., 2010; Theunissen et al., 2012) abnormalities have been reported in early information processing, as reflected by smaller N100 and P100 amplitudes or impaired sensory gating. However, adverse effects of cannabis use on pre-attentive information processing were not replicated in another report (D’Souza et al., 2012). Importantly, recent studies show that cannabis may have differential effects on information processing in schizophrenia patients as opposed to healthy cannabis users. That is, where cannabis use is associated with information processing impairments in healthy controls, there is some evidence that cannabis use may improve information processing abilities in schizophrenia patients. For instance, in a recent mismatch negativity (MMN) study (Rentzsch et al., 2011), cannabis-using schizophrenia patients showed increased frontal MMN compared to schizophrenia patients without cannabis use. However, these findings may be related to pre-existent differences in cognitive vulnerability between schizophrenia patients who develop the disorder without cannabis use and those with expression of the disorder after starting cannabis use. Further investigation of ERP components in schizophrenia patients with or without cannabis use through the different stages of the disease, including the prodromal phase, is therefore warranted.

A frequently applied method to identify patients that are putatively in the prodromal phase of schizophrenia is the Ultra High Risk (UHR) approach. The UHR concept consists of multiple clinical risk factors that indicate an increased risk of developing a psychosis within the next year (for details: Yung et al., 2007). ERP studies have demonstrated smaller P3 amplitudes in UHR subjects compared to healthy control subjects (Bramon et al., 2008; van der Stelt et al., 2005; Frommann et al., 2008; van Tricht et al., 2010). No consensus has yet been reached whether UHR subjects also show abnormalities in earlier information processing prior to the onset of first psychosis. Whereas some studies reported smaller N100 amplitudes in UHR subjects compared to controls (van Tricht et al., 2012; Brockhaus-Dumke et al., 2008), other studies found no evidence of abnormalities in these components in the prodromal phase (van Tricht et al., 2010; Bramon et al., 2008). In addition, to the best of our knowledge, no studies have yet yielded evidence of prolonged ERP latencies in UHR subjects. Although it has been frequently demonstrated that cannabis may provoke subclinical symptoms (for a review see: van der Meer et al., 2012) and is associated with neuropsychological dysfunctions in UHR subjects (Korver et al., 2010), studies investigating the relationship between cannabis use, information processing abilities, as assessed with ERPs, and subclinical psychotic symptoms in UHR subjects are lacking.

The aim of our study was threefold. First, we aimed at investigating whether cannabis using healthy subjects demonstrate similar information processing deficits as observed
in UHR subjects. Second, we investigated ERP differences between cannabis using and non-using UHR subjects, hereby exploring whether there is an association between cannabis use and information processing disabilities in UHR subjects. Third, we investigated relationships of ERPs with UHR symptom severity. To these aims, we assessed ERPs in UHR subjects using cannabis (UHR+C), UHR subjects without a history of cannabis use (UHR-C), healthy controls using cannabis (HC+C) and healthy controls without a history of cannabis use (HC-C). We expected UHR-C, UHR+C and HC+C to show impaired information processing, as reflected by smaller ERP amplitudes compared to HC-C. Prolonged ERP latencies were only expected in cannabis using subjects. Finally, we expected that more severe information processing deficits would be related to more severe UHR symptoms.

2. METHODS

2.1 Subjects

2.1.1 UHR group

Sixty-one UHR subjects were included. This sample overlaps with the sample of a previous study of our group (van Tricht et al., 2010). The UHR subjects were referred to the Academic Medical Centre (AMC), Amsterdam, The Netherlands, mainly by professionals from mental health services for a second opinion with the question whether a psychotic development was taking place. The subjects were examined within the Dutch Prediction of Psychosis Study of the AMC. The inclusion criteria for the UHR group were: a) age between 15 and 35 years, and b) subjects met one or more of the following inclusion criteria: 1) Genetic risk in combination with reduced functioning, 2) mild to moderate intermittent psychotic symptoms appearing several times per week for at least 1 week within the last three months and 3) Brief Limited Intermittent Psychotic Symptoms (BLIPS); i.e. frank psychotic symptoms occurring within the last 3 months and resolving spontaneously within 1 week (for details see: Miller et al., 2003).

