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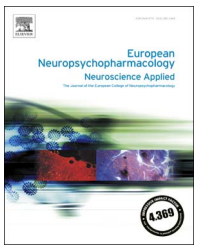

Probing the endocannabinoid system in healthy volunteers: Cannabidiol alters fronto-striatal resting-state connectivity

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Abstract
Tetrahydrocannabinol (THC) and Cannabidiol (CBD) are two substances from cannabis sativa that have beenimplicated in the treatment of mental and neurological disorders. We concentrated on a previously validated neuroimaging phenotype, fronto-striatal connectivity across different striatal seeds, because of this loop's relevance to executive functioning, decision making, salience generation and motivation and its link to various neuropsychiatric conditions. Therefore, we studied the effect of THC and CBD on fronto-striatal circuitry by a seed-voxel connectivity approach using seeds from the caudate and the putamen. We conducted a cross-over pharmaco-fMRI study in 16 healthy male volunteers with placebo, 10 mg oral THC and 600 mg oral CBD. Resting state was measured in a 3 T scanner. CBD lead to an increase of fronto-striatal connectivity in comparison to placebo. In contrast to our expectation that THC and CBD show opposing effects, THC versus placebo did not show any significant effects, probably due to insufficient concentration of THC during scanning. The effect of CBD on enhancing fronto-striatal connectivity is of interest because it might be a neural correlate of its anti-psychotic effect in patients.

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1. Introduction

The endocannabinoid system has been discussed in mental and neurological disorders, for example, patients suffering from schizophrenia show increased cerebrospinal levels of endocannabinoids (Leweke et al., 2007). The exogenic modulation of the endocannabinoid system has been investigated related to therapeutic and disease-mediating mechanisms for some time (Schubart et al. 2013). The consumption of tetrahydrocannabinol (THC) has been linked to psychotic symptoms in healthy volunteers (D'Souza et al., 2005). The effect of THC consumption on an epidemiological level is still a matter of debate. Several epidemiological studies on psychotic experiences and psychosis underscore the negative influence of THC on psychosis-prone individuals (Arseneault et al., 2004; Moore et al., 2007; Schubart et al., 2011; van Gastel et al., 2013). However, a twin study points to a genetic cause of cannabis consumption which is genetically correlated with psychosis risk (Nesvag et al., 2016). This genetic risk is reflected in an interaction between cannabis exposure and genetic risk for schizophrenia leading to a delayed brain maturation in adolescence (French et al., 2015).

THC is not the only potent phytocannabinoid in cannabis sativa. From several hundred active ingredients, cannabidiol (CBD) has received recent interest because of its opposite effects on psychosis in comparison to THC. Animal studies in psychosis models, pharmacologic psychosis-models in humans and treatment studies in schizophrenic patients point to an antipsychotic effect of CBD (Schubart et al., 2014; Zhornitsky and Potvin, 2012).

Cannabinoid receptor type 1 (CB1) receptors are found in the central and peripheral nervous system. There is strong expression of the CB1-receptor in the cerebellum, the limbic system (amygdala and hippocampus) and the basal ganglia (Glass and Felder, 1997; Herkenham et al., 1991; Mailleux et al., 1992). Especially in striatal neurons, dopaminergic signalling and endocannabinoid signalling are tightly linked (Glass and Felder, 1997).

Therefore, the fronto-striatal circuit makes a plausible target for assessment of systemic neural effects for THC and CBD. Recent studies identified a decrease in fronto-striatal coupling as an intermediate phenotype in schizophrenia (Dandash et al., 2014) with patients suffering from schizophrenia, their unaffected siblings as well as at-risk individuals showing a decrease in fronto-striatal coupling.These studies provide the rationale to examine the basal-ganglia as seed regions for studying connectivity.

In addition, neuroimaging of THC and CBD effects was done before by McGuire and colleagues in a neuroimaging study of 15 male subjects using a within-subject comparison. An overview of this study and subsequent analyses is given in (Colizzi and Bhattacharyya, 2017). Main finding of the authors was that THC and CBD had opposite effects in several different neuroimaging tasks capturing different aspects of emotion and cognition e.g. activation relative to placebo in the striatum during verbal recall, in the hippocampus during the response inhibition task or in the amygdala when subjects viewed fearful faces (Bhattacharyya et al., 2010). Therefore, we wanted to replicate these findings of opposite effects, and the previously reported impact on fronto-striatal connectivity (Bhattacharyya et al., 2015) and broaden these studies' perspective by using a hypothesis driven striatal seed-voxel resting-state approach.

Therefore, the present study aimed at identifying whether a well-known psychosis-related intermediate phenotype can (I) be linked to a low dose THC induced disturbance in healthy humans and (II) whether CBD shows the opposite pattern in resting-state fMRI (functional magnetic resonance imaging) underscoring the translational validity of functional connectivity measures in the THC/CBD-challenge pharmacological model.

2. Experimental procedures

2.1. Subjects

Subjects were recruited via local advertisement; those with psychiatric or other medical disease and medication were excluded (except for stable thyroid substitution). Positive drug urine test or regular drug use were other exclusion criteria. The human fMRI study took place in a single centre and was conducted as subject- and observer-blind, placebo-controlled, randomized, three-period cross-over study in healthy male subjects. The subjects received counterbalanced, single dose administrations of either saline (placebo condition), tetrahydrocannabinol (THC) 10 mg or cannabidiol (CBD) 600 mg. Scanning of resting state took place about 75 min after oral capsule intake. Approval was given by the local ethics committee (Medical Faculty Mannheim, University of Heidelberg, Germany). The study was registered as clinical study in the German clinical study registry (https://drks-neu.uniklinik-freiburg.de study-ID: DRKS00005442). Subjects underwent three consecutive fMRI sessions over the course of three weeks (max. 8 weeks apart). The Dissociative Symptoms Scale (DSS) was used to assess levels of depersonalization, derealization or gaps in awareness and memory (Carlson et al., 2018). The state anxiety inventory (STAI) was used to assess state dependent anxiety levels (Spielberger, 1973) and the positive and negative affect schedule (PANAS) was used assess positive and negative affect, valence and arousal (Janke and Glöckner-Rist, 2014; Watson et al., 1988). Rating was done 120 min after drug intake. Nineteen participants completed the study. Two subjects were dismissed because of lack of THC in blood samples, one subject did not complete the study because of side-effects (nausea). Therefore, the analysis was done with n = 16.

2.2. Drug application

On each day of the experiment, subjects received a light standardized meal (sandwich ~350 kcal) before capsule intake. Scanning took time 75 min later. For avoidance of order effects, the order of substance application was randomly permutated across all participants. The participants were supervised by a certified psychiatrist. Blinding took place at the University Pharmacy at the University of Heidelberg. Unblinding took place after all participants completed the study and the data were analysed. At the end of each session the participant, physician and experimenter had to indicate which substance they believed to have been administered. Pharmacokinetics were measured by HPLC-chromatography of blood samples before and after intake.

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