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ORIGINAL PAPER

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Psychomotor performance in relation to acute oral administration of Δ^9-tetrahydrocannabinol and standardized cannabis extract in healthy human subjects

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Abstract Abnormalities in psychomotor performance are a consistent finding in schizophrenic patients as well as in chronic cannabis users. The high levels of central cannabinoid (CB_1) receptors in the basal ganglia, the cerebral cortex and the cerebellum indicate their implication in the regulation of motor activity. Based on the close relationship between cannabis use, the endogenous cannabinoid system and motor disturbances found in schizophrenia, we expected that administration of cannabinoids may change pattern of psychomotor activity like in schizophrenic patients. This prospective, double-blind, placebo-controlled cross-over study investigated the acute effects of cannabinoids on psychomotor performance in 24 healthy right-handed volunteers (age 27.9 ± 2.9 years, 12 male) by comparing Δ^9-tetrahydrocannabinol (Δ^9-THC) and standardized cannabis extract containing Δ^9-THC and cannabidiol. Psychomotor performance was assessed by using a finger tapping test series. Cannabis extract, but not Δ^9-THC, revealed a significant reduction of right-hand tapping frequencies that was also found in schizophrenia. As to the pure Δ^9-THC condition, left-hand tapping frequencies were correlated with the plasma concentrations of the Δ^9-THC metabolite 11-OH-THC. These effects are thought to be related to cannabinoid actions on CB_1 receptors in the basal ganglia, the cerebral cortex and the cerebellum. Our data further demonstrate that acute CB_1 receptor activation under the cannabis extract condition may also affect intermanual coordination (IMC) as an index of interhemispheric transfer. AIR-Scale scores as a measure of subjective perception of intoxication were dose-dependently related to IMC which was shown by an inverted U-curve. This result may be due to functional changes involving GABAergic and glutamatergic neurotransmission within the corpus callosum.

Key words cannabinoids · psychomotor performance · interhemispheric transfer

Introduction

Abnormalities in psychomotor performance are a consistent finding in schizophrenic patients [56, 60]. Studies on first-episode, antipsychotic-naive patients have revealed that psychomotor abnormalities are present at the onset of illness and consequently not the result of antipsychotic medication [23]. Schizophrenic patients and their parents showed similar patterns of psychomotor disturbances, indicating that hereditary factors may be associated with deficient motor functions in schizophrenia [13]. The finger tapping procedure is a well established test to measure motor disturbances as well as changes in functional motor asymmetries and intermanual coordination (IMC) [19]. This test has been shown to be highly reliable (r = 0.94 for men, r = 0.86 for women) for normal subjects re-tested after 10 weeks [31]. In all experiments using the finger tapping test, the effects of handedness, gender and age have to be taken into consideration [53].

Diseases that involve the motor system, such as stroke, Parkinson's disease, Alzheimer's disease,

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alcoholism as well as psychotic disorders, were seen to have a significant effect on finger-tapping scores. In particular, schizophrenic patients have been found to perform worse in the finger tapping test in comparison to healthy controls [16, 20, 29, 51]. Moreover, finger-tapping speed worsened over time for both the right and the left hands of schizophrenic patients [14]. Males, both schizophrenic patients and healthy controls, typically achieved higher tapping frequencies than females [20]. In addition, the degree of motor disturbances was related to schizophrenic symptomatology and severity of illness [22], probably due to a specific imbalance of right- and left-sided motor neuron excitability resulting from disturbances of intrahemispheric and interhemispheric processes [15].

In terms of the functional motor asymmetry, right-handed schizophrenic patients with predominantly positive symptoms in contrast to patients with predominantly negative symptoms demonstrated a shift of the faster tapping frequency from the right to the left hand, indicating greater instabilities in their functional superiority of the dominant hand [18, 20]. This phenomenon of changing motor laterality may be related to reduced hemispheric asymmetries occurring during psychosis [8], and can be medicated by antipsychotic drugs [40].

