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The impact of early-onset cannabis use on functional brain correlates of working memory

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ABSTRACT

Cannabis is the most commonly used illicit drug. Prevalence rates are particularly high among adolescents. Neuropsychological studies have identified cannabis-associated memory deficits, particularly linked to an early onset of use. However, it remains unclear, whether the age of onset accounts for altered cortical activation patterns usually observed in cannabis users. Functional magnetic resonance imaging was used to examine cortical activation during verbal working memory challenge in (1) early-onset (onset before the age of sixteen; $n=26$) and (2) late-onset cannabis users (age at onset at least sixteen; $n=17$). Early-onset users showed increased activation in the left superior parietal lobe. Correlational analyses confirmed the association between an earlier start of use and increased activity. Contrariwise neither cumulative dose, frequency nor time since last use was significantly associated with cortical activity. Our findings suggest that an early start of cannabis use is associated with increased cortical activation in adult cannabis users, possibly reflecting suboptimal cortical efficiency during cognitive challenge. The maturing brain might be more vulnerable to the harmful effects of cannabis use. However, due to a lack of a non-using control group we cannot exclude alternative interpretations.

1. Introduction

Cannabis is the most commonly used drug in western industrial nations and prevalence rates are particularly high among adolescents and young adults (EMCDDA, 2007; Monshouwer et al., 2005; OFDT, 2005; UNO WDR, 2006). An increasing number of studies reported various cognitive impairments in heavy cannabis users. In particular, deficits were found in working and episodic memory, as well as in executive and attentional functions (Block and Ghoneim, 1993; Bolla et al., 2002; Messinis et al., 2006; Solowij et al., 2002). However, if these adverse effects persist with prolonged abstinence or are merely transient remains controversial. Some studies reported recovery with prolonged abstinence (Pope et al., 2001; Schaeffer et al., 1981), while others reported persisting impairments in several cognitive domains such as attention, working memory and executive functioning (Bolla et al., 2002; Grant et al., 2003; Solowij et al., 2002).

Given these contrasting results, several studies have addressed the question whether specific characteristics of use might account for a varying degree of the observed deficits (Bolla et al., 2002; Ehrenreich et al., 1999; Pope et al., 2003; Schwartz et al., 1989; Solowij et al., 2002). Converging lines of evidence suggest that the development and persistence of these deficits are particularly linked to the onset of use. It has been shown, that the initiation of use prior to the age of 16 or 17 leads to enduring deficits on specific attentional functions (Ehrenreich et al., 1999) and short-term memory (Schwartz et al., 1989). Furthermore, only users who initiated use before the age of 17 showed persisting impairments in several neuropsychological measures after 28 days of monitored abstinence (Pope et al., 2003). Together with a report on reduced cortical grey matter in early-onset users (Wilson et al., 2000) it might be hypothesized that, if regular cannabis use starts during early and middle adolescence, it might produce permanent or at least long lasting alterations in neurocognitive functioning.

Although fundamental cognitive abilities evolve during childhood, existing cognitive abilities refine throughout adolescence (Spear, 2000). Findings from longitudinal studies suggest that neurodevelopment accompanies cognitive development with parietal and prefrontal associative cortices, involved in higher-order cognitive functioning, maturing last (Gogtay et al., 2004; Sowell et al., 2004).

Abbreviations: ADHD, attention hyperactivity disorder; ANCOVA, Analysis of covariance; BA, Brodmann area; BOLD, blood oxygenation level-dependent; DLPFC, dorsolateral prefrontal cortex; EOU, early-onset cannabis users; FDR, False discovery rate; fMRI, functional magnetic resonance imaging; FWE, Family Wise Error; LOU, late-onset cannabis users; MDMA, 3,4-Methylenedioxymethamphetamine; SOA, stimulus onset asynchrony; SPL, superior parietal lobe; ROI, region of interest; THC, Δ9-Tetrahydrocannabinol; WURS, Wender Utah Rating Scale.

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Brain dynamic changes during adolescence are basically driven by complex interactions between the nervous system and gonadal steroid hormones (Sisk and Foster, 2004) and continue throughout adolescence and young adulthood (Casey et al., 2005; Gogtay et al., 2004; Sowell et al., 2004). Given that the endocannabinoid system regulates fundamental neuromaturational processes (Harkany et al., 2007) and cannabis affects multiple endocrine systems (Brown and Dobs, 2002), cannabis use during this vulnerable period might interfere with regular brain development.

To investigate the neural correlates of cannabis-associated cognitive impairments, a growing number of studies employed functional magnetic resonance imaging (fMRI). Chronic users usually display altered activation of brain networks associated with the specific cognitive domain despite normal task performance (Chang et al., 2006; Jager et al., 2006; Kanayama et al., 2004). In terms of spatial and verbal working memory, increased activation in the superior parietal cortex, prefrontal cortex and anterior cingulate regions, have been reported (Jager et al., 2006; Kanayama et al., 2004).

Bearing in mind adolescent neuromaturational processes and the suggested associations between an early initiation of cannabis use and the development of cannabis-associated cognitive deficits, it, hence, might be of special interest if the age of onset accounts for altered cortical activation patterns in cannabis users. The purpose of this study was to clarify whether an early onset of cannabis use is linked to altered neural activity during working memory challenge.

