Archival Report

Biological Psychiatry: CNNI

Opposing Effects of Cannabis Use on Late Auditory Repetition Suppression in Schizophrenia Patients and Healthy Control Subjects

Johannes Rentzsch, Golo Kronenberg, Ada Stadtmann, Andres Neuhaus, Christiane Montag, Rainer Hellweg, and Maria Christiane Jockers-Scherübl

ABSTRACT

BACKGROUND: Chronic cannabis use may cause neurocognitive deficits and increase the risk of psychosis. Nevertheless, the effects of cannabis use on neurocognitive functioning in schizophrenia have remained largely unspecified.

METHODS: Here, we studied repetition suppression of auditory event-related responses in a paired-stimulus design in a mixed sample of schizophrenia patients ($n = 34$) and healthy control subjects ($n = 45$) with chronic heavy cannabis use and schizophrenia patients ($n = 33$) and healthy control subjects ($n = 61$) without cannabis use.

RESULTS: Repeated measures analysis yielded an overall significant reduction of P50 amplitude between first and second stimulus ($p < .02$), which was not different between the groups, a reduction of N100 amplitude, which was different for schizophrenia patients compared with healthy control subjects independent of cannabis use ($p < .02$), and a significant interaction between diagnosis and chronic cannabis use on the reduction of the P200 amplitude ($p < .001$). While chronic cannabis use was related with increased P200 suppression ratios in control subjects (with chronic cannabis use: 0.55 ± 0.04; without chronic cannabis use: 0.40 ± 0.03; $p < .02$), the reverse effect was found in schizophrenia (with chronic cannabis use: 0.36 ± 0.05; without chronic cannabis use: 0.54 ± 0.05; $p < .02$). This result remained significant after inclusion of potential confounders. Total lifetime cannabis use showed a significant correlation with the P200 suppression ratio in otherwise healthy control subjects ($r = .28$, $p < .007$). By contrast, the duration of time since last cannabis use was significantly correlated with the P200 suppression ratio in schizophrenia patients ($r = .42$, $p < .002$).

CONCLUSIONS: In aggregate, these diverging effects of chronic cannabis use on P200 repetition suppression may suggest underlying alterations in the endocannabinoid system in schizophrenia.

Keywords: Addiction, Cannabis, Event-related potential, Repetition suppression, Schizophrenia, Sensory gating

http://dx.doi.org/10.1016/j.bpsc.2016.10.004

The relationship between cannabis use and schizophrenia remains complex and often confusing. Cannabis is one of the most widely consumed illicit drugs worldwide (1). Not surprisingly, cannabis use is also prevalent in patients suffering from psychosis (2). On the one hand, cannabis use is associated with an elevated risk and earlier onset of schizophrenia. Moreover, psychosocial outcomes in schizophrenia patients with cannabis use seem to be generally poorer (3). On the other hand, several studies of cannabis users with schizophrenia found fewer negative symptoms (4,5). Similarly, at least during abstinence, schizophrenic cannabis users displayed better neuropsychological functioning relative to cannabis nonusers with schizophrenia (6,7), a finding that runs counter to the effects commonly described in healthy cannabis users [e.g., (8)]. Further paradoxical findings have come from epidemiological research demonstrating more suicide attempts (9) and a higher level of neurological soft signs (10) in healthy cannabis users as compared with nonusers, whereas the reverse, again, seems to be the case in patients diagnosed with psychotic disorders (11–14). Interestingly, Koola *et al.* (15) also found a lower mortality risk in cannabis-using psychotic disorder patients as compared with cannabis nonusers despite subjects having similar symptoms and treatments.

Unfortunately, there are as yet only a small number of studies that directly compared schizophrenia patients with and without cannabis use and simultaneously also investigated healthy cannabis users as control subjects. On the whole, these studies yielded either no interaction between cannabis use and schizophrenia [e.g., regarding cerebellar white matter volume (16,17), cannabinoid receptor type 1 (CB_1R) density (18), mesocorticolimbic functional connectivity (19), face and

SEE COMMENTARY ON PAGE 209

ISSN: 2451-9022

affect recognition (20), sustained attention (21)] or some evidence of positive effects of cannabis in schizophrenia [e.g., regarding cerebral gray matter volume (22) and memory function (8)].

Neurocognitive processes are successfully conceptualized within the predictive coding framework, which posits constant comparisons between sensory input and top-down expectations, thus converging into the prediction error, which is reflected by higher neuronal responses to unexpected stimuli and reduced neuronal responses to repeated stimuli (23,24). The brain's ability to suppress its response to repeated stimuli has been construed as a form of sensory gating or—according to the predictive coding hypothesis—repetition suppression (25) that protects higher brain centers from being flooded with irrelevant information (26,27). When presenting two identical stimuli the neuronal response evoked by the second stimulus is reduced compared with the first one. In the predictive coding view, the second stimulus increases the stability of the internal model of the environment, which conforms to a decrease of the prediction error. Accumulating evidence suggests that the capacity to gate out or suppress responses to irrelevant, repeated information is altered in patients with schizophrenia, the family members of patients with schizophrenia, and individuals with high risk of psychosis (28–31), reflecting abnormal prediction error generation. Interestingly, it appears that repetition suppression is also impaired in individuals with chronic cannabis use (32).

