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Alterations of theory of mind network activation in chronic cannabis users

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1. Introduction

Cannabis is one of the most commonly used illicit drug worldwide (Perkonigg et al., 2008). Its well documented psychotropic effects are primarily produced by the plant cannabinoid Δ^9 -tetrahydrocannabinol (Δ^9 -THC) via the central cannabinoid receptor CB₁ (Pertwee, 2008). Cannabis-induced cognitive impairments particularly include deficits in attention, learning, memory, and executive functioning (Pope et al., 2001; Solowij et al., 2002; Lundqvist, 2005), and may be present even after 28 days of abstinence (Bolla et al., 2002; Medina et al., 2007). Consistent with these neuropsychological findings, brain imaging studies in cannabis users have revealed altered morphology, function, blood flow, and metabolism in prefrontal, hippocampal, and cerebellar regions (Lundqvist et al., 2001; Quickfall and Crockford, 2006; Yücel et al., 2008). These brain regions are critically involved in cognition and characterized by high densities of CB₁ receptors (Herkenham et al., 1990). Interestingly, cognitive impairments appear to increase with duration and frequency of cannabis use, suggesting persistent deficits as a result of long-term changes due to a neurotoxic effect of long-term cannabis exposure (Bolla et al., 2002; Solowij et al., 2002; Roser et al., 2010).

Numerous studies reported a close relationship between chronic cannabis use and schizophrenia (D'Souza, 2007; Moore et al., 2007). In healthy subjects, cannabis use represents an environmental risk

ABSTRACT

Chronic cannabis use is associated with cognitive impairment and has been identified as a risk factor for schizophrenia. Patients with schizophrenia show profound deficits in social cognition such as the ability to attribute mental states to others, referred to as "theory of mind" (ToM). Aberrant activation of the ToM network has been demonstrated across different phases of schizophrenia, including at-risk stages. Accordingly, we aimed to investigate the ToM network in chronic cannabis users. Fifteen cannabis users received functional brain imaging during performance of a ToM cartoon story task. Findings were compared with 14 control subjects. Cannabis users showed less activation in the left parahippocampal gyrus, the right precuneus and cuneus, but greater activation in the left cuneus and the right anterior cingulate gyrus compared to healthy controls. These activation patterns resemble those found in at-risk populations, suggesting that cannabis use can affect the processing of social information similar to other risk factor constellations for psychosis. © 2012 Elsevier B.V. All rights reserved.

factor for the development of psychotic symptoms, particularly in subjects with an underlying genetic predisposition for psychosis (Henquet et al., 2005a, 2005b). Moreover, repeated cannabis use may increase the risk for psychosis by impacting on the persistence of psychotic symptoms, independent of age, gender, socioeconomic status, use of other drugs, urban environment, and childhood trauma (Kuepper et al., 2011). With regard to the clinical symptomatology, many psychotropic effects caused by cannabis use closely resemble the signs and symptoms of schizophrenia (D'Souza et al., 2009). Acute administration of Δ^9 -THC to healthy subjects induced characteristic positive, negative, and cognitive schizophrenia-like symptoms (D'Souza et al., 2004). In schizophrenia patients, acute administration of Δ^9 -THC was associated with a transient exacerbation of core psychotic symptoms and cognitive deficits (D'Souza et al., 2005). Moreover, chronic cannabis use has been demonstrated to worsen positive symptoms of schizophrenia and to result in a poor outcome and greater liability to relapse (Linszen et al., 1994; Bersani et al., 2002). However, the question of a causal relationship between cannabis use and schizophrenia remains unresolved (Arseneault et al., 2004).

Social cognitive impairments, including deficits to attribute mental states to others, are a common feature in schizophrenia (Brüne, 2005; Green et al., in press). The ability to explain other people's behavior in terms of their beliefs, intentions, and dispositions, has been referred to as "theory of mind" (ToM) (Frith and Frith, 1999; for a more recent overview of ToM deficits in neuropsychiatric disorders, see Brüne and Brüne-Cohrs, 2006). Mental state attribution or ToM has extensively been studied in schizophrenia and found consistently impaired, with some differences between syndromal subtypes (Abdel-Hamid et al., 2009). In addition, functional brain imaging studies have shown that

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patients with schizophrenia often underactivate brain regions involved in ToM performance, foremost areas of the prefrontal cortex and the anterior cingulate cortex, with more inconsistent findings regarding posterior regions such as the temporoparietal junction (Brunet-Gouet and Decety, 2006; Brüne et al., 2008, 2011).

Anomalous patterns of brain activation during ToM task performance have also been shown in at-risk stages of psychosis (Modinos et al., 2010; Brüne et al., 2011). This suggests that people who are at increased genetic risk of developing psychosis, or who fulfill the criteria for clinical at-risk states according to the Structured Interview for Prodromal Symptoms (SIPS; Miller et al., 2002), activate the ToM network differently when compared with psychologically healthy subjects, and this may also be the case in individuals with chronic cannabis use.

Accordingly, the present study sought to investigate the brain activity of cannabis users during ToM performance. We predicted that, similar to what has been described in at-risk stages of schizophrenia, subjects with chronic cannabis use would deviate in activating the ToM network compared to a control group who had never used cannabis.