The exclusion criteria for the UHR group were: previous psychotic episode for more than one week (as assessed with the Structured Clinical Interview for Diagnosis, sections B and C; Spitzer et al., 1992), symptoms due to substance abuse (as assessed with the Comprehensive International Diagnostic Interview (CIDI), sections J and L; WHO, 1993; Kessler & Ustun, 2004), estimated premorbid IQ below 85 (as assessed with the Dutch National Adult Reading Test (NART; Schmand et al., 1991), vision disorders, endocrine disease and known neurological impairments (e.g., closed head injury). UHR subjects were allowed to use cannabis, but they were excluded if they used other drugs or if the UHR symptoms were only apparent after cannabis use. This was determined as follows: subjects who used cannabis were asked whether they had a period of symptoms in which they did not use cannabis; if not, they were asked to stop using for 2 weeks to see if symptoms continued. If a significant reduction or even full remission was observed, the at-risk symptom in question would not be considered an expression of a UHR state. UHR participants were excluded from the current study if the at-risk symptoms remitted when cannabis use was ceased.
Within the UHR group, a division was made into cannabis and non-cannabis users based on CIDI criteria (frequency of > 5 times cannabis use lifetime). As it has been described that effects of cannabis use may fade out after a month (e.g. Hirvonen et al., 2012) and to enhance the comparability with the cannabis using controls, an additional inclusion criterion for the UHR+C group was that they used cannabis in the past month. Subjects with a history of cannabis use, but who did not use cannabis in the past month, were excluded from this study.

2.1.3 Healthy control groups

Twenty-one healthy controls with cannabis use (HC+C) and twenty-nine subjects without a history of cannabis use (HC-C) were included. Inclusion criteria were age between 15 and 35 and, for HC+C, current cannabis use at least four times a week. Controls were matched on age and estimated premorbid IQ of the UHR subjects.

The exclusion criteria for HC were the same as for the UHR subjects, with the addition of the following criteria (i) psychiatric disorder in the past or present; (ii) psychiatric family history (evaluated for first and second degree relatives); and (iii) scoring on the Structured Interview for Prodromal Syndromes (SIPS; Miller et al., 2003) in the UHR range. The HC subjects received a fee for their participation of 40 Euros. None of the HC subjects used psychoactive medication.

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The study design was approved by the Medical Ethical Committee of the AMC. All participants gave written informed consent after the nature of the procedures had been fully explained.

2.2 Materials

2.2.1 ERP recording

ERPs were assessed using an active auditory-oddball paradigm. The subjects were seated in a comfortable chair with eyes open, in a dimly lit, quiet room. A total of 300 tones were presented, of which 80% were non-targets (1000Hz) and 20% targets (2000Hz), with a duration of 100 ms in a random sequence. The stimuli were generated with an inter-stimulus interval of 1480 ms, i.e. a stimulation frequency of 0.67 Hz. The subjects were instructed to count the targets and respond to them with a button press. To familiarize the subjects with the task, three practice trials with target and non-target stimuli were presented.

The EEG was recorded with an analogue band-pass filter of 0.04–300 Hz and digitally stored with a 1000 Hz sampling rate in a database for subsequent off line analysis using Brainvision Analyzer (Brainproducts; http://www.brainproducts.com). Twenty-one silver silver disc electrodes (impedances < 5 kΩ) were attached to electrode sites (10–20 system), with a reference electrode on linked mastoids and a ground electrode on the forehead. Additionally four electrodes were attached at the outer canthi of both eyes and above and below the left eye for the registration of eye movements and
blinks. Vertical and horizontal eye-movements were detected and removed using eye-
movement detection measures developed by Gratton and colleagues (Gratton et al.,
1982). After baseline correction, the signals were digitally filtered with a low-pass filter
of 30 Hz and a high-pass filter of 0.10 Hz (24 dB/oct) and were epoched at 50 ms pre-
stimulus and 450 ms post-stimulus. The maximum allowed absolute difference between
two values in one segment was 200 μV and the maximum allowed voltage step was
50 μV. Epochs were averaged separately for non-target and target tones. For both target
and non-target trials, the recording was excluded from further analyses if less than 50
percent of the trials included artefact free trials.

2.2.2 Calculation of ERP components
Peak amplitudes were semi-automatically detected and calculated relative to pre-
stimulus baseline of 50 ms. Following previous studies (Salisbury et al., 2010;Ford et
al., 2001; O’Donnell et al., 2004), N100 (N1) and P200 (P2) components were measured
from averages elicited by non-target tones. N1 amplitudes were detected as the most
negative point between 75 and 125 ms post stimulus whereas P2 amplitudes were
detected as the most positive point following the N1, with a latency range of 150-220
ms. N200 (N2) and P3 components were calculated as waveforms generated by target
tones. The N2 was scored within a timeframe of 180-320 ms post-stimulus, whereas the
P3 was defined as the largest positive value between 250 and 450 ms post-stimulus.
Based on the literature (Salisbury et al., 2010; Salisbury et al., 1994; Bramon et al., 2004),
N1 and N2 components were assessed at central midline (Cz) scalp site, P2 at parietal
scalp site (Pz), and P3 components at parietal, central and frontal (Fz) scalp sites. All
peaks were visually inspected.

2.3 Medication
To compare effects of different types of medication prescription on ERPs, subjects were
assigned to one of the following categories: (i) antipsychotic medication (subjects using
antipsychotic medication and other medication were also assigned to this category),
(ii) other psychotropic medication, for instance benzodiazepines, antidepressants or
psychostimulants, or (iii) no medication. As only one subject used typical antipsychotic
medication, no analyses were conducted comparing effects of typical vs. atypical
antipsychotic medication. Possible effects of medication on ERPs were assessed by
comparing ERPs between these three groups and between the two categories ‘no
medication’ and ‘medication’ (category one and two combined). Additionally, associations
between chlorpromazine equivalents and the distinct ERP components were determined.

2.4 Procedure
In all participants, ERPs were assessed in a session of approximately 20 min., within a week
after the psychiatric questionnaires were administered. Participants were instructed not
to smoke, use drugs or drink coffee or other caffeine holding drinks the day of the ERP
recording. Before the ERP recording, participants were asked whether they complied
with this instruction. No additional urine tests were conducted to check for drug use. As cannabis use and possession are both morally and legally accepted in The Netherlands, data from the CIDI are considered to be reliable.

2.5 Statistical analyses
Differences between the groups in ERP parameters were examined using multivariate analyses of variance (MANOVA / General Linear Model (GLM)), with ERP latencies and amplitudes as dependent variables and Group as fixed factor. Post hoc Tukey HSD tests were applied when indicated, to reduce the probability of Type 1 errors. Given the unequal distribution of the SIPS scores, group differences in SIPS scores were examined using Kruskal Wallis test, whereas correlations between ERP parameters, cannabis use and UHR symptoms were examined with nonparametric correlation tests (Spearman's rho). Moreover, linear regression analyses with scores on the SIPS subscales as dependent variable, ERP components as independent variables in a first block and ‘Group’ as a second block, were conducted to investigate whether the ERP components might predict variance in the severity of UHR symptoms. Group differences in gender were analyzed using a Chi-square test. Group differences in age and estimated premorbid IQ were analyzed using an ANOVA. Data were analyzed with the statistical package for social sciences (SPSS 18.0). If not described otherwise, p ≤ .05 was considered significant.

