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Compared to high and low cannabis use, moderate use is associated with fewer cognitive deficits in psychosis

Ashley M. Schnakenberg Martin [a,b], Kelsey A. Bonfils [b,c], Beshaun J. Davis [b,c], Elizabeth A. Smith [b,d], Kelly Schuder [b,d], Paul H. Lysaker [b,e,*]

[a] Department of Psychological and Brain Sciences, Indiana University-Bloomington, 1101 E 10th Street, Bloomington, IN 47405, USA
[b] Roudebush VA Medical Center, Day Hospital 116H, 1481 West 10th Street, Indianapolis, IN 46202, USA
[c] Department of Psychology, Indiana University–Purdue University, 402 N. Blackford Street, Indianapolis, IN 46202, USA
[d] Department of Psychology, Indiana State University, B-207 Root Hall, 200 North Seventh Street, Terre Haute, IN 47809, USA
[e] Department of Psychiatry, Indiana University School of Medicine, 355 W. 16th St., Suite 4800, Indianapolis, IN 46202, USA

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ABSTRACT

Literature on the relationship of cannabis use and cognition in schizophrenia provides the paradoxical view that cannabis use is sometimes linked with less severe impairment in neurocognition. This paper explored the possibility that this is a reflection of a dose related response between lifetime cannabis use and two forms of cognition, neurocognition and metacognition, in schizophrenia. It was hypothesized that three groups of patients could be differentiated, those with (1) little to no cannabis use with poor levels of cognition, (2) moderate cannabis use and relatively better levels of cognition and (3) high cannabis use with relatively poorer levels of cognition. Sixty-six adults with schizophrenia completed assessments of neurocognition, metacognition and months of lifetime cannabis use. A k-means cluster analysis yielded three distinct groups based on these assessments. The clusters included: (1) low cannabis/poor cognition ($n = 34$); (2) heavy cannabis/moderately impaired cognition ($n = 10$); and (3) moderate cannabis/higher cognition ($n = 22$). Consistent with our hypothesis, participants with high and moderate lifetime cannabis use had lesser impairment of neurocognition and metacognition compared to low lifetime cannabis use. Participants with moderate lifetime cannabis use also had lesser impairment of metacognition compared to low and heavy use. These findings suggest that a dose related relationship exists between cannabis use and cognition. Results could be due to an influence of pre-existing cognitive level on likelihood of lifetime cannabis use, or to an interaction between use and cognitive function.

1. Introduction

Cannabis use is a common comorbidity with schizophrenia (Kavanagh et al., 2002; Nesvåg et al., 2015), with approximately 64.4% of individuals with schizophrenia reporting lifetime use (Barnes et al., 2006) and 16% and 27% meeting the criteria for current and lifetime cannabis use disorder (Koskinen et al., 2010). Cannabis use has been associated with an earlier onset of schizophrenia (Galvez-Buccollini et al., 2012; Veen et al., 2004). Further, individuals who continue to use cannabis after their first episode of psychosis have a worse prognosis, with increased relapse and hospitalizations (Alvarez-Jimenez et al., 2012), even when controlling for other substances (Foti et al., 2010). Additionally, acute intoxication from Δ-9-tetrahydrocannabinol (Δ-9-THC), the psychoactive component in cannabis, has been shown to exacerbate psychotic symptoms in schizophrenia (D'Souza et al., 2005).

While cannabis use may exacerbate symptoms of schizophrenia, its impact on neurocognition, the most prominent form of cognition, is less clear. In particular, studies on the relationship of cannabis use and cognition in persons with schizophrenia present a paradox. On one hand, cannabis seems to negatively affect cognition in persons without schizophrenia. For example, acute, dose-related cognitive impairments have been observed in healthy individuals with cannabis (Pope et al., 1996; 2001; Bolla et al., 2002; Lundqvist, 2005; Solowij & Battisti, 2008; Crean, Crane & Mason, 2011), its psychoactive constituent Δ-9-THC (D'Souza et al., 2004; Ranganathan and D'souza 2006; Morrison et al., 2009), and synthetic cannabinoids (Gunderson et al., 2012). Additionally, cannabis use has been associated with long-term cognitive decline in healthy individuals (Fried et al., 2002; Meier et al., 2012). In schizophrenia, acute Δ-9-THC IV

* Corresponding author at: Roudebush VA Medical Center, Day Hospital 116H, 1481 West 10th Street, Indianapolis, IN 46202, USA.
E-mail address: plysaker@iupui.edu (P.H. Lysaker).

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administration has also shown intensified cognitive dysfunction, as indexed by greater cognitive impairment in learning and memory (D'Souza et al., 2005). Additionally, schizophrenia patients displayed greater sensitivity to these cognitive impairments from Δ-9-THC compared to healthy controls.

On the other hand, lifetime cannabis use has been associated with less severe neurocognitive impairment in schizophrenia (de la Serna et al., 2010; Hanna et al., 2016; Jockers-Scherübl et al., 2007; Schnell et al., 2009; Yücel et al., 2012). Specifically, these studies suggest that persistent cannabis use prior to the age of 17 years old and before the onset of psychotic symptoms is associated with elevated cognitive performance compared to non-cannabis using peers. However, other studies have failed to find an association between cannabis use and elevated cognitive performance (Cleghorn et al., 1991; Pencer and Addington, 2003).