2. Methods

2.1. Participants

Subjects in the present study were part of a larger study on the effects of drug use on neurocognition. Participants were examined with an extensive neurocognitive test battery and fMRI. Findings from the neurocognitive test battery for the entire sample will be published in a separate report. For the fMRI study, subjects were included if they reported a minimum cannabis lifetime usage of 10 g. All subjects were required to be at least 18 years old and right-handed. Exclusion criteria were: (1) any current or previous axis I psychiatric diagnosis (except for cannabis abuse), (2) childhood diagnosis of attention hyperactivity disorder (ADHD), (3) regular use of all other illicit substances except for cannabis (more than five occasions), (4) history of alcohol abuse and/or dependence (according to DSM-IV criteria, APA, 1994), (5) regular intake of any medication, (6) intake of any legal or illegal psychotropic substances or medication except for cannabis seven days prior to testing, (7) consumption of cannabis on the day of the examination, (8) pregnancy, or (9) other known contraindications for MRI scanning. All subjects gave written informed consent and received remuneration.

Forty-three cannabis users were enrolled in the present study. To obtain information about the impact of the age of onset of cannabis use on cortical activation, we median-split the entire sample into two groups according to the age of onset of cannabis use: (1) early-onset users (EOU), who first used cannabis before the age of sixteen ($n=26$) and (2) late-onset users (LOU), whose age at first cannabis use was at least sixteen ($n=17$). Previous studies used a comparable age at first use to distinguish between early- and late-onset users (Ehrenreich et al., 1999; Pope et al., 2003; Schwartz et al., 1989).

2.2. Cognitive task

Subjects performed three verbal n-back tasks with increasing memory load. N-back tasks have been shown to reliably initiate working memory activation in healthy subjects and drug using populations (Daumann et al., 2003a,b, 2004; Owen et al., 2005). A blocked periodic design was used incorporating alternating active and control conditions. Six alternating control and active blocks (duration each: 30 s) were presented per n-back task. In each block a sequence of twelve single capital letters was visually presented, each for 2100 ms (SOA 2500 ms) by means of a prismatic mirror. The switch between control and active conditions was indicated by a shift in the colour of the presented letters. In all conditions participants were asked to respond by button press when the target letter appeared. In the control (0-back) condition the target letter was designated ("G"). In the three active conditions 1-, 2- and 3-back, the target letter was defined as any letter that was identical to the one presented in the preceding 1, 2, or 3 trials, respectively. Each of the three n-back tasks comprised the same quantity of correct responses. Total scanning time per n-back task was 3:09 min, total experiment time was 9:27 min. The three n-back tasks were separately introduced by a verbal instruction.

2.3. Procedure

All subjects underwent a structured interview according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV). To exclude participants with childhood ADHD all participants completed the German version of the Wender Utah Rating Scale (WURS). The WURS retrospectively assesses childhood ADHD by self-reported symptom severity between the age of 8 and 10 (Ward et al., 1993). Participants were excluded if they exceeded the recommended cut-off score of 46 (Ward et al., 1993). In addition, we took a medical history and detailed history of drug use including the following parameters of cannabis use: (1) age of first use, (2) time since the last use in days, (3) average frequency of use measured by average days of use per month, (4) maximum days of use per month ever, (5) estimated cumulative lifetime dose, (6) average and (7) highest daily dose ever used, as well as (8) duration of regular use in months. Studies validating self-reported voluntary substance use found a high reliability of the reported drug quantity (Martin et al., 1988; Rothe et al., 1997). Randomly taken hair samples by the Institute of Legal Medicine of the University of Cologne confirmed the self-reported substance use. In addition, qualitative drug screens were performed on the day of the examination with urine samples for amphetamines, benzodiazepines, cocaine, methadone, MDMA and cannabis (enzyme-multiplied immunoassay, von Minden GmbH). Participants were allowed to smoke cigarettes ad libitum before MRI acquisition. Participants were part of a larger study and underwent an extensive neurocognitive test battery. For an overview, measures of verbal working memory, mental flexibility and motor speed for the fMRI subsample will be reported in the present paper. Verbal working memory performance was assessed using the Digit Span Backwards test (from the WAIS-R, German version; Tewes, 1991). To measure mental flexibility and motor speed the Trail Making test (Trails A and Trails B; Reitan, 1955) was administered. This test is frequently used for screening for cognitive impairments in substance abusing populations (see e.g. Roberts and Horton, 2001). In order to control for confounding variables intellectual functioning and the use of alcohol and nicotine were assessed. Current intellectual functioning was assessed by the Raven Standard Progressive Matrices (Raven, 2000). In addition the use of alcohol (frequency of alcoholic drinks per week during the previous year) and nicotine (cigarettes per week) was assessed by means of separate questions within the cannabis use interview. The study was in accordance with the Helsinki Declaration of 1975 and was approved by the local ethics committee of the Medical Faculty of the University of Cologne.

2.4. Imaging parameters

MRI employing blood oxygenation level-dependent (BOLD) contrast was performed on a clinical 1.5 T Philips ACS NT Gyroscan (Philips, Eindhoven, The Netherlands) using a singleshot multislice T2* weighted gradient echo EPI sequence (imaging parameters: