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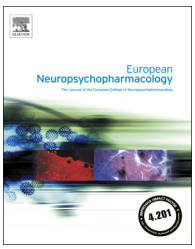

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Impairment of inhibitory control processing related to acute psychotomimetic effects of cannabis

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Abstract
Cannabis use can induce acute psychotic symptoms and increase the risk of schizophrenia. Impairments in inhibitory control and processing are known to occur both under the influence of cannabis and in schizophrenia. Whether cannabis-induced impairment in inhibitory processing is related to the acute induction of psychotic symptoms under its influence is unclear.
We investigated the effects of acute oral administration of 10 mg of delta-9-tetrahydrocannabinol (delta-9-THC), the main psychoactive ingredient of cannabis, on inhibitory control and regional brain activation during inhibitory processing in humans and examined whether these effects are related to the induction of psychotic symptoms under its influence using a repeated-measures, placebo-controlled, double-blind, within-subject design. We studied thirty-six healthy, English-speaking, right-handed men with minimal previous exposure to cannabis and other illicit drugs twice using functional magnetic resonance imaging (fMRI) while they performed a response inhibition (Go/No-Go) task.

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Relative to placebo, delta-9-THC caused transient psychotic symptoms, anxiety, intoxication and sedation, inhibition errors and impaired inhibition efficiency. Severity of psychotic symptoms was directly correlated with inhibition error frequency and inversely with inhibition efficiency under the influence of delta-9-THC. Delta-9-THC attenuated left inferior frontal activation which was inversely correlated with the frequency of inhibition errors and severity of psychotic symptoms and positively with inhibition efficiency under its influence. These results provide experimental evidence that impairments in cognitive processes involved in the inhibitory control of thoughts and actions and inferior frontal function under the influence of cannabis may have a role in the emergence of transient psychotic symptoms under its influence.

1. Introduction

Use of cannabis, one of the most widely used illicit drugs worldwide (UNODC, 2011), is associated with impaired psychomotor control and impulsive behaviour resulting in road-traffic accidents and risky behavior. 'Response inhibition' i.e., inhibition of a pre-potent behavioural response constitutes one well-characterized component within the broader domain of impulsivity (Aichert et al., 2012; Roberts and Garavan, 2010). However, few studies have examined the acute effects of cannabis or its principal psychoactive ingredients on psychomotor control function under experimental conditions and the results have been inconsistent. Studies that have employed tasks requiring the withdrawal of a motor response that has already been triggered by a 'Go' signal (Costa et al., 2013; Rubia et al., 2001), such as the Stop task, have a higher load on response inhibition and predominantly engage motor inhibition processes and report acute impairments induced by delta-9-tetrahydrocannabinol (delta-9-THC) (McDonald et al., 2003; Ramaekers et al., 2006), the major psychoactive ingredient in cannabis. However, other studies that have employed tasks that engage more selective inhibition processes (Go/No-Go task) and have a higher load on response selection than on inhibition because of prior knowledge about whether to respond or not (Costa et al., 2013; Rubia et al., 2001), did not report any effects (Borgwardt et al., 2008; McDonald et al., 2003).

Cannabis and delta-9-THC also induce transient psychotic-like symptoms acutely (Bhattacharyya et al., 2012a, 2009) and regular cannabis use increases the risk of schizophrenia (Moore et al., 2007). Inhibitory control impairments are well recognized in schizophrenia (Kiehl et al., 2000). However, whether cannabis-induced impairment in inhibitory processing is related to the acute psychotomimetic effects of cannabis is unclear. We have previously reported that an acute dose of delta-9-THC modulates engagement of the inferior frontal gyrus during a response inhibition task (Borgwardt et al., 2008) consistent with the critical role played by the inferior frontal cortex in the inhibition of motor responses (Garavan et al., 1999; Rubia et al., 2001). The lateral prefrontal cortex has a high density of CB1 receptors (Elphick and Egertova, 2001) and studies in cannabis users have shown altered neural activity in this region during inhibitory processing (Eldreth et al., 2004; Gruber and Yurgelun-Todd, 2005; Tapert et al., 2007) and related motor control tasks (Weinstein et al., 2008). Altered inferior frontal activation during inhibitory processing (Kiehl et al., 2000) and other cognitive paradigms (Shergill et al., 2000) has also been reported in schizophrenia. However, whether the acute induction of transient psychotic-like symptoms under the influence of cannabis is related to impairments in inhibitory processing and altered function of its neural substrate under the influence of its major psychoactive ingredient, delta-9-THC, has not been investigated before. Here, we investigated this using a combination of pharmacological challenge with delta-9-THC and functional magnetic resonance imaging (fMRI) while performing an inhibitory processing paradigm inside the MRI scanner in the largest such sample studied to date of healthy volunteers with minimal previous exposure to cannabis.

2. Experimental procedures

In this study, we wanted to specifically test the hypotheses that oral administration of delta-9-THC would impair the inhibition of pre-potent motor responses and engagement of the inferior frontal cortex during a response inhibition task and that these effects would be related to the severity of psychotic symptoms induced by it.

Employing an established, repeated-measures, placebo-controlled, double-blind, within-subject design with counterbalanced order of drug administration (Bhattacharyya et al., 2012a, 2012c, 2009; Borgwardt et al., 2008), that we have employed before, we examined 36 right-handed, English-speaking, healthy males [mean age of 25.97±5.58 years and NART (Nelson, 1982) IQ of 97.7±6], without a personal or family history of psychiatric illness in first-degree relatives. Illicit substance use including cannabis use was assessed using the Addiction severity index and abuse was defined as "moderate use of small quantities regularly or large amounts occasionally" (McLellan et al., 1980). All participants had used cannabis at least once but less than 25 times in their lifetime and had minimal use of alcohol or other illicit drugs (Table 1). None of them used more than 21 units/week of alcohol or other illicit drugs on a regular basis. They had not used cannabis or other illicit drugs for at least a month before entering the study and were asked to abstain from all recreational drugs for the duration of the study. Ethical approval and written informed consent was obtained and the study was conducted in accordance with the Declaration of Helsinki.

We employed a double-blind, crossover design to compare the effects of orally administered 10 mg of THC (approximately 99.6% pure, THC-Pharm, Frankfurt, Germany) with matched placebo capsules. This dose of delta-9-THC was chosen as it is