One possible explanation for this paradox is that moderate cannabis use modulates a pathway to psychosis which is distinct from other pathways in that it does not affect neurocognition at the trait level. In other words, perhaps moderate cannabis use increases risk for psychosis without concurrent neurocognitive deficits and hence those individuals appear to be more neurocognitively intact. Alternatively, there may be other persons who are heavy cannabis users who develop cognitive deficits similar to the deficits found in heavy using healthy controls. This would suggest a model in which there are at least three groups of persons including those with little to no cannabis use with poor levels of cognition, moderate cannabis use and relatively better levels of cognition and high cannabis use with relatively poorer levels of cognition. Support for this model (Fig. 1) comes from three primary findings in the literature. Firstly, there appears to be a consistent dose-dependent relationship between lifetime cannabis exposure and the later development of psychosis (Andréasson et al., 1987; Gage et al., 2016; Henquet et al., 2005a; Van Os et al., 2002; Zammit et al., 2002). Secondly, the cannabinoid system has been implicated in the potential disruption of cognitive processes observed in schizophrenia (Volk and Lewis, 2016). Finally, recent evidence suggests that people with schizophrenia with lifetime cannabis use demonstrate less cognitive impairments, compared to non-using peers (de la Serna et al., 2010; Hanna et al., 2016; Jockers-Scherübl et al., 2007; Schnell et al., 2009; Yücel et al., 2012). Important to note, these pathways are in regard to lifetime cannabis use, while acute and residual cannabis use would be anticipated to have differential effects on cognition and potentially psychotomimetic effects.

To test this possibility the current study sought to determine whether cluster analyses would differentiate three groups of patients with schizophrenia on the basis of lifetime cannabis use and neurocognition. We also included another form of cognition, metacognition, in our cluster analysis. While the relationship between metacognition, cannabis use and schizophrenia has not been extensively studied, metacognition appears to be an intuitively important domain of cognition that has potential impact on one's ability to achieve recovery. As neurocognition directly refers more to raw ability to focus, remember and process information, metacognition encompasses the specific ability to think about one's self, others and the ability to use this knowledge. Originally used in the education literature to describe an individual's awareness of learning style, the term metacognition has since been expanded to refer to a spectrum of mental activities. Metacognitive acts range from discrete processes, such as thinking about a thought, to more synthetic acts that require thoughts, feelings, and intentions to be integrated into complex representations that later enable individuals to recognize and respond to life challenges (Lysaker et al., 2013; Semerari et al., 2003). While metacognition partially overlaps conceptually with neurocognition, one operational difference between the two is that more synthetic forms of metacognition are assessed by analyzing discourse and not by the accuracy of a response to a task. Decrements in metacognition have been broadly observed in schizophrenia and contribute to functional impairment and decreased quality of life, independent of neurocognition (Lysaker et al., 2014). Previous studies have linked different forms of substance use with phenomena related to metacognition such as alexithymia (Saladin et al., 2012) and the ability to use metacognitive knowledge to respond to challenges (Lysaker et al., 2014). Chronic cannabis users have shown altered neural networks when completing a theory of mind task, similar to those at risk for the development of psychosis (Roser et al., 2012). It has also been suggested that persistent cannabis use results in difficulty determining and discriminating facial emotions (Bayrakçı et al., 2015).

2. Methods

2.1. Participants

Sixty-six participants (females = 3) with a diagnosis of schizophrenia ($n = 43$) or schizoaffective disorder ($n = 23$), as confirmed by the Structured Clinical Interview for DSM-IV (SCID-I) (Spitzer et al., 1995), were recruited from the Psychiatry Service of a VA Medical Center in Indianapolis, Indiana for a larger investigation on the effects of cognitive remediation on work outcome. Demographic information can be found in Table 1. During their participation, participants were being prescribed antipsychotic medication, receiving outpatient care and were stable as evidenced by no recent (1 month) hospitalizations, or changes in housing or medication. Participants with intellectual disability, defined as a chart diagnosis of mild mental retardation, or current substance dependence (including cannabis dependence, but excluding tobacco) were excluded.

2.2. Clinical assessments

Neurocognition was indexed via the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery (MCCB), a commonly used index of cognition in schizophrenia (Nuechterlein et al., 2008). The MCCB assesses speed of processing, attention, working memory, verbal learning, visual

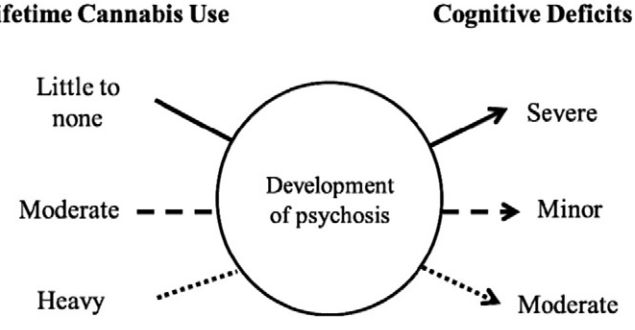

Fig. 1. Hypothetical paths to psychosis with lifetime cannabis use mediating cognitive impairment.