Disturbances of interhemispheric transfer may be a central problem in schizophrenia [10]. IMC is related to interhemispheric transfer and can be determined by alternating tapping [17]. The size of the corpus callosum can serve as an index of interhemispheric transfer. Accordingly, deficits in bimanual motor performance were seen to be related to an atrophy of anterior callosal regions, to callosal agenesis or to callosotomy [38, 49]. In most investigations, the corpus callosum in schizophrenic patients was found to be significantly smaller in size in comparison to healthy controls [63]. In this connection, it is interesting to note that in schizophrenia different clinical subgroups may be associated with different scores in interhemispheric transfer. While patients with residual schizophrenia and chronic symptoms showed smaller sizes of callosal areas [55], lower values in interhemispheric EEG coherence [52] and lower values in IMC as assessed by alternating tapping, patients with paranoid schizophrenia and acute symptoms as well as patients with substance-induced psychotic disorder, particularly those with chronic cannabis abuse, revealed considerably higher values in IMC [17]. In accordance with the latter finding, daily cannabis users indicated increased interhemispheric EEG coherence values of theta activity in frontal areas in both psychiatric patients and normal subjects [57, 58].

Cannabis sativa is one of the oldest and most frequently used illicit drugs. Over 60 exocannabinoids have been identified in the *C. sativa* plant of which Δ^9-tetrahydrocannabinol (Δ^9-THC) was found to be the major psychoactive constituent [34]. The psychotropic activity of Δ^9-THC is mediated by partial agonistic effects at the central cannabinoid (CB_1) receptor [33] and includes alterations in mood, perception, cognition and memory [26]. The highest density of CB_1 receptors is seen in the cerebral cortex, particularly the dorsolateral prefrontal cortex, basal ganglia, hippocampus and cerebellum, all of which are brain regions critically involved in the pathogenesis of schizophrenic disorders [24]. The high levels of CB_1 receptors in the basal ganglia, a group of brain nuclei involved in motor processing, also indicate their implication in the regulation of motor activity including fine and gross movements as well as complex motor coordination [48].

11-OH-Δ^9-Tetrahydrocannabinol (11-OH-THC) is the most important psychoactive metabolite of Δ^9-THC which is connected with a similar spectrum of effects and kinetic profiles as the parent molecule. 11-nor-9-carboxy-tetrahydrocannabinol (THC-COOH) is the most important non-psychoactive metabolite of Δ^9-THC that possesses anti-inflammatory and analgesic properties produced by mechanisms similar to that of non-steroidal anti-inflammatory drugs [21]. Cannabidiol (CBD) is the second most abundant constituent of *C. sativa*. Several studies found neuroprotective and antipsychotic properties of CBD [35, 43]. In contrast to Δ^9-THC, CBD has no psychoactive properties. CBD binds with low affinity to the orthosteric site on the CB_1 receptor, thus reducing several psychotropic effects of Δ^9-THC via allosteric modification [39].

A number of studies suppose a close relationship between cannabis use, the endogenous cannabinoid system and schizophrenia [11]. There are several lines of evidence supporting such a hypothesis. Acute administration of Δ^9-THC to normal volunteers induced characteristic psychomotor alterations [41], psychotic reactions [27] and cognitive impairments [12, 54] closely resembling signs and symptoms of schizophrenia. In schizophrenic patients, cannabis consumption has been found to worsen positive and cognitive symptoms of schizophrenia even when the patients are under a regular antipsychotic medication [61, 62]. It also results in a poor outcome and liability to relapse [32]. In addition, different epidemiological studies have shown that cannabis use may increase the risk for schizophrenia [1]. Accordingly, Leweke and colleagues [30] found twofold higher endocannabinoid levels in cerebrospinal fluid of schizophrenic patients in comparison to non-schizophrenic controls. Moreover, two independent post-mortem studies have revealed an increased density of CB_1 receptors in the prefrontal cortex of schizophrenic patients [9, 64]. Most recently, our group found several cognitive deficits in healthy subjects due to the acute administration of Δ^9-THC that were similar to those found in schizophrenic patients [28, 44]. Some of them were associated with susceptibility genes of schizophrenia [45].

The specific aim of this study was to evaluate the acute effects of oral Δ^9-THC, standardized cannabis extract and placebo on psychomotor performance in young healthy subjects. Based on the close relationship between cannabis use, the endogenous cannabinoid system and motor disturbances found in schizophrenia, we expected that the administration of Δ^9-THC and cannabis extract in comparison to placebo may produce reduced finger tapping frequencies, greater instabilities in functional motor laterality and higher values in IMC. A further aim of this study was to detect differences between psychomotor performances produced by Δ^9-THC and cannabis extract. Moreover, cannabinoid plasma concentrations were predicted to correlate with subjective perception of intoxication and tapping values.

