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Modulation of acute effects of delta-9-tetrahydrocannabinol on psychotomimetic effects, cognition and brain function by previous cannabis exposure

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Abstract
Cannabis use has been associated with psychosis and cognitive dysfunction. Some evidence suggests that the acute behavioral and neurocognitive effects of the main active ingredient in cannabis, (−)-trans-Δ9-tetrahydrocannabinol (Δ9-THC), might be modulated by previous cannabis exposure. However, this has not been investigated either using a control group of non-users, or following abstinence in modest cannabis users, who represent the majority of recreational users. Twenty-four healthy men participated in a double-blind, randomized, placebo-controlled, repeated-measures, within-subject, Δ9-THC challenge study. Compared to non-users (N=12; <5 lifetime cannabis joints smoked), abstinent modest cannabis users (N=12; 24.5±9 lifetime cannabis joints smoked) showed worse performance and stronger right hemispheric activation during cognitive processing, independent of the acute challenge (all $P \leq 0.047$). Acute Δ9-THC administration produced transient anxiety and psychotomimetic symptoms (all $P \leq 0.02$), the latter being greater in non-users compared to users (P=0.040). Non-users under placebo (control group) activated specific brain areas to perform the tasks, while deactivating others. An opposite pattern was found under acute (Δ9-THC challenge in non-users) as well as residual (cannabis users under placebo) effect of Δ9-THC. Under Δ9-THC, cannabis users showed brain activity patterns intermediate between those in non-users under placebo (control group), and non-users under Δ9-THC (acute effect) and cannabis users under placebo (residual effect). In non-users, the more severe the Δ9-THC-induced psychotomimetic symptoms and cognitive impairments, the more pronounced was the

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neurophysiological alteration (all $P \leq 0.036$). Previous modest cannabis use blunts the acute behavioral and neurophysiological effects of Δ9-THC, which are more marked in people who have never used cannabis.
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1. Introduction

Cannabis is widely used, with approximately 200 million users worldwide (National Academies of Sciences and Medicine, 2017). Both cannabis (Henquet et al., 2005; Skinner et al., 2011; van Gastel et al., 2012; Colizzi and Murray, 2018) and its key psychoactive ingredient delta-9-tetrahydrocannabinol (Δ9-THC) (Bhattacharyya et al., 2012a; Bhattacharyya et al., 2009; D'Souza et al., 2004) can induce psychotic symptoms and trigger the onset of psychosis in vulnerable individuals (Colizzi et al., 2015a; Colizzi et al., 2015b; Moore et al., 2007; Morrison et al., 2015). Moreover, cannabis use can exacerbate psychotic symptoms (Ouellet-Plamondon et al., 2017; Schoeler et al., 2016a; Seddon et al., 2016), increase risk of non-remission (Colizzi et al., 2016a) and cause relapse (Patel et al., 2016; Schoeler et al., 2016b) in patients with established psychosis in a dose-dependent manner (Schoeler et al., 2016c).

Cannabis use has also been associated with cognitive impairments in similar domains to those where impairments are seen in patients with schizophrenia, such as memory and attention (Ganzer et al., 2016; Solowij and Michie, 2007). However, there is inconsistency with regard to the precise nature and extent of the effects of cannabis on human cognition (Bolla et al., 2002; Jockers-Scherubl et al., 2007; Pope et al., 2001; Solowij et al., 2002; Colizzi and Bhattacharyya, 2017). Long-lasting detrimental effects of cannabis use on cognition are still debated and appear to be more prominent on specific cognitive domains, such as verbal and visual memory, as suggested by meta-analytic evidence (Grant et al., 2003; Schoeler et al., 2016d). Results from experimental studies investigating the acute neurocognitive effects of Δ9-THC are more consistent and suggest that Δ9-THC administration in healthy volunteers acutely impairs several cognitive domains, including verbal (Curran et al., 2002; D'Souza et al., 2004; Ranganathan and D'Souza, 2006) and working memory (D'Souza et al., 2004; Ranganathan and D'Souza, 2006) and inhibitory control (McDonald et al., 2003; Ramaekers et al., 2009; Ramaekers et al., 2006; Weinstein et al., 2008a) processing. Additional evidence from neuroimaging studies suggests that acute Δ9-THC administration disrupts the neurophysiological underpinnings of a variety of cognitive processes that are also impaired in patients with psychosis, including verbal memory (Bhattacharyya et al., 2012a; Bhattacharyya et al., 2009), inhibitory control processing (Bhattacharyya et al., 2015a; Hester et al., 2009; Weinstein et al., 2008b), emotional processing and attentive salience (Bhattacharyya et al., 2012b; Bhattacharyya et al., 2015b; Bhattacharyya et al., 2010), and visual and auditory processing (Bhattacharyya et al., 2010; Winton-Brown et al., 2011).