3. RESULTS
3.1 Demographic and clinical characteristics
After removal of UHR subjects who did not use cannabis in the past month (n=11) and of whom details of recency or frequency of cannabis use were unknown (n=2), the final UHR sample consisted of nineteen UHR subjects with, and twenty-nine UHR subjects without a history of cannabis use. Furthermore, twenty-one cannabis using healthy subjects and twenty-nine healthy controls were assessed. Demographic and clinical characteristics of these subjects are presented in Table 1. No group differences were found in age or NART scores. We did find differences between the groups with respect to gender and medication prescription. As preliminary analyses yielded no significant differences in ERP components between the male or female subjects included in our study (all p values > .16), subjects ascribed to the three medication categories (all p values > .21) or between subjects who did or did not use medication (all p values >.11), controlling for these variables did not seem warranted. No significant difference in medication prescription was found between both UHR groups ($\chi^2= 3.75, p = .15$). Finally, we found no significant differences in frequency of alcohol ($\chi^2= 6.11, p=.13$) or nicotine ($\chi^2= 7.43, p=.12$) use between the groups.

3.2 Event Related Potentials
Multivariate analyses of variance (MANOVA) yielded a significant effect (Wilks' Lambda; F= 2.19; p<.001). With regard to the ERP amplitudes, univariate tests yielded group
differences in P3 amplitudes at Fz, Cz and Pz (Table 2). Post-hoc Tukey HSD tests revealed larger P3 amplitudes at Pz and Cz in HC-C compared to the other three groups. At Fz, we found smaller P3 amplitudes in UHR+C compared to HC-C and in HC+C compared to HC-C (statistical trend). No significant group differences were found for N1, N2 and P2 amplitudes. Except for a trend for reduced P3 Pz amplitudes in UHR+C, no amplitude differences were found between UHR+C and HC+C. Additionally, no amplitude differences were found between UHR+C and UHR-C.

Regarding the ERP latencies, we found significant group effects for N2 latencies at Cz and P3 latencies at Pz. Post hoc tests showed prolonged N2 latencies in HC+C compared to HC-C and UHR-C. In addition, P3 Pz latencies were prolonged in HC+C compared to UHR-C. No differences in ERP latencies were found between UHR+C and UHR-C or between UHR+C and HC-C.

**Medication**

To further reduce the possibility that medication use biased our results, we ran all analyses again while including only medication naïve subjects. These analyses yielded similar results in medication naïve subjects as in the full UHR sample. In addition, we found no significant associations between chlorpromazine equivalents and the distinct ERP components.

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**Table 1** Socio-demographic characteristics of the UHR group with (UHR+C) or without (UHR-C) cannabis use, otherwise healthy cannabis (HC+C) group and healthy control group without cannabis use (HC-C).