Materials and methods

Subjects

Twenty-seven healthy right-handed subjects were screened and randomised, from which 24 (12 male, 12 female, mean age 27.9 ± 2.9 years) finished the study according to the protocol. Three female subjects suffering from panic attacks after administration of study medication were excluded from the study. All subjects were recruited from the Humboldt University Berlin by advertisements and were paid for their participation in the study. They had to have occasional cannabis consumption in the past in order to avoid hypersensitivity reactions but they had been completely drug free for at least 1 month before the onset of the study. According to a structured psychiatric interview (M.I.N.I.-SCID), they had no addictive or other psychiatric disease and did not take any medication during the study. The study was approved by the Ethics Committee of the University Hospital Charité Berlin. After the procedure was explained, all subjects gave their written informed consent.

Study medication

Liquid extract from *C. sativa* (solvent 96% ethanol) and plant-isolated Δ^9-THC were prepared by the Society of Cancer Research, Arlesheim, Switzerland. The soft-gelatine capsules containing 2.5 mg Δ^9-THC, cannabis extract with 2.5 mg Δ^9-THC and 1.35 mg CBD, or placebo (a mixture of mono-, di- and triglycerides and glycerol) were produced by Scherer GmbH & Co. KG, Eberbach, Germany.

Study design

The study was performed in a prospective, double-blind, placebo-controlled cross-over design. On three consecutive weeks, each subject received four capsules with either cannabis extract (total dose of 10 mg Δ^9-THC and 5.4 mg CBD), Δ^9-THC (total dose of 10 mg) or placebo together with 200 ml water in a fasting state (last meal at least 8 h before application) that lasted for 4 h after drug intake. No alcohol, nicotine or caffeine was allowed the day before the test until the end of the test in order to avoid behavioral and pharmacological interactions with the study medication. All subjects were either non-smokers or occasional smokers (a maximum of 10 cigarettes per day was allowed). No nicotine withdrawal was seen. One hour before the study medication was administered, the urine of the subjects was tested for amphetamines and ecstasy, benzodiazepines, cannabinoids, cocaine, methadone and opiates. Two hours after drug administration, blood samples were taken and checked for Δ^9-THC, its main metabolites 11-OH-THC and THC-COOH, as well as for CBD by the Institute of Legal Medicine of the University Hospital Charité Berlin. The exact pharmacokinetic profiles were previously presented by Nadulski and colleagues [36]. Furthermore, the visual Analog Intoxication Rating Scales (AIR-Scales) as an established measure of subjective perception of intoxication were assessed. The AIR-Scale used a 10-cm line with one end marked "not intoxicated" and the other marked "extremely intoxicated" [4]. The subjects had to place a single vertical slash mark through the line, and the distance (in cm) from the mark to the left edge was measured.

Table 1 Finger tapping test series

Session	Task
A	Right- and left-hand tapping
B	Right- and left-hand tapping + reading
C	Right- and left-hand tapping
D	Right- and left-hand tapping + humming
E	Alternating tapping

Procedure

Handedness was assessed by using the Edinburgh Handedness Questionnaire [37]. According to the items of the handedness questionnaire, a laterality quotient $LQ = [(R - L)/(R + L)] \times 100$ was assessed for all subjects. In this study, only right-handed subjects with a laterality quotient of 60–100 were included. After the handedness questionnaire was completed, hand-skill asymmetry was assessed by using a tapping test series.

The finger tapping test was performed 2 h after drug administration and consisted of five consecutive parts (Table 1). In all sessions, the subjects were required to press a button as fast as possible for a period of 15 s. In session A to D, they were asked to tap first with their right and then with their left index fingers. In contrast to session A and C, in session B and D finger tapping was carried out with concurrent tasks. In session B, the subjects were instructed to tap while reading aloud a passage from a text, and in session D while simultaneously humming a tune. In session E, the subjects had to tap alternatingly with their right and left index fingers. From the tapping data the following parameters were assessed.

Finger tapping asymmetry

For all subjects, finger tapping asymmetry (FTA) was assessed. Taking the frequency of the right-hand taps as 100%, the percent difference in the frequency of left-hand taps compared to right-hand taps was calculated for sessions A to D: $[(L \times 100)/R] - 100$ (L = left-hand taps; R = right-hand taps) [19]. A mean value of the four percentile right-left differences was determined for each individual subject (=FTA). If the frequencies in left-hand taps are below the frequencies in right-hand taps, a negative value in FTA is obtained. This parameter is independent of individual tapping frequency.

