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Cannabidiol enhances verbal episodic memory in healthy young participants: A randomized clinical trial

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ABSTRACT

Cannabis contains a multitude of different compounds. One of them, cannabidiol – a non-psychoactive substance – might counteract negative effects of Δ-9-Tetrahydrocannabinol on hippocampus-dependent memory impairment. The aim of the present study was to investigate the effect of vaping cannabidiol on verbal episodic memory in healthy young subjects. We used a double-blind, placebo-controlled, randomized crossover trial in 39 healthy young subjects. Participants received once a single dose of cannabidiol e-liquid (0.25 ml, 5% cannabidiol, 12.5 mg cannabidiol) and once placebo for vaping after learning 15 unrelated nouns. The primary outcome measure was the short delay verbal memory performance (number of correctly free recalled nouns) 20 min after learning. 34 participants (mean age: 22.26 [3.04]) completed all visits and entered analyses (17 received cannabidiol and 17 received placebo first). Cannabidiol enhanced verbal episodic memory performance (placebo: 7.03 [2.34]; cannabidiol 7.71 [2.48]; adjusted group difference 0.68, 95% CI 0.01 to 1.35; $R_{2\beta} = .028$, $p = .048$). Importantly, we did not detect medication effects on secondary outcome measures attention or working memory performance, suggesting that CBD has no negative impact on these basic cognitive functions. The results are in line with the idea that vaping cannabidiol interacts with the central endocannabinoid system and is capable to modulate memory processes, a phenomenon with possible therapeutic potential. Further studies are needed to investigate optimal dose-response and time-response relationships.

1. Introduction

Cannabis is one of the most commonly used illicit drugs in the world (*United Nations Office on Drugs and Crime*, 2019). Meta-analyses investigating the effect of cannabis use consistently showed adverse effects of cannabis on memory performance (besides a number of other effects on behavior, see (Grant et al., 2003; Ranganathan & D'Souza, 2006; Schoeler and Bhattacharyya, 2013; Schoeler et al., 2016; Solowij and Battisti, 2008)). In particular, small- (Grant et al., 2003; Schoeler et al., 2016) to medium-sized adverse effects on verbal memory performance (Schreiner and Dunn, 2012), and medium-sized effects on prospective memory (Schoeler et al., 2016) were reported.

The major compound of cannabis, Δ-9-Tetrahydrocannabinol (THC), is most prominently known to be psychoactive and presumably responsible for the adverse effects of cannabis on cognition (Schoeler et al., 2016). Cannabidiol (CBD), another compound of cannabis, acts opposite to THC with many regards. CBD is non psychoactive and has antipsychotic, anxiolytic, anti-seizure and anti-inflammatory properties (Rong et al., 2017). Moreover, CBD has experimentally been shown to inhibit paranoid symptoms elicited by THC (Bhattacharyya et al., 2010; but see also: Morgan et al., 2018).

Whereas THC is a CB1R and CB2R partial agonist (Pertwee, 2008), CBD seems to act as a non-competitive antagonist on CB1Rs as well as an inverse agonist on CB2Rs, and inhibits the reuptake and enzymatic degradation of the endogenous cannabinoid anandamide (N-arachidonoylethanolamine; AEA) (for an overview see: Rong et al., 2017). Numerous non-CB1R targets have been proposed for CBD as well, including the serotonin 1A receptor (5-HT1A), sigma (σ) and mu (μ)

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opioid receptors, vanilloid receptor 1 (TRPV1), dopamine D2 receptors, and fatty acid amide hydrolase (FAAH) (for an overview see: Jacobson et al., 2019).

Due to the assumed adverse effects of THC on cognition, several studies investigated if CBD might be able to counteract these adverse effects. CBD counteracted hippocampus-dependent memory impairment when administered prior to intravenous THC (Englund et al., 2013). THC and CBD also showed opposite effects relative to placebo on brain activations during cognitive tasks, but not on a behavioral level (Bhattacharyya et al., 2010). Moreover, naturalistic studies showed memory impairment to be attenuated in subjects smoking cannabis with high amounts of cannabidiol, as opposed to low amounts ((Morgan et al., 2012; Morgan et al., 2010); but see also (Morgan et al., 2018)).

An open-label clinical study found promising effects of prolonged CBD treatment on psychological symptoms and cognition in regular cannabis users, while they continued to use cannabis as usual (Solowij et al., 2018). Also animal studies found beneficial effects of CBD administration on cognitive outcomes. Chronic administration of CBD attenuated social and cognitive deficits in schizophrenia rat models (Osborne et al., 2017a), and CBD improved cognition in multiple preclinical models of cognitive impairment (Osborne et al., 2017b). However, CBD did neither improve prose recall during tobacco abstinence (Hindocha et al., 2015), nor prose recall in cannabis users (Morgan et al., 2018), or verbal recall in healthy subjects (Bhattacharyya et al., 2009), or patients with psychosis (Bhattacharyya et al., 2018; O'Neill et al., 2021).

In safety studies, no cognitive change after one-year of CBD treatment (Martin et al., 2019) or three months of treatment was found in treatment resistant epilepsy patients (Metternich et al., 2021), nor after single administration of CBD in a highly sensitive population of polydrug users compared to control (Schoedel et al., 2018).

Given the ambiguous evidence for pro-cognitive effects of CBD, we aimed at investigating the effect of CBD on episodic memory performance in healthy young humans in the present double-blind, placebo-controlled, randomized trial. The results may have implications for the treatment of episodic memory deficits, which are not only hallmarks of Alzheimer's Disease, but are also prevalent in many psychiatric disorders like schizophrenia (Barch, 2005), bipolar disorders (Balanza--Martinez et al., 2008), or posttraumatic stress disorders (D. J. de Quervain and Margraf, 2008). Moreover, subjects under stress and stress-related exhaustion are showing episodic memory deficits (D. de Quervain et al., 2017). Importantly, we are still lacking effective drugs to counter episodic memory deficits in neuropsychiatric conditions.