In this study, we posed the question of whether cannabis use results in impairment of the brain's ability to suppress its response to stimuli lacking relevant information (repetition suppression) using an auditory paired click-stimuli design, thereby targeting a fundamental neurocognitive mechanism. Moreover, we hypothesized that the effects of cannabis use on repetition suppression might differ between schizophrenia patients and healthy control subjects. To address these questions, we chose a 2 × 2 study design that would allow us to dissect and understand the precise effects of schizophrenia and of cannabis use. Repetition suppression was assessed for auditory P50, N100, and P200 event-related potentials (ERPs). These components cover different stages of information processing from preattentive to early and late attentive stages (24,33–35) and reflect the activity of different neural networks (36).

METHODS AND MATERIALS

Participants

Four groups of participants were included in the study: 1) 34 schizophrenia patients with a history of chronic heavy cannabis use (SZCA), 2) 33 schizophrenia patients without chronic drug use (SZ), 3) 45 otherwise healthy subjects with chronic heavy cannabis use (COCA), and 4) 61 healthy subjects without chronic drug use (CO). Chronic cannabis use was defined as consumption on at least 3 days/week for at least 1 year as indicated by self-reports. However, given that this was a relatively naturalistic study conducted in a busy urban center and focusing, in particular, on the effects of chronic heavy cannabis use, we did not require study participants in the SZ and CO groups to have never consumed cannabis. Further details are given in Table 1 as well as in the Supplemental Methods. The protocol had been approved by the local ethics committee and written informed consent was obtained from each participant according to the Declaration of Helsinki.

ERP Recordings and Analysis

A detailed description of the procedures is given in the Supplemental Materials. Briefly, auditory stimuli (100 identical pairs of clicks, interclick interval 500 ms, and 118 distractor novelty tones) were presented in pseudorandomized order through earphones (interpair interval 2632 ± 731 ms). Electroencephalography was recorded using an electrode cap with 29 electrodes. Offline ERP analysis was performed using Brain Vision Analyzer Version 2 (Brain Products GmbH, Gilching, Germany) and EEGlab Version v13.1.1 (37). After artifact correction procedures, data were transformed to current source density, filtered (P50: 10 Hz high pass; N100 and P200: 30 Hz low

Table 1. Study Population

	SZ (n = 33)	SZCA (n = 34)	COCA (n = 45)	CO (n = 61)	Statistics
Gender, Male	19 (75.6)	28 (82.4)	26 (57.8)	28 (45.9)	$\chi^2_3 = 11.97$, $p < .01$
Age, Years	34.2 ± 10.2	28.9 ± 7.4	31 ± 8.6	30.1 ± 7.7	$F_{3,169} = 2.55$, $p < .06$
MWT-B Score	29.5 ± 4.4	29.9 ± 3.2	30.2 ± 2.9	31.1 ± 3.1	$F_{3,169} = 1.91$, $p > .1$
Subjects With German Higher School Certificate	12 (13)	10 (10.9)	26 (28.3)	44 (47.8)	$\chi^2_3 = 20.61$, $p < .001$
Subjects in Current Relationship	11 (13.4)	9 (11)	31 (37.8)	31 (37.8)	$\chi^2_3 = 17.22$, $p < .001$
Edinburgh Laterality Index	74.7 ± 45.9	76.2 ± 38.4	78.2 ± 30.5	77.6 ± 40.4	$F_{3,169} = 1.14$, $p > .9$
Age at Onset of Schizophrenia, Years	27.5 ± 7.3	22.6 ± 4.99	—	—	$t_{56} = 3.18$, $p < .003$
Number of Hospitalizations	2.5 ± 1.8	3.1 ± 2.6	—	—	$t_{65} = 1.15$, $p > .2$
PANSS-Positive	12.1 ± 3.2	12.1 ± 2.9	—	—	$t_{65} = 0.44$, $p > .9$
PANSS-Negative	19.9 ± 5.8	16.7 ± 3.9	—	—	$t_{56} = 3.04$, $p < .004$
Duration of Illness	6.7 ± 6.9	6.2 ± 6.2	—	—	$t_{65} = 0.29$, $p > .7$
Chlorpromazine Equivalent Dose	524.4 ± 257.8	494 ± 364.7	—	—	$t_{62} = 0.38$, $p > .7$

Values are mean ± SD or n (%).

CO, healthy control subjects; COCA, otherwise healthy control subjects with cannabis use; MWT-B, Multiple Choice Vocabulary Intelligence Test; PANSS, Positive and Negative Syndrome Scale; SZ, schizophrenia patients without cannabis use; SZCA, schizophrenia patients with cannabis use.