The standard deviation (SD) of the mean value representing deviations in percentile right-left tapping differences from session A to D were used as indicators for stability or instability in the functional motor laterality of the finger-tapping task. In the motor laterality test, a low SD reflects stability, whereas a high SD is characteristic of instability [18]. The following example explains the procedure:

Session	A		B		C		D	
Finger-tapping	Right	Left	Right	Left	Right	Left	Right	Left
Finger-tapping Taps/15 s	75	61	67	64	74	65	68	60
[L × 100)/R] − 100	−18.67		−4.48		−12.16		−11.76	

FTA (mean value of −18.67, −4.48, −12.16, −11.76) = −11.77
SD = 5.80

The negative value of the FTA indicates that the mean frequency in left-hand taps is 11.77% lower than that in the right-hand taps.

Intermanual coordination

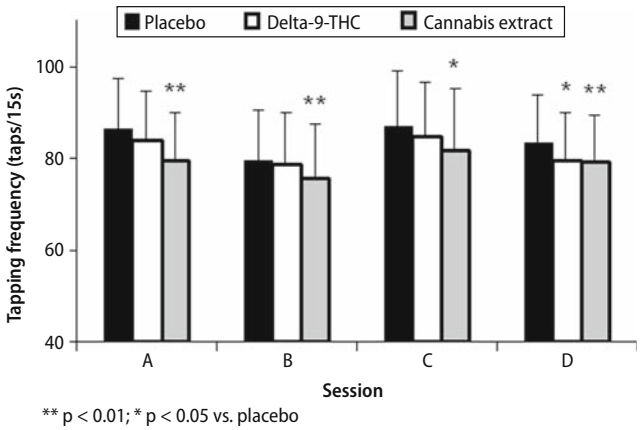
Intermanual coordination was assessed by alternating tapping (session E). Alternating tapping is a rapid change in right- and left-finger tapping which is based on a well-balanced IMC. To eliminate individual variations in tapping frequency, a mean tapping frequency of both hands was established for each individual subject (mean value of right- and left-hand taps in sessions A and C) and alternating tapping was related to this mean score. Thus, IMC was defined as the percent frequency of alternating tapping in relation to the mean tapping frequency of both hands: IMC = [(alternating tapping (R + L) × 100)/mean R- and L-hand taps in sessions A and C] − 100 [19]. If the alternating tapping frequency is higher than the mean number of taps in the sessions A and C, a positive value will be obtained. This can be illustrated by the following example:

Alternating tapping [right-hand taps (44) + left-hand taps (44)] = 88
Mean value of right- and left-hand taps = 68.75[calculated from control session A (75/61) and C (74/65)]
IMC = [(88 × 100)/68.75] − 100 = 28

The positive value obtained for this subject indicates that alternating tapping is 28% above the mean tapping frequency.

Statistical analysis

Almost all variables analyzed were approximately normally distributed. Group differences were assessed by MANOVA with one factor (group) and paired *t* tests. Pearson's correlation coefficients or *t* tests for independent groups were used to detect relationships between cannabinoid plasma concentrations and different variables such as psychomotor performances, AIR-Scale scores and gender. Statistical significance was taken as $P \leq 0.05$. All statistical analyses were carried out by using the statistical analysis software package SPSS 15.0® (Munich, Germany).



** p < 0.01; * p < 0.05 vs. placebo

Fig. 1 Right-hand tapping frequencies under Δ9-THC and cannabis extract versus placebo (in mean and SD)

Results

Tapping test parameters in relation to Δ^9-THC and cannabis extract

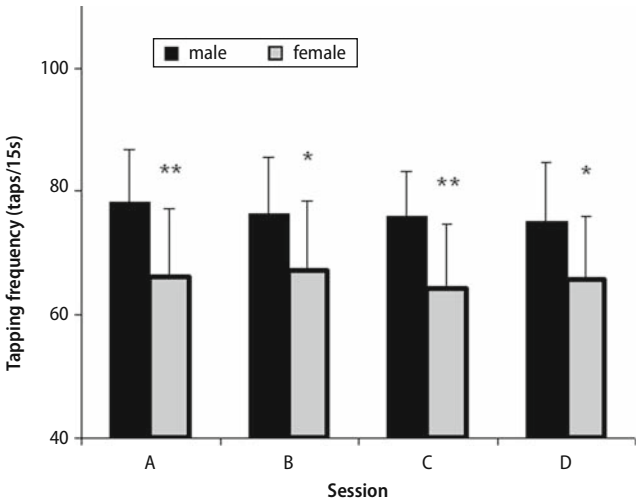
In all conditions (Δ^9-THC, cannabis extract and placebo) and in all sessions (A to D), right-hand tapping frequencies were significantly faster than left-hand tapping frequencies ($P < 0.001$).