<table>
<thead>
<tr>
<th></th>
<th>UHR-C (n = 29)</th>
<th>UHR+C (n = 19)</th>
<th>HC+C (n = 21)</th>
<th>HC-C (n = 29)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, SD)</td>
<td>19.0 (3.3)</td>
<td>19.5 (2.9)</td>
<td>20.0 (3.3)</td>
<td>19.5 (3.6)</td>
<td>F = 2.33, p = .07</td>
</tr>
<tr>
<td>Gender (no. male/female)</td>
<td>16/13</td>
<td>16/3</td>
<td>19/2</td>
<td>14/15</td>
<td>χ² = 14.1, p = .003</td>
</tr>
<tr>
<td>Chlorpromazine equivalents</td>
<td>43.1 (55.7)#</td>
<td>22.1 (50.7)</td>
<td>-</td>
<td>-</td>
<td>p = .28</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>10 (35)</td>
<td>2 (11)</td>
<td>-</td>
<td>-</td>
<td>χ² = 39.3, p &lt; .001</td>
</tr>
<tr>
<td>Medication usage (no., %)</td>
<td>Other ¹</td>
<td>7 (24)</td>
<td>5 (26)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>12 (41)</td>
<td>12 (63)</td>
<td>21 (100)</td>
<td>29 (100)</td>
</tr>
<tr>
<td>DART IQ score (mean, SD)</td>
<td>103.5 (9.1)</td>
<td>102.1 (8.6)</td>
<td>103.5 (10.3)</td>
<td>106.5 (10.4)</td>
<td>F = 1.2, p = .31</td>
</tr>
<tr>
<td>SIPS</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>11.5 (3.6)</td>
<td>11.8 (4.4)</td>
<td>2.7 (1.6)</td>
<td>1.0 (1.3)</td>
<td>χ² = 64.9, p &lt; .001</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>13.4 (6.7)</td>
<td>15.7 (6.9)</td>
<td>2.0 (2.8)</td>
<td>.8 (1.5)</td>
<td>χ² = 62.8, p &lt; .001</td>
</tr>
<tr>
<td>General Psychopathology</td>
<td>10.3 (4.2)</td>
<td>10.3 (4.2)</td>
<td>2.0 (1.6)</td>
<td>1.3 (1.5)</td>
<td>χ² = 72.1, p &lt; .001</td>
</tr>
<tr>
<td>Frequency cannabis use (no., %)</td>
<td>Every day</td>
<td>-</td>
<td>13 (68)</td>
<td>16 (76)</td>
<td>χ² = 7.9, p = .05</td>
</tr>
<tr>
<td></td>
<td>3-4 days per week</td>
<td>-</td>
<td>1 (8)</td>
<td>5 (19)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1-2 days per week</td>
<td>-</td>
<td>4 (21)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1-3 days per month</td>
<td>-</td>
<td>1 (8)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Last time cannabis use</td>
<td>Past 2 weeks</td>
<td>-</td>
<td>14 (73)</td>
<td>17 (81)</td>
<td>χ² = .30 p = .43</td>
</tr>
<tr>
<td></td>
<td>2 wks - 1 month ago</td>
<td>-</td>
<td>5 (27)</td>
<td>4 (19)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: No. = number; DART = Dutch Adult Reading Test. UHR =Ultra High Risk; PANSS = positive and negative symptoms scale; SIPS = Structured Interview for Prodromal Syndromes. # data of one subject missing. Other psychotropic medication types include: antidepressants (n = 8), anxiolytics (n = 3), and psychostimulants (n = 1).
Table 2 ERP parameters of the ultra high risk sample (UHR+C) and without (UHR+C) cannabis use, otherwise healthy cannabis users (HC+C) and healthy controls without cannabis use (HC-C)