2. Methods

2.1. Study design and participants

We performed a double-blind, placebo-controlled, randomized, crossover trial comparing the effect of vaping cannabidiol (CBD) e-liquid (0.25 ml, 5% CBD, 12.5 mg CBD) with vaping a placebo e-liquid. We recruited healthy participants from the Basel, Zurich, and Bern area of Switzerland through Internet advertisements. 34 participants entered final analyses. The experiment took place at the University of Basel.

To meet the inclusion criteria, participants had to be between 18 and 30 years old, have a body mass index (BMI) between 18 and 30 kg/m2, be native or fluent German-speaking and normotensive (blood pressure between 90/60 mmHg and 140/90 mmHg). Exclusion criteria were one or more of the following conditions as assessed with a self-report health questionnaire: acute or chronic psychiatric or somatic disorders, long-term systemic medication or topical steroids to treat an underlying disease within the last 3 months, known hypersensitivity or allergy to propylene glycol, substance consumption (smoking $>$ 5 cigarettes per day, intake of CBD/THC within 7 days of the present study, alcohol intake 12 h before start of the study visits, suspected alcohol or drug abuse), participation in a study with CBD/THC within 30 days of the present study, participation in one of the division's previous studies using the same verbal test in the past 2 years, having any personal connections to the investigator, inability to follow the procedures of the study, and the intention to become pregnant, pregnancy or breast-feeding.

The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The local ethics committee approved the study (registration number: EKNZ, 2018-01125), and the study was registered with ClinicalTrials.gov (NCT03627117) and kofam.ch (SNCTP000002921). All participants provided written informed consent and received a compensation of CHF 70 for their participation.

2.2. Randomization and masking

After study inclusion, participants were randomly allocated to receive either CBD or placebo (perfumed e-liquid) first. Each eligible participant was allocated to one of the two randomization lists (one list for males, one list for females) by using block randomization (each block of 4 containing two placebo and two CBD conditions).

CBD e-liquid and perfumed e-liquid were filled in identically looking vaporization tanks and labelled with a randomization number. Furthermore, the vaporization tanks were wrapped with colorized tape to cover e-liquid color. Both vapes (CBD, placebo) had a citrus fruits taste. Generation of computer randomization lists and labelling of the vaporization tanks were done by the primary statistician, who did not collect data. Participants and data collector study member were blinded to treatment group. Participants vaped under supervision of the data collector on a quiet balcony to avoid contaminating the air in the examination room with CBD vapors.

2.3. Procedures

The study took place on two study days at the University of Basel, Basel, Switzerland from September to December 2018.

After a potential participant contacted the study team, more detailed information about the study was sent by e-mail along with the main inclusion and exclusion criteria. Thereafter, a telephone screening did take place to pre-assess inclusion and exclusion criteria and to schedule eligible participants for the study. In the telephone screening, we not only asked for the use of medications (prescribed and self-purchased) in the last three months, but also for the use of any medication (prescribed and self-purchased) at the time point of screening. None of the participants indicated to have used any medication at the time point of screening or within the past 3 months.

During the first part of visit 1, information regarding the aim and procedure of the study, the drug under investigation and potential risks were given again to the participant (orally and in writing). Thereafter, written informed consent was obtained from all participants without time limitation. Then, inclusion and exclusion criteria were checked by assessing medical history, vitals signs (blood pressure and heart rate), and the BMI, as well as by applying a sociodemographic and mental health questionnaire, and a self-rating questionnaire assessing depressive symptoms (MADRS-S) (Svanborg and Asberg, 2001). The software SoSci Survey was used for the assessment of questionnaires (Leiner, 2014). As all female participants could assure not to be pregnant, no pregnancy tests were performed.

Before the assessment of the outcome measures, a urine THC test with a sensitivity of 50 ng/ml was performed to exclude THC consumption three to five days prior to the start of the study. Furthermore, participants were asked about sleep duration, psychoactive drug intake and alcohol consumption the day before the visit.

After word learning and immediate recall, subjects vaped for approximately 15 min under supervision. Then, participants were instructed and trained on an n-back task. The training was repeated once if for a given subject, the correct response rate was below 90% in the 0-

back and below 70% in 2-back training task, respectively. This was followed by the main n-back task, assessing attention and working memory. Subsequently, subjects had to indicate on visual analog scales (VAS) their current state of relaxation, fatigue, motivation and mood, as well as if they had any headaches and how well they tolerated the vaping. Twenty minutes after learning, a word recall test was conducted to assess episodic memory performance. After a wash-out period of at least 14 days (approximately 10 half-lifes of CBD (Ujvary and Hanus, 2016)), but no longer than 39 days (mean wash-out period 17.85 day, SD = 6.11), participants were invited to visit 2. There, they received the treatment (CBD or placebo) complementary to the one from the first visit. On visit 2, adverse events and concomitant medication were also recorded, with the procedure being otherwise identical to visit 1.

2.4. Outcomes

The primary outcome measure was delayed free recall in a verbal learning task. In this task, participants viewed and were instructed to learn three series of five semantically unrelated German nouns presented at a rate of one word every 2 s (15 words in total). Each series of five nouns was followed by an immediate recall task to control if participants paid attention to the presentation of words. Immediate recall took place before study medication and therefore will not be treated as a primary outcome measure. 20 min after the word-learning task, participants were asked in an expected free recall task to write down all the remembered words of the particular visit. The words were taken from the collections of Hager and Hasselhorn (1994).

Our two secondary outcome measures were attention (0-back) and working memory (2-back) performances and were tested to control for possible effects of CBD on cognitive functions unrelated to episodic memory. They were assessed by two pictorial n-back tasks with different cognitive load (low load: 0-back; high load: 2-back) using neutral pictures. During the 0-back condition, subjects needed to respond as quickly as possible to the occurrence of a target picture. The 0-back condition induces only low cognitive load and is supposed to mainly require general attention processes (Owen et al., 2005). In the 2-back condition, subjects had to judge whether the currently presented picture was identical to the one presented two positions before. The 2-back condition induces a high cognitive load and served to assess working memory performance due to its requirement of online monitoring, updating, and manipulation of remembered information (Owen et al., 2005). In total, the task comprised 6 blocks (three blocks per condition), presented in a quasi-randomized order. In each block, four different pictures were quasi-randomly presented eight times, resulting in a total of 32 presented pictures per block. Each block contained eight target stimuli and twenty-four non-target stimuli, resulting in a target-rate of 25%. Subjects had to react to these targets as quickly as possible.

All pictures used for the n-back task were selected from the Geneva Affective Picture System (GAPED; Dan-Glauser and Scherer, 2011), the International Affective Picture System (IAPS; Lang et al., 2008), or in-house standardized picture sets. All pictures comprised neutral, single inanimate objects (e.g., chairs, clocks, or tables).

Control outcomes were assessed by means of VAS ratings, ranging from 0 (lowest level to 10 (highest level). VAS assessed relaxation, tiredness, motivation, mood, headache, and tolerance of vaping.

All tasks were presented by using the Presentation® software (version 20.1; Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com).

2.5. Intervention

The experimental intervention consisted of 0.25 ml of CBD e-Liquid containing 5% CBD (low-temperature extracted Cannabidiol from Cannabis sativa L., 99% purity), Glycerine (vegetable), Propylene Glycol, and water (brand: PharmaHemp, Slovenia) with citrus fruit taste. The control intervention consisted of 0.25 ml of e-Liquid (La Baronne Jaune) containing: Foodstuff fragrance additives, 80% Glycerine (vegetable), 20% Propylene Glycol. The control intervention had a lemon and madeleines taste. Vaping was conducted by using a vaporizer (Canna Vape Kit). Vaping was chosen as a method for administration due to the faster absorption rates compared to oral administration (Millar, Stone, Yates and O'Sullivan, 2018). We chose a CBD e-liquid with a 5% concentration, as this was the highest concentration that could be purchased regionally. 0.25 ml was chosen, as this is an amount that can be vaped by most smokers in 15 min. Vaping for more than 15 min was not considered practicable. This resulted in a dose of 12.5 mg.

2.6. Statistical analyses

A power analysis estimated a sample size of 34 (dependent t-tests, dz 0.5, power 0.8, software: G*Power 3.1). All statistical analyses were performed in R (version 3.6.2) by using linear mixed models in combination with ANOVA (SS II). Subject-IDs were included as random effects. Dependent variables were our primary and secondary outcome measures. The independent variable was the within-subject factor condition (CBD or placebo). Sex and age were entered as covariates.

We present results as means (SDs) for the intervention and control condition, associated two-sided p values, as well as adjusted group differences with 95% CIs ("emmeans" package).

Effect sizes for repeated measures are indicated by generalized semi-partial R2 ($R_{2\beta}$), a generalization of the widely used marginal R2-statistics (Nakagawa and Schielzeth, 2013) which is comparable to effect size measures of between-subject designs. $R_{2\beta} > 0.01$, $R_{2\beta} > 0.09$ and $R_{2\beta} > 0.25$ are considered small, intermediate and large effects, respectively.

A Fisher exact test was conducted to examine the association between the treatment order group (received CBD on visit1 or received CBD on visit2) and the subject's belief on which day to have received CBD.

The significance threshold was set to $p < .05$ for the primary outcome. For the secondary outcomes (attention, working memory performance), we set the significant threshold to $p < .025$ (Bonferroni correction for 2 independent tests). No data monitoring committee oversaw the study. A clinical trial monitor oversaw data collection and entry according to a written monitoring plan, which was approved by the Independent Ethics Committee before trial conduction.

3. Results

Between September 2018 and December 2018, 39 individuals were screened for trial participation (see Fig. 1). None were excluded after screening. Consequently, 39 individuals were enrolled and underwent randomization for treatment order (see Table 1 for baseline characteristics).

20 subjects were allocated to receive CBD (intervention condition), 19 to receive placebo on visit 1. Four subjects dropped out and did not participate on visit 2 (the reasons were: alcohol intake < 12h before visit 2 (n = 1), declined to continue participation (n = 3)). 35 subjects underwent the procedure of visit 2. One subject did not undergo the whole procedure of visit 2 due to the inability to vape the full dose in the time given. Therefore, complete data of 34 subjects were available and analyzed (17 received CBD and 17 received placebo on visit 1).

3.1. Effects of study medication on primary outcome measure

For episodic memory, quantified by word free recall as our primary outcome, there was a significant main effect of study medication ($F_{(1,33)} = 11.12$, $p = .048$, $R_{2\beta=}$ .028), indicating better performance under CBD with a small effect size (see Table 2, Fig. 2). This enhancing drug effect was independent of sex (interaction between sex and medication: $p = .85$) or age (interaction between age and medication: $p = .19$).

To control for other possible confounders, we also included MADRS,

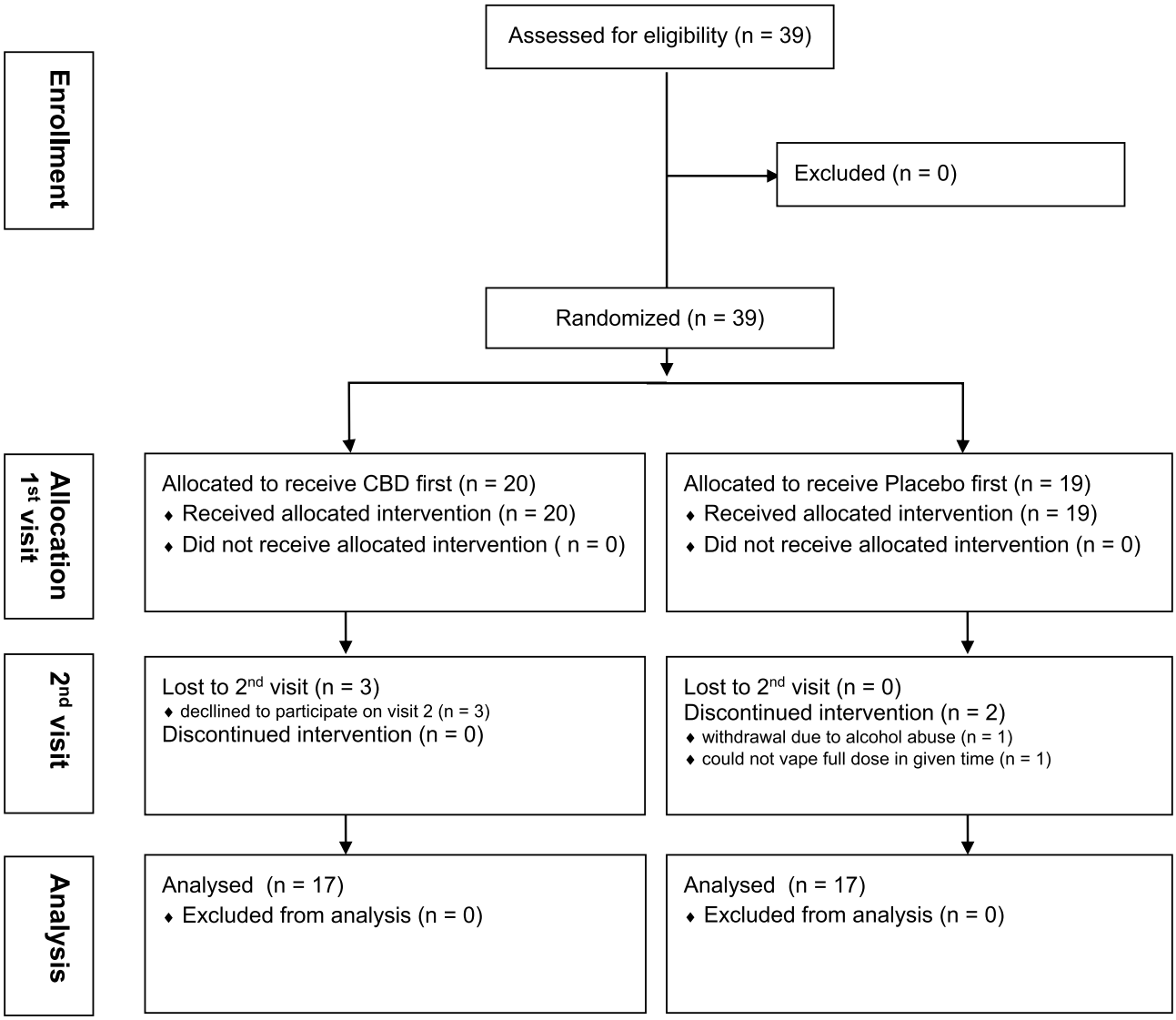

Fig. 1. Flow diagram of the process through study phases.

Table 1
Baseline characteristics.

Age	22.26 (3.04; 18–29)
Sex	17/17
BMI	22.76 (2.71; 18.60–28.10)
MADRS-S	2.69 (2.50; 0–10)
Frequency of annual cannabis consumption	2.24 (3.2; 0–12)
Cannabis consumption per year/number of participants:	0/15, 1/6, 2/1, 3/4, 4/2, 5/2, 6/1, 10/2, 12/1

Data are numbers of participants or mean (SD; range).

BMI, frequency of cannabis consumption in one year, and the ratings after vaping (relaxation, tiredness, motivation, mood, vaping tolerance) as covariates. Each covariate was thereby entered separately into the model and tested for its interaction with medication. The enhancing drug effect was independent of any of these covariates (interaction between covariates and medication: $p > .33$), except for BMI ($F_{(1,32)} = 4.49$, $p = .042$). The interaction between BMI and drug on word recall indicated that CBD administration affected words recall as a function of BMI, i.e. a higher BMI was associated with a higher number of recalled words under CBD compared to placebo (see Fig. 3).

Immediate recall before vaping was not different between conditions ($p = .99$).

3.2. Effects of study medication on secondary and control outcome measures

For the secondary outcome measures assessing attention and working memory, no significant effects of medication on 0-back (accuracy: $F_{(1,33)} = 1.3$, $p = .26$; dprime: $F_{(1,33)} = 3.42$, $p = .07$) or 2-back performance were detected (accuracy: $F_{(1,33)} = 0.05$, $p = .83$; dprime: $F_{(1,33)} = 0.02$, $p = .89$, see Table 2).

Participants did not differ in relaxation, mood, headache, motivation or fatigue after vaping CBD or placebo (all $p > .18$). However, there was a nominal effect of CBD on vaping tolerance ($F_{(1,33)} = 4.5$, $p = .041$), indicating higher vaping tolerance in the placebo condition (see Table 2).

No serious adverse event occurred. One mild adverse event was reported in one participant (2.6%) under the influence of CBD (headache), and one mild adverse event was reported in one participant (2.8%) under the influence of placebo (abdominal pain).

Furthermore, there was no association between the treatment order and the subjects' believe about when to have received CBD ($\chi 2$ (2) = 0.55, p = .81).

Table 2
Outcome measures and differences between conditions.