As shown in Table 2 and Fig. 1, intraindividual comparisons revealed significantly lower right-hand tapping frequencies for sessions A to D under cannabis extract versus under placebo (A: $P = 0.009$; B: $P = 0.009$; C: $P = 0.014$; D: $P = 0.005$), while left-hand frequencies were reduced for session B ($P = 0.026$)

Table 2 Tapping frequencies (taps/15 s) under Δ^9-THC and cannabis extract versus placebo

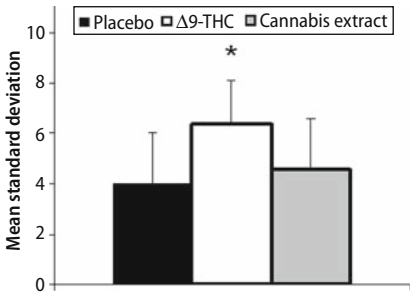
	Placebo Mean (SD)	Δ^9-THC Mean (SD)	Cannabis extract Mean (SD)	*F*(1/23)	P_a	P_b
Session A						
Right	86.63 (10.97)	83.75 (11.25)	79.58 (10.53)**	4.626	NS	0.009
Left	74.71 (9.59)	72.17 (11.62)	70.08 (12.51)	1.996	NS	NS
Session B						
Right	79.46 (10.90)	78.75 (11.04)	75.46 (12.01)**	4.268	NS	0.009
Left	72.79 (9.50)	71.67 (11.25)	68.67 (13.10)*	3.805	NS	0.026
Session C						
Right	86.88 (12.36)	84.75 (11.97)	81.75 (13.44)*	3.629	NS	0.014
Left	72.21 (9.89)	70.04 (10.54)	70.58 (15.82)	0.539	NS	NS
Session D						
Right	83.38 (10.39)	79.46 (10.53)*	79.13 (10.56)**	5.995	0.014	0.005
Left	72.92 (9.66)	70.54 (10.73)	70.79 (14.49)	1.328	NS	NS
Session E	114.58 (23.96)	112.21 (19.43)	109.46 (23.22)	1.116	NS	NS
FTA	−12.860 (6.173)	−12.322 (10.116)	−9.973 (10.577)	1.297	NS	NS
IMC	43.146 (26.043)	44.754 (19.340)	46.088 (27.956)	0.174	NS	NS

P_a = *P* value (Δ^9-THC vs. placebo); P_b = *P* value (cannabis extract vs. placebo)
**$P < 0.01$; *$P < 0.05$ versus placebo



** p < 0.01; * p < 0.05

Fig. 2 Gender differences in left hand tapping frequencies under Δ9-THC (in mean and SD)



* p < 0.05 vs. placebo

Fig. 3 Gender differences in mean standard deviations of the percentile right-left tapping differences of all female subjects under Δ9-THC, cannabis extract and placebo

and with a small trend for session A ($P = 0.090$). In contrast to cannabis extract, right-hand tapping frequencies under the pure Δ^9-THC was reduced only for session D ($P = 0.014$). As to FTA and IMC, there were no significant differences neither under Δ^9-THC nor under cannabis extract in comparison to placebo. But it is interesting to note that values in FTA were decreased and scores in IMC were increased, especially under the cannabis extract condition.

Figure 2 demonstrates significant gender differences in the left-hand tapping frequencies. It became evident that in all sessions male subjects showed faster left-hand taps than the females. These differences were significant under the Δ^9-THC condition for session A to D (A: $P = 0.007$; B: $P = 0.040$; C: $P = 0.005$; D: $P = 0.028$). Under the cannabis extract condition, left-hand tapping frequencies were significantly lower for session A ($P = 0.005$) and session C ($P = 0.031$).

The SDs of the percentile right-left tapping differences in female subjects were significantly higher under the Δ^9-THC condition in comparison to the placebo condition ($P = 0.015$), but not under the cannabis extract condition (Fig. 3). In male subjects, SDs of the percentile right-left tapping differences did not differ among each other. Interestingly, there were no gender differences in the tapping frequencies under the placebo condition.

Cannabinoid plasma concentrations and AIR-Scale scores: their relation to tapping test parameters

The mean plasma concentrations of Δ^9-THC, 11-OH-THC, THC-COOH and CBD, as well as the AIR-Scale scores under the different conditions are presented in Table 3.

Table 3 Plasma concentrations of Δ^9-THC, CBD, 11-OH-THC and THC-COOH (ng/ml) and AIR-Scale scores under different conditions (Δ^9-THC, cannabis extract, placebo)

	Gender	Placebo Mean (SD)	Δ^9-THC Mean (SD)	Cannabis extract Mean (SD)
Δ^9-THC	Male	0	1.20 (0.86)	1.49 (0.91)
	Female	0	1.91 (1.22)	1.78 (0.72)
CBD	Male	0	0	0.36 (0.36)
	Female	0	0	0.61 (0.35)
11-OH-THC	Male	0	2.50 (1.05)	3.31 (1.76)
	Female	0	4.95 (2.56)**	4.39 (1.49)
THC-COOH	Male	0	23.83 (9.36)	29.83 (9.51)
	Female	0	36.12 (12.31)*	36.37 (12.59)
AIR-Scale	Male	0.17 (0.33)	2.88 (1.52)	4.75 (2.49)
	Female	0.13 (0.31)	4.58 (2.57)	4.92 (2.82)

**$P < 0.01$; *$P < 0.05$ versus male subjects

Plasma concentrations of Δ^9-THC, 11-OH-THC and THC-COOH under the pure Δ^9-THC condition did not markedly differ from those under the cannabis extract condition. As expected, AIR-Scale scores under both Δ^9-THC and cannabis extract were significantly higher than those under placebo ($P < 0.001$), but did not differ among each other. With regard to gender differences, female subjects, in contrast to male subjects, revealed significantly higher levels of 11-OH-THC ($P = 0.008$) and THC-COOH ($P = 0.012$) as well as a trend to higher AIR-Scale scores ($P = 0.064$) under Δ^9-THC, but not under cannabis extract.

11-OH-Δ^9-Tetrahydrocannabinol, the principal psychoactive metabolite of Δ^9-THC, was significantly correlated with left-hand tapping frequencies under the Δ^9-THC condition, showing lower frequencies with higher concentrations. This fact has been found for session A ($r = -0.427$, $P = 0.037$) and session C ($r = -0.545$, $P = 0.006$, Fig. 4). In addition, 11-OH-THC concentration was negatively correlated with FTA under the Δ^9-THC condition ($r = -0.421$, $P = 0.041$). There were no additional significant correlations under the 11-OH-THC condition.

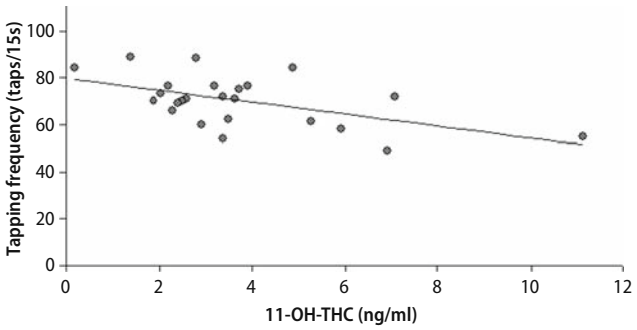


Fig. 4 Relationship between 11-OH-THC plasma concentrations and left-hand tapping frequencies of session C under Δ9-THC

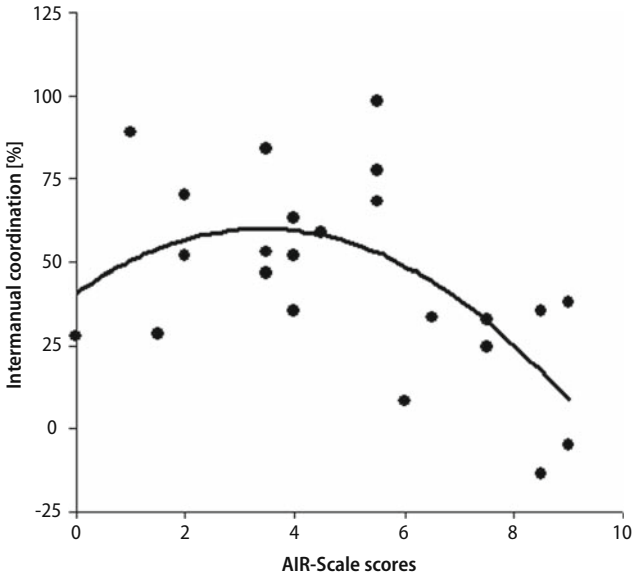


Fig. 5 Relationship between AIR-Scale scores and intermanual coordination (IMC) under cannabis extract

Interestingly, AIR-Scale scores as a measure of subjective perception of intoxication was dose-dependently related to IMC under the cannabis extract condition, but not under the Δ^9-THC condition. Regression analysis showed a curvilinear relationship ($r^2 = 0.375$, $P = 0.007$, Fig. 5). The turning point occurred at an AIR-Scale score of about 3.5. As expected, there was no influence of age on any tapping test parameter.