<p>| Table 2 ERP parameters of the ultra high risk sample with (UHR+C) and without (UHR+C) cannabis use, otherwise healthy cannabis users (HC+C) and healthy controls without cannabis use (HC-C) |
|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>UHR-C (n = 29)</th>
<th>UHR+C (n = 19)</th>
<th>HC+C (n = 21)</th>
<th>HC-C (n = 29)</th>
<th>Statistics (Multivariate GLM)</th>
<th>Post hoc tests (Tukey HSD)</th>
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<td></td>
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<tr>
<td>N100</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Amplitude</td>
<td>-7.02 (2.8)</td>
<td>-6.82 (2.9)</td>
<td>-7.07 (2.9)</td>
<td>-7.91 (4.0)</td>
<td>F=.58, p=.632</td>
<td>p=.73</td>
</tr>
<tr>
<td>Latency</td>
<td>90.24 (8.2)</td>
<td>92.63 (7.7)</td>
<td>92.14 (8.9)</td>
<td>90.10 (7.7)</td>
<td>F=.59, p=.621</td>
<td>p=.10</td>
</tr>
<tr>
<td>P200</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplitude</td>
<td>3.11 (3.2)</td>
<td>3.26 (2.3)</td>
<td>2.77 (1.6)</td>
<td>4.41 (2.6)</td>
<td>F= 2.07, p=.110</td>
<td>p=.22</td>
</tr>
<tr>
<td>Latency</td>
<td>174.69 (38.9)</td>
<td>184.68 (35.1)</td>
<td>190.10 (29.5)</td>
<td>182.59 (33.1)</td>
<td>F=.88, p=.469</td>
<td>p=.82</td>
</tr>
<tr>
<td>N200</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplitude</td>
<td>-1.55 (5.5)</td>
<td>-1.52 (4.6)</td>
<td>-.40 (5.6)</td>
<td>-2.00 (5.9)</td>
<td>F=.49, p=.692</td>
<td>p=.99</td>
</tr>
<tr>
<td>Latency</td>
<td>184.93 (23.6)</td>
<td>197.89 (22.0)</td>
<td>200.86 (13.6)</td>
<td>184.24 (20.4)</td>
<td>F=4.21, p=.008</td>
<td>p=1.00</td>
</tr>
<tr>
<td>P300</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Amplitude</td>
<td>9.94 (6.0)</td>
<td>6.28 (4.2)</td>
<td>6.86 (4.1)</td>
<td>10.56 (6.2)</td>
<td>F=3.97, p=.014</td>
<td>p=.97</td>
</tr>
<tr>
<td>Latency</td>
<td>307.00 (33.5)</td>
<td>310.58 (27.5)</td>
<td>317.52 (18.1)</td>
<td>319.48 (22.2)</td>
<td>F= 1.21, p=.311</td>
<td>p=.32</td>
</tr>
<tr>
<td>Fz</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplitude</td>
<td>14.59 (6.6)</td>
<td>11.64 (4.9)</td>
<td>14.99 (5.5)</td>
<td>19.48 (7.6)</td>
<td>F=6.24, p=.001</td>
<td>p=.02</td>
</tr>
<tr>
<td>Latency</td>
<td>294.59 (31.2)</td>
<td>298.53 (34.3)</td>
<td>310.67 (26.5)</td>
<td>296.03 (28.8)</td>
<td>F= 1.34, p=.265</td>
<td>p=.97</td>
</tr>
<tr>
<td>Cz</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplitude</td>
<td>15.28 (6.8)</td>
<td>12.87 (3.4)</td>
<td>17.72 (6.1)</td>
<td>22.92 (7.5)</td>
<td>F= 11.53, p &lt;.001</td>
<td>p&lt;.001</td>
</tr>
<tr>
<td>Latency</td>
<td>301.66 (31.0)</td>
<td>315.11 (32.4)</td>
<td>326.76 (23.9)</td>
<td>308.55 (30.8)</td>
<td>F= 3.06, p=.032</td>
<td>p=.82</td>
</tr>
<tr>
<td>Pz</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplitude</td>
<td>99.4</td>
<td>99.7</td>
<td>99.1</td>
<td>99.2</td>
<td>F=.98, p=.60</td>
<td>-</td>
</tr>
<tr>
<td>Latency</td>
<td>43 (.1)</td>
<td>42 (.1)</td>
<td>42 (.2)</td>
<td>40 (.1)</td>
<td>F=1.30, p=.24</td>
<td>-</td>
</tr>
<tr>
<td>Hit rate (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction time (sec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean (SD). F and p values for MANOVA. Significant test results are presented in bold; statistical trends in italics.
3.3 Relationship between ERP components and frequency / recency of cannabis use

Due to the unequal group distributions across the categories of frequency of cannabis use, effects of frequency of use were investigated in two samples: cannabis users (i.e. UHR+C and HC+C) who used daily and cannabis users who used less than daily. We found prolonged N1 latencies (p=.042) and smaller N1 (p=.032) and P2 amplitudes (p=.004) in subjects who used daily compared to subjects who used less than daily. No significant ERP differences were found between subjects who used in the past two weeks as compared to subjects who used cannabis more than two weeks ago (all p values > .16). In addition, no significant associations were found between the age at onset of cannabis use and the distinct ERP components.

3.4 Relationship between ERP components and severity of UHR symptoms in cannabis users

Associations between ERP components and severity of UHR symptoms as determined with the SIPS were assessed in UHR+C and HC+C separately. In UHR+C, we found that prolonged N2 latencies were related to a higher severity of negative UHR symptoms.
(rho=.512, p=.025), whereas prolonged N1 latencies were related to higher rates of general psychopathology (rho=.621, p=.002). No other significant associations were found in the UHR+C group. In the HC+C sample, higher scores on the subscale positive symptoms were associated with smaller N2 (rho= -.53, p=.02) and P2 (rho= -.47, p=.03) amplitudes. In addition, longer N1 latencies were related to higher scores on the subscales general psychopathology (rho=.44, p=.04) and positive symptoms (rho=.43, p=.05). Due to the small ranges of SIPS scores in HC+C (Table 1), these findings should be interpreted with caution. Only the association between N1 latencies and severity of general psychopathology as observed in the UHR+C sample would survive a Bonferroni correction for multiple comparisons (p=.05/15 =0.0033).