Previous cannabis exposure has been associated with less marked effects of acute Δ9-THC administration on cognitive functioning (memory) as well as behavioral measures (observed and experienced psychiatric symptoms) and electrophysiological (gamma (γ)-band oscillations and P300 wave), neurochemical ((brain-derived neurotrophic factor (BDNF)), and neuroendocrine markers (cortisol) (Cortes-Briones et al., 2015; D'Souza et al., 2008a; D'Souza et al., 2008b; D'Souza et al., 2012; Ramaekers et al., 2009; Ranganathan et al., 2009; Schoeler and Bhattacharyya, 2013). While this may suggest a development of tolerance to the effects of Δ9-THC in cannabis users (Gonzalez et al., 2005; Hirvonen et al., 2012; Jones et al., 1981), the interpretation of these findings is challenging in light of methodological heterogeneity between the studies in terms of pattern of cannabis use and abstinence period prior to assessment. Some studies conducted exploratory analyses of the association between recent exposure to cannabis (in 30 days before study participation) and electrophysiological measures within a single group of subjects with a wide variation in the extent of previous cannabis exposure in terms of lifetime use (from <5 to >1000 times lifetime), frequency of use during periods of heaviest use (from ≤ 1 per year to daily), and in recent times (from 0 to 29 days in the last month) (Cortes-Briones et al., 2015; D'Souza et al., 2012). On the other hand, a study that compared 2 separate groups did not include a control group of non-users, comparing heavy (on average, 340 occasions in the last year and 6.2 years of history of exposure) and occasional cannabis users (on average, 55 occasions in the last year and 7.4 years of history of exposure) with no abstinent period prior to assessment (Ramaekers et al., 2009). Other studies compared frequent users ($\geq$ 100 times lifetime) with a history of sustained and/ or daily use and with no or modest ($\geq$ 72 h to $<$ 1 month) abstinence period prior to assessment, and controls with a wide range of previous cannabis exposure in terms of frequency ($<$ 5 to $>$ 100 times lifetime) and either a relatively short ($<$ 1 month) or a heterogeneous abstinence period ($>$ 1week and $<$ 10 years) (D'Souza et al., 2008a; D'Souza et al., 2008b; Ranganathan et al., 2009). Hence, whether modest previous exposure to cannabis, that reflects the typical pattern of use of the majority of recreational cannabis users (National Academies of Sciences and Medicine, 2017), affect the acute cognitive and psychotomimetic effects of its key psychoactive ingredient (Δ9-THC) as well as the neurophysiological effects that may underlie these behavioural effects, remains unclear.

We sought to address this issue by systematically investigating how the acute behavioural and neurophysiological effects (as indexed using functional magnetic resonance imaging; fMRI) of Δ9-THC differ between non-users and abstinent cannabis users with modest previous cannabis exposure who have a negative result on urine drug screen.

Employing a placebo-controlled acute pharmacological challenge design in conjunction with fMRI, we examined the following hypotheses: 1) modest cannabis use would be

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