Discussion

The objective of the present study was to examine the acute effects of oral Δ^9-THC, standardized cannabis extract and placebo on psychomotor performance and their relationship with cannabinoid plasma concentrations and subjective perception of intoxication in a cohort of young healthy subjects. The results indicate that, compared to placebo, cannabis extract containing Δ^9-THC and CBD reduced right-hand tapping frequencies in all parts of the tapping test series, an effect consistent with the psychomotor disturbances seen in schizophrenic patients [16, 20, 29, 51]. The effects of cannabis extract on left-hand tapping frequencies were less pronounced. In contrast to cannabis extract, the pure Δ^9-THC had no marked effect on tapping test parameters compared to placebo. Nevertheless, we found a significantly negative correlation between the plasma concentration of 11-OH-THC, the principal psychoactive metabolite of Δ^9-THC, and left-hand tapping frequencies in almost all parts of the tapping test series under the pure Δ^9-THC condition.

Several lines of evidence suggest a role of the endogenous cannabinoid system in the regulation of motor activity [41, 48]. In our study, the psychoactive Δ^9-THC metabolite 11-OH-THC revealed the most distinct impact on motor function due to its strong CB_1-agonistic activity [21]. The basal ganglia with their high levels of CB_1 receptors represent the neural substrate which is responsible for the well-known motor actions of cannabinoids [48]. Hokama and colleagues [25] found a significant correlation between the volume of the basal ganglia and the performance on the finger tapping test. The three principle neurotransmitters in the basal ganglia include the predominantly excitatory transmitter glutamate, the predominantly inhibitory transmitter γ-aminobutyric acid (GABA) and dopamine. These neurotransmitter systems have been found to be markedly influenced by CB_1-agonistic cannabinoids such as 11-OH-THC [7, 42, 59]. Other possible explanations concerning the underlying mechanisms of cannabinoid-induced psychomotor disturbances, as seen in our study, may include effects of CB_1 agonists in the cerebral cortex and in the cerebellum [41]. These brain regions also show a high level of CB_1 receptors and are also related to motor activity.

Gender differences in tapping test performance have been detected for the Δ^9-THC and, less pronounced, for the cannabis extract condition. Female subjects performed worse than males, but, unexpectedly, only for left-hand tapping frequencies. Based on the high SDs of the percentile right-left tapping differences under Δ^9-THC in female subjects, greater instabilities in their functional superiority of the preferred hand may be assumed. It is of note that instability in functional motor laterality has been considered a characteristic feature of psychotic patients [18]. In accordance with this result, female subjects showed greater perception of intoxication as well as higher levels of 11-OH-THC under the Δ^9-THC condition compared to male subjects. Therefore, it may be possible that females are more sensitive to the acute effects of cannabinoids on psychomotor performance in comparison to male subjects. This finding may be due to the higher cannabinoid levels and,

subsequently, the greater subjective perception of intoxication. As to the placebo condition, no significant gender differences in tapping test parameters were seen, although several studies consistently reported higher tapping rates in healthy males [50].

Cannabis extract and pure Δ^9-THC revealed different results concerning the right- and left-hand tapping frequencies. The exact reason for this finding remains unclear, but pharmacokinetic and pharmacodynamic diversities may be responsible for these differences. For example, CBD may alter the pharmacological profile of Δ^9-THC and produce higher concentrations of Δ^9-THC and, subsequently, of its metabolites under cannabis extract. Simultaneous administration of CBD and Δ^9-THC may increase the plasma Δ^9-THC level by inhibiting hepatic microsomal THC metabolism through inactivation of the cytochrome P-450 oxidative system [5]. In fact, we found higher cannabinoid levels under cannabis extract in comparison to under pure Δ^9-THC in our study, but this finding failed to reach statistical significance. In addition, interindividual pharmacokinetic differences concerning resorption and distribution have to be taken into consideration. On the other hand, CBD shows low ligand activity of its own at the CB_1 receptor [35], but it does not act only through this known receptor. Various, not well characterized, new cannabinoid receptors were found [6]. It is possible that CBD may be a ligand of one or more of these receptors. Most recently, Ryberg and colleagues [46] identified the receptor GPR55 as a novel cannabinoid receptor. CBD as well as CB_1-agonistic exo- and endocannabinoids such as CP-55,940 and anandamide were seen to affect this receptor. Moreover, CBD might act through some other biochemical system and exhibit some of its effects via non-cannabinoid receptors as well. For example, agonistic properties of CBD at the vanilloid VR_1 receptor have been described [2]. It is also possible that the effects of CBD are due to its inhibition of anandamide reuptake and enzymatic hydrolysis, and due to its antioxidative effect mediated by an unknown receptor [35].