2. Materials and methods

2.1. Subjects

Fifteen male subjects with chronic cannabis use (mean age $26.5 \pm$ 2.9 years) and 14 male healthy controls (mean age 27.3 ± 3.5 years) were recruited. The study was approved by the Ethics Committee of the Medical Faculty of the Ruhr-University Bochum, Germany; all participants gave their informed consent in writing. The minimum requirement for participation as a cannabis user was regular use of at least 3 times per week for a period of at least 2 years. All cannabis users met the criteria for current cannabis abuse as assessed by the Structured Clinical Interview for DSM-IV (First et al., 2001). The group of nonuser controls was matched for age, education, and nicotine consumption. The control subjects had never used cannabis in the past according to their statement in the questionnaire. Both cannabis users and controls had no history of any psychiatric or neurological disorders, except for cannabis use disorder in the users group, but no abuse of any other substance. Cannabis users were instructed to abstain from cannabis for at least 24 h prior to testing in order to minimize acute cannabis effects. No cannabis withdrawal was seen nor reported. For both cannabis users and controls, alcohol consumption was not allowed either for at least 24 h prior to testing. Moreover, the urine of all subjects was tested for amphetamines and ecstasy, benzodiazepines, cannabinoids, cocaine, methadone, and opiates before the test session in order to ensure that they had not

Table 1

Demographic and psychometric variables of chronic cannabis users (CN) and healthy controls (HC) in means \pm SD.

	CN (n=15)	HC (n=14)	p Value
Age (years)	26.5 ± 2.9	27.3 ± 3.5	n.s.
Education (years)	17.8 ± 2.8	18.7 ± 2.8	n.s.
Smokers (yes/no)	12/3	9/5	n.s.
Nicotine (cigarettes per day)	14.9 ± 13.2	8.0 ± 9.0	n.s.
MWT-B (IQ)	109.3 ± 9.0	116.2 ± 13.4	n.s.
BDI	6.1 ± 4.1	4.1 ± 3.2	n.s.
HAMD	2.8 ± 2.1	2.1 ± 2.0	n.s.
BPRS	22.0 ± 3.0	21.0 ± 2.7	n.s.
TCI personality traits			
Self-directedness	31.0 ± 7.4	33.0 ± 7.1	n.s.
Cooperativeness	31.6 ± 6.9	29.6 ± 7.0	n.s.
Self-transcendence	10.6 ± 6.5	9.1 ± 5.6	n.s.
Novelty seeking	23.5 ± 4.9	21.5 ± 4.7	n.s.
Harm avoidance	12.5 ± 7.0	13.1 ± 4.6	n.s.
Reward dependence	14.9 ± 3.7	14.6 ± 3.3	n.s.
Persistence	2.7 ± 1.5	3.9 ± 1.6	n.s.

(n.s. = not significant).

consumed any illegal drug prior to testing, and to verify the use of cannabis in the users group. None of the subjects took medication before or during the study.

2.2. Psychological dimensions

Depressive symptoms were quantified with the Beck Depression Inventory (BDI; Beck et al., 1961) and the Hamilton Depression Rating Scale (HAMD; Hamilton, 1960). Psychotic symptoms were assessed with the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962). Verbal intelligence was determined with the Multiple Choice Verbal Comprehension Test (MWT-B; Lehrl, 2005). The Temperament and Character Inventory (TCI; Cloninger et al., 1993) was used to assess personality traits. The TCI is a 240-item questionnaire and operates with seven dimensions of personality traits, comprising four temperaments (i.e., novelty seeking, harm avoidance, reward dependence and persistence) and three characters (i.e., self-directedness, cooperativeness and self-transcendence). The demographic and psychometric variables of the entire study sample are provided in Table 1.

2.3. Cannabis use variables and plasma concentrations of $\Delta^9\mbox{-THC},$ 11-OH-THC, and THC-COOH

Cannabis use variables were assessed by using a standardized questionnaire. The severity of cannabis craving was measured with a visual analog scale ranging from 0 (no craving) to 10 (extreme craving). Prior to testing, blood samples were taken and controlled for and its main metabolites 11-OH-THC and THC-COOH by using a gas chromatography–mass spectrometry method (Nadulski et al., 2005). Cannabis use variables and cannabinoid plasma concentrations are presented in Table 2.

2.4. Theory of mind (ToM)

The ToM task consisted of six different cartoon stories with four pictures each, showing scenarios of a) cooperation of two persons depicting reciprocality, b) deception, where one person deceives another person associated with overt unfairness, and c) cooperation of two persons to the disadvantage of a third person, i.e., two cartoon stories of each type. To contrast activation elicited by ToM demands with non-ToM activation, we introduced a control (non-ToM) condition, where the same stories were presented, but with pictures in jumbled order (Fig. 1).

Stories were presented to participants via fMRI-ready LCD-goggles (Visuastim Digital, Resonance Technology Inc., Northridge, CA, USA). All four pictures of a given story were shown simultaneously on the screen, arranged in two rows in left to right order. In each condition, at first the cartoon story was presented alone for 15 s, then two questions were successively superimposed upon the screen (between the first and the second row of pictures) for 12 s each. The task of the participant was to attentively watch the story during the first phase and to think about the answer to each question as long as the question was displayed on the screen.

Table 2

Cannabis use variables and cannabinoid plasma concentrations in chronic cannabis users (CN) in means \pm SD.

	CN (n=15)
Frequency of cannabis use (times per week)	5.2 ± 1.4
Quantity of cannabis use (joints per week)	13.1 ± 7.4
Duration of cannabis use (years)	8.5 ± 3.0
Abstinence of cannabis use (hours)	25.1 ± 1.1
Severity of cannabis craving (VAS)	1.7 ± 2.0
Δ^9 -THC (ng/ml)	4.14 ± 4.78
11-OH-THC (ng/ml)	1.75 ± 2.16
THC-COOH (ng/ml)	94.56 ± 112.05

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