Linear regression analyses yielded that group as well as ERP components significantly predicted variance in the scores on the three subscales of the SIPS (Table 1). Subsequent t-tests yielded that, when controlling for group differences, the parietal P3 amplitude predicted variance in scores on the subscale ‘positive symptoms’ (B=-.25, Beta = -.33, t= -1.95, p=.05). None of the other ERP components contributed to the prediction of SIPS scores after controlling for group differences.

4. DISCUSSION
The aim of our study was to investigate whether cannabis using healthy subjects demonstrate similar information processing deficits as observed in UHR subjects. Moreover, we investigated ERP differences between cannabis using and non-using UHR subjects and explored interrelationships of information processing abilities with the severity of UHR symptoms. Our results showed that UHR subjects as well as healthy cannabis users demonstrate P3 amplitude reductions at parietal and central scalp positions compared to non-using controls. Moreover, we found reduced P3 Fz amplitudes in both cannabis using groups compared to controls. With regard to the ERP latencies, HC+C subjects demonstrated prolonged N2 latencies compared to non-using UHR and HC subjects. In addition, P3 latencies were prolonged in HC+C compared to UHR-C. Except for a trend for reduced P3 Pz amplitudes in UHR+C, no amplitude or latency differences were found between UHR+C and HC+C. Moreover, no ERP differences were found between UHR+C and UHR-C, nor did we observe group differences for N1 or P2 components.

The amplitude reductions in both UHR subjects and cannabis users support the view of similar neurophysiological impairments, particularly in P3 generation, in cannabis users and subjects with a disorder in the psychosis spectrum. In addition, the prolonged ERP latencies in healthy cannabis users lend some support to the hypothesis that cannabis use may disrupt the endocannabinoid system in healthy subjects, resulting in reduced information processing speed (Johnson et al., 1997; Solowij & Michie, 2007). However, as other studies found no evidence of associations between cannabis use and prolonged ERP latencies (D’Souza et al., 2012; Stadelmann et al., 2011), further investigations are warranted.

No significant ERP differences were found between cannabis using and non-using UHR subjects. Contrary to the neuropsychological findings as reported in a previous study
of our group (Korver et al., 2010), we thus found no evidence to support the hypothesis that cannabis use is associated with more severe information processing impairments in UHR subjects. In addition, our results did not support the view of a differential impact of cannabis use in schizophrenia patients as compared to healthy controls (Rentszch et al., 2007, Rentszch et al., 2011), i.e. where cannabis using schizophrenia patients present superior neuropsychological (Rabin et al., 2011; Yücel et al., 2012) and neurophysiological (Scholas-Balog & Martin-Iverson, 2011) functioning compared to cannabis naïve patients. One explanation for the absence of significant ERP differences between both UHR groups might be that the hypothesized differences in the endocannabinoid system between schizophrenia patients and healthy controls (Rentzsch et al., 2011), only emerge after the onset of a first psychotic episode. More likely, the absence of differences is due firstly to the relatively small sample size of the UHR+C group. Secondly, as a relationship between the frequency of cannabis use and information processing has been demonstrated (Moore et al., 2007; Solowij & Michie, 2007; Pesa et al., 2012), the absence of significant findings may be due to the generally low frequency of cannabis use in the UHR+C group. Indeed, UHR+C used cannabis less frequently compared to HC+C. Moreover, our analyses showed more ERP abnormalities, particularly in earlier ERP components, in subjects who used daily as compared to subjects using less frequently.

With regard to the relationship between information processing deficits and severity of psychopathology, regression analyses showed that parietal P3 amplitude predicted variance in scores on the subscale ‘positive symptoms’ of the SIPS. Additionally, correlation analyses yielded some associations between the severity of UHR symptoms and ERP components in UHR+C as well as HC+C. However, only the association between N1 latencies and severity of general psychopathology as assessed with the SIPS survived a Bonferroni correction for multiple comparisons. Hence, future studies are warranted before any statements can be made concerning the associations between information processing and clinical UHR symptoms.

Regarding the neurobiological mechanisms underlying the stimulus processing deficits in both HC+C and UHR subjects, recent reports show that endocannabinoids modulate the activity of several neurotransmitters in the brain, mainly through the central cannabinoid (CB1) receptors, the primary target of Δ9-THC. These CB1 receptors may in turn modulate prefrontal, striatal and hippocampal functions during information processing in both mice and men (Bhattacharyya et al., 2012; Guillen et al., 2007; Bhattacharyya et al., 2012). Specifically, the (AAT)n triplet repeat polymorphism in the CNR1 gene, that encodes for CB1 receptors, may be involved in the P3 generation in healthy subjects (Johnson et al., 1997; Stadelmann et al., 2011). Additionally, neuropharmacological and histopathological studies have provided evidence for the association of CB1 receptors with the pathophysiology of schizophrenia (D’Souza et al., 2004; Dean et al., 2001; Zavitsanou et al., 2004). Along with the conclusions of a previous report (Dissanayake et al., 2012), we therefore propose that information processing impairments, as hypothetically induced by dysregulation of the endocannabinoid system (van Winkel et al., 2012), might indeed be the ‘missing link’ between cannabis use and the aetiology of schizophrenia.
We acknowledge several limitations of this study. First, differences between the groups were present with respect to gender distribution. Although preliminary analyses yielded no ERP differences between male and female subjects included in our study, we cannot completely rule out that sex differences may account for our results. Indeed, ERP differences between male and female subjects have been previously described (Yuan et al., 2008; Turetsky et al., 1998). Furthermore, to rule out acute nicotine or caffeine effects, subjects were asked to refrain from all smoking and caffeine intake the day of the recording. Although all subjects maintained their usual smoking and caffeine habits the day prior to the ERP recording and were only asked to refrain from its use for a short period, we cannot exclude the possibility that we measured withdrawal effects. Indeed, reduction of the P3 amplitude after over-night nicotine deprivation has been reported (Evans et al., 2009). Another limitation is that no additional urine tests were conducted to check for (other) drug use. However, since cannabis use and possession is both morally and legally accepted in The Netherlands, data from the CIDI are considered to be reliable. With regard to possible confounding effects of medication, we found no indication that medication use biased the results in our sample; analyses yielded no evidence of associations between medication prescription and ERPs and similar results were obtained when examining only medication naive subjects. Finally, as our study was cross-sectional, it is possible that ERP differences between the groups are attributable to premorbid characteristics rather than cannabis use. Longitudinal neurophysiological studies, including a pre-cannabis use ERP assessment, are needed before firm conclusions can be drawn on the adverse effects of cannabis use in young individuals.

We conclude that cannabis use in healthy control subjects may lead to comparable P3 amplitude abnormalities as observed in UHR subjects. Moreover, the prolonged ERP latencies found in cannabis users indicate that cannabis use may slow down information processing. As abnormalities were only found in cognitive related ERPs, and not in components associated with early pre-attentive processing, we hypothesize that cannabis use as well as the UHR status are associated with specific rather than generalized information processing impairments. Based on these results one may argue that adolescents should be informed about the risks of using cannabis. Specifically, as neuropsychological decline seems to occur predominantly in adolescence-onset users, and not in adult-onset users (Meier et al., 2012), interventions should aim at delaying the onset of cannabis use in young adults. Longitudinal studies in larger samples of healthy cannabis users should be conducted to investigate the course of these information processing abilities after cessation or continuation of cannabis use.

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CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

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