Finger tapping asymmetry as an index of laterality in finger tapping was not markedly altered neither under the Δ^9-THC nor under the cannabis extract condition. The same was true of IMC. However, there was a significantly negative correlation between the 11-OH-THC plasma concentration and FTA under the Δ^9-THC condition. Moreover, we found a curvilinear relationship between AIR-Scale scores and IMC under the cannabis extract condition.

Disturbances of both FTA and IMC may be characteristic findings in schizophrenic patients. Patients with acute psychotic symptoms showed higher values in IMC, whereas chronic schizophrenics revealed lower scores in IMC [20]. In this context, altered motor laterality and IMC in schizophrenic patients are thought to be related to functional and structural changes of the brain, in particular of the corpus callosum [3]. In our study, IMC as a functional index of interhemispheric transfer was affected under the cannabis extract condition. Under this condition, AIR-Scale scores were decisively changed. We found a dose-dependent relationship between AIR-Scale scores and IMC under cannabis extract. This was shown by an inverted U-curve. Mild states of intoxication revealed increased scores of IMC, whereas higher states of intoxication led to reduced values of IMC. Although there was no direct relationship between cannabinoid plasma levels and IMC, the AIR-Scale scores may indirectly serve as an index of cannabinoid activity in the brain. Our finding is in accordance with a study demonstrating a dose-dependent effect of Δ^9-THC on motor function in rats [47]. Thus, it may be assumed that in this study, disturbances of interhemispheric processing do not depend on structural changes but may be related to functional neuromodulatory properties of cannabinoids on GABAergic and glutamatergic neurons within the corpus callosum.

Several limitations of the study have to be considered. First, the data was collected from an only moderately large group of subjects (n = 24). Second, the present results of the potential effects of CBD are related to a cannabis extract which contains Δ^9-THC and additional cannabinoids in small amount. We used this extract because pure CBD at that time was not approved by the authorities for clinical research. In fact, the use of pure CBD would have resulted in a more effective control of the variables by avoiding interactive effects on psychomotor performance. Third, the concentrations of the different cannabinoids were measured in plasma. Nevertheless, based on its high lipophilicity, Δ^9-THC easily passes the blood–brain-barrier so that plasma cannabinoid levels may indeed reflect central cannabinoid activity. Moreover, penetration of the more psychoactive Δ^9-THC metabolite 11-OH-THC into the brain has been found to be faster and higher than that of the parent molecule [21]. Fourth, the oral route of cannabinoid administration may demonstrate a great interindividual variability of plasma cannabinoid concentrations. We did not choose the intravenous route of administration in order to minimize subjects' stress levels caused by intoxication and test procedures. And finally, since this was a pilot study, the results have to be interpreted with caution.

In summary, our data demonstrate that standardized cannabis extract and Δ^9-THC changed finger motor activity in different ways. While cannabis extract predominantly reduced right-hand tapping frequencies, the psychoactive metabolite of Δ^9-THC, 11-OH-THC after pure Δ^9-THC administration was negatively correlated with left-hand tapping frequencies and laterality in finger tapping (FTA). These effects may be related to the complex actions of CB_1-agonistic cannabinoids in the basal ganglia, the cerebral cortex

and the cerebellum. Furthermore, it could be shown that acute CB_1 receptor activation under the cannabis extract condition may also affect IMC as an index of interhemispheric transfer. AIR-Scale scores indicating subjective perception of intoxication were dose-dependently related to IMC which was shown by an inverted U-curve. This result may be due to functional changes involving GABAergic and glutamatergic neurotransmission within the corpus callosum. Further investigations are required to identify the exact neurochemical mechanisms and structural substrates which are responsible for the effects of cannabinoids on psychomotor function.

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