	CBD	Placebo	Adjusted group difference (95% CI)	Effect size	Nominal p value
Primary Outcome					
Delayed free recall	7.71 (2.48)	7.03 (2.34)	0.68 (0.01, 1.35)	.028	.048
Other outcomes					
0-back accuracy	0.98 (0.03)	0.98 (0.04)	0.01 (−0.01, 0.02)	.013	.26
2-back accuracy	0.87 (0.07)	0.87 (0.07)	−0.00 (−0.03, 0.03)	.001	.83
0-back dprime	4.2 (0.49)	4.01 (0.76)	0.19 (−0.02, 0.41)	.027	.07
2-back dprime	2.34 (0.74)	2.32 (0.71)	0.02 (−0.27, 0.30)	.0002	.89
Relaxation	3.08 (2.35)	3.18 (2.24)	−0.10 (−0.82, 0.61)	.001	.77
Mood	7.55 (1.66)	7.78 (1.64)	−0.23 (−0.81, 0.34)	.006	.41
Headache	0.38 (1.00)	0.32 (0.54)	0.06 (−0.28, 0.40)	.001	.73
Motivation	7.57 (1.56)	7.20 (1.77)	0.37 (−0.18, 0.92)	.015	.18
Fatigue	3.75 (2.23)	3.92 (2.24)	−0.17 (−1.01, 0.67)	.002	.68
Tolerance	7.41 (2.09)	8.44 (1.98)	−1.04 (−2.03, −0.04)	.063	.04

Data are mean (SD). Adjusted group difference (CBD – placebo) for age, sex and drug.

4. Discussion

Here, we investigated the acute effects of vaping CBD (12.5 mg) on episodic memory performance in healthy young subjects. The present study revealed an average increase of recalled words 20 min after vaping CBD compared to placebo condition by 10%. Importantly, we did not detect medication effects on attention or working memory performance, suggesting that CBD has no negative impact on these basic cognitive functions. This is in line with two other studies, which did not report effects of CBD on working memory performance by using 15 mg of CBD in cannabis users (Morgan et al., 2018) or 800 mg of CBD during tobacco abstinence (Hindocha et al., 2015).

The effect of CBD on episodic memory was independent of age, sex, depressive symptoms, frequency of cannabis consumption in a year, and the ratings after vaping (relaxation, tiredness, motivation, mood, tolerance). However, the effect was not independent of BMI. The interaction between BMI and drug suggests that the dose for subjects with lower BMI might have been too high to increase memory. Due to bioavailability differences between different types of CBD administration (Millar et al., 2018), we cannot compare our dose to doses of studies that used different administration methods to estimate an optimal dose-response relationship. Further, the relationship between CBD dose and effect on episodic memory may also follow an inverted-U-shape curve rather than a linear relationship, comparable to the inverted-U-shape dose-response effects of CBD on anxiety (Crippa et al., 2018).

One study using oral administration of 600 mg CBD found effects on brain activation (Bhattacharyya et al., 2010), but not on memory performance, or when administered doses ≥ 750 mg (Schoedel et al., 2018). Other studies combined the administration of CBD with THC. 600 mg of oral CBD counteracted hippocampus-dependent memory impairment

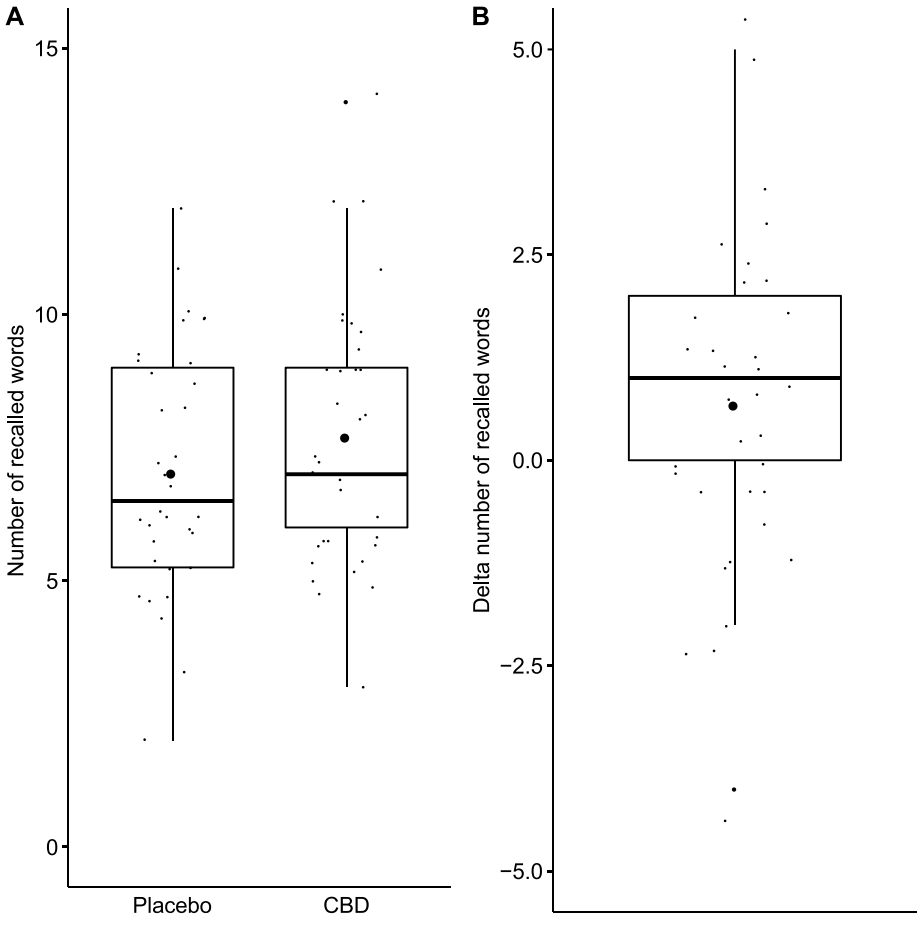

Fig. 2. Effect of CBD on episodic memory performance (short delay).
Small dots represent individual values; the big dot represents the group mean. A: The boxplot displays the number of recalled words during delayed free recall in each condition.
B: The boxplot displays the difference score (delta) by subtracting the numbers of freely recalled words during CBD by the numbers of freely recalled words during placebo.

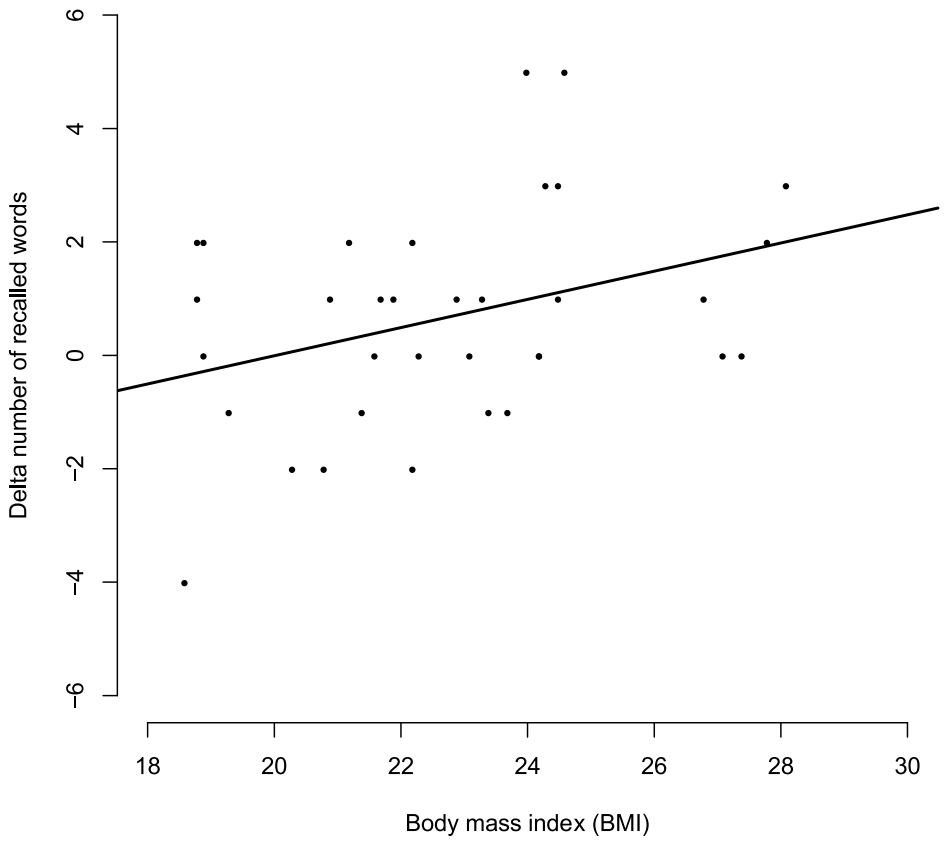

Fig. 3. Treatment effect on episodic memory during delayed free recall as a function of body mass index (BMI). Positive values on the y-axis represent more recalled words during CBD as compared to placebo.

when administered prior to intravenous THC (Englund et al., 2013), but not 5 mg of IV CBD immediately before IV THC (1.25 mg) (Bhattacharyya et al., 2010), or co-administration of 16 mg CBD + 8 mg of THC administered by inhalation (Morgan et al., 2018). However, 200 mg of oral CBD over 10 weeks exhibited cognitive improvements relative to baseline in regular cannabis users, while they continued to use cannabis as usual (Solowij et al., 2018). Other studies did not find cognitive changes relative to baseline after three months (Metternich et al., 2021) or one year (Martin et al., 2019) of CBD administration in treatment resistant epilepsy patients.

We would like to stress that we assessed acute effects of CBD on episodic memory 20 min after encoding, thus preventing any conclusions about CBD effects on memory consolidation. Therefore, besides the unknown dose-response relationship and that the results cannot be generalized to other types of CBD administration, further studies are needed to investigate isolated effects of CBD on the distinct memory phases of consolidation and retrieval. Our conclusions are based on a single use of CBD e-liquid. It is unclear whether repeated administration of CBD would lead to similar effects. This should be investigated in further studies in healthy subjects and in neuropsychiatric patients with episodic memory deficits. Further limitations should be noted. We did not assess any measure of anxiety. Given that CBD is thought to have strong anxiolytic effects (Rong et al., 2017), this may be a confounder to the results, although the experimental setting and the tasks did not contain any fear-inducing elements. Furthermore, we only instructed subject not to use any illicit drugs or CBD during study duration, but did not perform any laboratory tests on them. Moreover, health status was based on self-declaration as assessed with a health questionnaire and not based on a clinical or structured interview to rule out mental illness.

CBD is non-psychoactive and easily applicable. Therefore, CBD might prove useful to enhance disease-related memory impairments being present in psychiatric disorders (for example Balanza-Martinez et al., 2008), neurodegenerative disorders (such as Alzheimer's disease (Gold and Budson, 2008)), as well as in stress and stress-related exhaustion related to episodic memory deficits (D. de Quervain et al., 2017).

To conclude, while further research is needed to identify dose-response and time-response relationships, our results show that CBD can improve episodic memory, a drug effect with possible therapeutic potential.

Author contributions

Janine Hotz: Conceptualization, Methodology, Investigation, Project administration **Bernhard Fehlmann:** Validation **Andreas Papassotiropoulos:** Supervision, Funding, Resources **Dominique JF de Quervain:** Supervision, Funding, Resources **Nathalie S Schicktanz:** Formal analysis, Data curation, Writing - original draft preparation, Visualization **All authors:** Writing –Review and Editing.

Declaration of interests

All authors declare no conflicts of interest.

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Data sharing

Anonymised participant data that underlie the results reported in this article will be available to investigators for studies that have received approval from independent research committees or research ethics boards. Data are available from the publication date of this article onwards. Study proposals and data access requests should be sent to Prof. Dr. Dominique de Quervain Dominique.dequervain@unibas.ch. Data sharing agreements between the requestors and the sponsor investigators need to be completed before accessing the data. Approved Study protocol by the local ethics committee is available on ClinicalTrials.gov (NCT03627117).

References

Balanza-Martinez, V., Rubio, C., Selva-Vera, G., Martinez-Aran, A., Sanchez-Moreno, J., Salazar-Fraile, J., Tabares-Seisdedos, R., 2008. Neurocognitive endophenotypes (endophenocognitypes) from studies of relatives of bipolar disorder subjects: a systematic review. S0149-7634(08)00089-4 Neurosci. Biobehav. Rev. 32 (8), 1426–1438. https://doi.org/10.1016/j.neubiorev.2008.05.019 [pii].

Barch, D.M., 2005. The cognitive neuroscience of schizophrenia. Annu. Rev. Clin. Psychol. 1, 321–353. https://doi.org/10.1146/annurev.clinpsy.1.102803.143959.

Bhattacharyya, S., Fusar-Poli, P., Borgwardt, S., Martin-Santos, R., Nosarti, C., O'Carroll, C., McGuire, P., 2009. Modulation of mediotemporal and ventrostriatal function in humans by Delta9-tetrahydrocannabinol: a neural basis for the effects of Cannabis sativa on learning and psychosis. Arch. Gen. Psychiatr. 66 (4), 442–451. https://doi.org/10.1001/archgenpsychiatry.2009.17.

Bhattacharyya, S., Morrison, P.D., Fusar-Poli, P., Martin-Santos, R., Borgwardt, S., Winton-Brown, T., McGuire, P.K., 2010. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology 35 (3), 764–774. https://doi.org/10.1038/npp.2009.184.

Bhattacharyya, S., Wilson, R., Appiah-Kusi, E., O'Neill, A., Brammer, M., Perez, J., McGuire, P., 2018. Effect of cannabidiol on medial temporal, midbrain, and striatal dysfunction in people at clinical high risk of psychosis: a randomized clinical trial. JAMA Psychiatry 75 (11), 1107–1117. https://doi.org/10.1001/jamapsychiatry.2018.2309.

Crippa, J.A., Guimaraes, F.S., Campos, A.C., Zuardi, A.W., 2018. Translational investigation of the therapeutic potential of cannabidiol (CBD): toward a new age, 2009 Front. Immunol. 9. https://doi.org/10.3389/fimmu.2018.02009.

Dan-Glauser, E.S., Scherer, K.R., 2011. The Geneva affective picture database (GAPED): a new 730-picture database focusing on valence and normative significance. Behav. Res. Methods 43 (2), 468–477. https://doi.org/10.3758/s13428-011-0064-1.

de Quervain, D., Schwabe, L., Roozendaal, B., 2017. Stress, glucocorticoids and memory: implications for treating fear-related disorders. Nat. Rev. Neurosci. 18 (1), 7–19. https://doi.org/10.1038/nrn.2016.155.

de Quervain, D.J., Margraf, J., 2008. Glucocorticoids for the treatment of post-traumatic stress disorder and phobias: a novel therapeutic approach. Eur. J. Pharmacol. 583 (2–3), 365–371. https://doi.org/10.1016/j.ejphar.2007.11.068.

Englund, A., Morrison, P.D., Nottage, J., Hague, D., Kane, F., Bonaccorso, S., Kapur, S., 2013. Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. J. Psychopharmacol. 27 (1), 19–27. https://doi.org/10.1177/0269881112460109.

Gold, C.A., Budson, A.E., 2008. Memory loss in Alzheimer's disease: implications for development of therapeutics. Expert Rev. Neurother. 8 (12), 1879–1891. https://doi.org/10.1586/14737175.8.12.1879.

Grant, I., Gonzalez, R., Carey, C.L., Natarajan, L., Wolfson, T., 2003. Non-acute (residual) neurocognitive effects of cannabis use: a meta-analytic study. J. Int. Neuropsychol. Soc. 9 (5), 679–689. https://doi.org/10.1017/S1355617703950016.

Hager, W., Hasselhorn, M., 1994. Handbuch Deutschsprachiger Wortnormen. Hoegrefe, Göttingen.

Hindocha, C., Freeman, T.P., Schafer, G., Gardener, C., Das, R.K., Morgan, C.J., Curran, H.V., 2015. Acute effects of delta-9-tetrahydrocannabinol, cannabidiol and their combination on facial emotion recognition: a randomised, double-blind, placebo-controlled study in cannabis users. Eur. Neuropsychopharmacol 25 (3), 325–334. https://doi.org/10.1016/j.euroneuro.2014.11.014.

Jacobson, M.R., Watts, J.J., Boileau, I., Tong, J., Mizrahi, R., 2019. A systematic review of phytocannabinoid exposure on the endocannabinoid system: implications for psychosis. Eur. Neuropsychopharmacol 29 (3), 330–348. https://doi.org/10.1016/j.euroneuro.2018.12.014.

Lang, P.J., Bradley, M.M., Cuthbert, B.N., 2008. International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual. University of Florida, Gainesville, FL.

Leiner, D.J., 2014. SoSci Survey [Computer software]. Available at:, Version 2.5.00-i. https://www.soscisurvey.de.

Martin, R.C., Gaston, T.E., Thompson, M., Ampah, S.B., Cutter, G., Bebin, E.M., Szaflarski, J.P., 2019. Cognitive functioning following long-term cannabidiol use in adults with treatment-resistant epilepsy. Epilepsy Behav. 97, 105–110. https://doi.org/10.1016/j.yebeh.2019.04.044.

Metternich, B., Wagner, K., Geiger, M.J., Hirsch, M., Schulze-Bonhage, A., Klotz, K.A., 2021. Cognitive and behavioral effects of cannabidiol in patients with treatment-resistant epilepsy. Epilepsy Behav. 114 (Pt A), 107558. https://doi.org/10.1016/j.yebeh.2020.107558.

Millar, S.A., Stone, N.L., Yates, A.S., O'Sullivan, S.E., 2018. A systematic review on the pharmacokinetics of cannabidiol in humans. Front. Pharmacol. 9. ARTN 136510.3389/fphar.2018.01365.

Morgan, C.J.A., Freeman, T.P., Hindocha, C., Schafer, G., Gardner, C., Curran, H.V., 2018. Individual and combined effects of acute delta-9-tetrahydrocannabinol and cannabidiol on psychotomimetic symptoms and memory function. Transl. Psychiatry 8. ARTN 18110.1038/s41398-018-0191-x.

Morgan, C.J.A., Gardener, C., Schafer, G., Swan, S., Demarchi, C., Freeman, T.P., Curran, H.V., 2012. Sub-chronic impact of cannabinoids in street cannabis on cognition, psychotic-like symptoms and psychological well-being. Psychol. Med. 42 (2), 391–400. https://doi.org/10.1017/S0033291711001322.

Morgan, C.J.A., Schafer, G., Freeman, T.P., Curran, H.V., 2010. Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study: naturalistic study [corrected]. Br. J. Psychiatry 197 (4), 285–290. https://doi.org/10.1192/bjp.bp.110.077503.

Nakagawa, S., Schielzeth, H., 2013. A general and simple method for obtaining R2 from generalized linear mixed-effects models. Methods in Ecology and Evolution 4 (2), 133–142. https://doi.org/10.1111/j.2041-210x.2012.00261.x.

O'Neill, A., Wilson, R., Blest-Hopley, G., Annibale, L., Colizzi, M., Brammer, M., Bhattacharyya, S., 2021. Normalization of mediotemporal and prefrontal activity, and mediotemporal-striatal connectivity, may underlie antipsychotic effects of cannabidiol in psychosis. Psychol. Med. 51 (4), 596–606. https://doi.org/10.1017/S0033291719003519.

Osborne, A.L., Solowij, N., Babic, I., Huang, X.F., Weston-Green, K., 2017a. Improved social interaction, recognition and working memory with cannabidiol treatment in a prenatal infection (poly I:C) rat model. Neuropsychopharmacology 42 (7), 1447–1457. https://doi.org/10.1038/npp.2017.40.

Osborne, A.L., Solowij, N., Weston-Green, K., 2017b. A systematic review of the effect of cannabidiol on cognitive function: relevance to schizophrenia. Neurosci. Biobehav. Rev. 72, 310–324. https://doi.org/10.1016/j.neubiorev.2016.11.012.

Owen, A.M., McMillan, K.M., Laird, A.R., Bullmore, E., 2005. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. Hum. Brain Mapp. 25 (1), 46–59. https://doi.org/10.1002/hbm.20131.

Pertwee, R.G., 2008. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. Br. J. Pharmacol. 153 (2), 199–215. https://doi.org/10.1038/sj.bjp.0707442.

Ranganathan, M., D'Souza, D.C., 2006. The acute effects of cannabinoids on memory in humans: a review. Psychopharmacology (Berl) 188 (4), 425–444. https://doi.org/10.1007/s00213-006-0508-y.

Rong, C., Lee, Y., Carmona, N.E., Cha, D.S., Ragguett, R.M., Rosenblat, J.D., McIntyre, R. S., 2017. Cannabidiol in medical marijuana: research vistas and potential opportunities. Pharmacol. Res. 121, 213–218. https://doi.org/10.1016/j.phrs.2017.05.005.

Schoedel, K.A., Szeto, I., Setnik, B., Sellers, E.M., Levy-Cooperman, N., Mills, C., Sommerville, K., 2018. Abuse potential assessment of cannabidiol (CBD) in recreational polydrug users: a randomized, double-blind, controlled trial. Epilepsy Behav. 88, 162–171. https://doi.org/10.1016/j.yebeh.2018.07.027.

Schoeler, T., Bhattacharyya, S., 2013. The effect of cannabis use on memory function: an update. Subst. Abuse Rehabil. 4, 11–27. https://doi.org/10.2147/SAR.S25869.

Schoeler, T., Kambeitz, J., Behlke, I., Murray, R., Bhattacharyya, S., 2016. The effects of cannabis on memory function in users with and without a psychotic disorder: findings from a combined meta-analysis. Psychol. Med. 46 (1), 177–188. https://doi.org/10.1017/S0033291715001646.

Schreiner, A.M., Dunn, M.E., 2012. Residual effects of cannabis use on neurocognitive performance after prolonged abstinence: a meta-analysis. Exp. Clin. Psychopharmacol 20 (5), 420–429. https://doi.org/10.1037/a0029117.

Solowij, N., Battisti, R., 2008. The chronic effects of cannabis on memory in humans: a review. Curr. Drug Abuse Rev. 1 (1), 81–98. https://doi.org/10.2174/1874473710801010081.

Solowij, N., Broyd, S.J., Beale, C., Prick, J.A., Greenwood, L.M., van Hell, H., Yucel, M., 2018. Therapeutic effects of prolonged cannabidiol treatment on psychological symptoms and cognitive function in regular cannabis users: a pragmatic open-label clinical trial. Cannabis Cannabinoid Res 3 (1), 21–34. https://doi.org/10.1089/can.2017.0043.

Svanborg, P., Asberg, M., 2001. A comparison between the beck depression inventory (BDI) and the self-rating version of the montgomery Asberg depression rating scale (MADRS). J. Affect. Disord. 64 (2–3), 203–216. Retrieved from. https://www.ncbi.nlm.nih.gov/pubmed/11313087.

United Nations Office on Drugs and Crime, 2019. United Nations Publications, New York.