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Anxiety mediates the association between cannabis use and attenuated positive psychotic symptoms

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ABSTRACT

Cannabis use has been associated with a continuum of psychotic experiences. However, it is unclear whether mood and anxiety symptoms account for increases in attenuated positive psychotic symptoms (APPS) among cannabis users. We predicted that depression and anxiety symptoms would mediate the relation between cannabis use and APPS, and between cannabis use and endorsement of eight or more distressing APPS (D-APPS), a potentially more clinically meaningful group. Young adults ($n=674$) completed the Prodromal Questionnaire (PQ); Drug Use Frequency measure; Center for Epidemiologic Studies Depression Scale; State-Trait Anxiety Inventory, Trait Form, Anxiety Subscale; and Social Phobia Scale. Results indicated that symptoms of trait anxiety, but not symptoms of depression or social anxiety, mediated the relationship between cannabis use and APPS, as well as the relationship between cannabis use and D-APPS. Results indicate that symptoms of trait anxiety may play a role in the relation between cannabis use and APPS. Findings underscore the importance of considering clinical characteristics co-occurring with psychotic symptoms, such as affective symptoms, when examining the association between cannabis use and psychotic symptoms.

1. Introduction

Cannabis use has been repeatedly associated with the continuum of psychotic experiences, ranging from subthreshold psychotic symptoms in non-clinical samples, to clinical high risk for psychosis, and to clinical psychotic disorders (Linszen et al., 1994; Caspari, 1999; Corcoran et al., 2008; Kuepper et al., 2011). Subthreshold psychotic symptoms, which are common, yet brief, attenuated, or limited symptoms that are not in themselves clinically significant, and occur in the absence of current substance use, have been found to be more highly prevalent among cannabis users in the general population compared to non-users (Johns et al., 2004; van Os et al., 2009; Binbay et al., 2012; van Gastel et al., 2012; Ruiz-Veguilla et al., 2013). Similarly, there is a clear dose–response relationship between the frequency of cannabis consumption and increased risk for psychosis (Andreasson et al., 1987; van Os et al., 2002; Caspi et al., 2005; Moore et al., 2007; Matheson et al., 2011). Cumulatively, findings suggest that a history of cannabis use impacts the rate of subclinical psychotic experiences, as well as the severity and course of psychosis.

Despite these associations, it is unclear whether specific individual-level factors increase the likelihood of cannabis use among those with increases in attenuated positive psychotic symptoms (APPS). Studies have controlled for a number of variables, such as minor or previous psychotic symptoms (Arseneault et al., 2002), intelligence (Zammit et al., 2002), and use of psychostimulants (van Os et al., 2002) to examine the possibility of cannabis use as self-medication among psychotic populations. Although some clinical symptoms occurring during the prodromal or premorbid periods have been examined, a paucity of research has explored the role of depression and anxiety symptoms in the relationship between cannabis use and psychotic experiences. Depression and anxiety are key symptoms to examine because they (1) commonly occur prior to the onset of psychosis (Yung et al., 2004; Rosen et al., 2006; Myles-Worsley et al., 2007), (2) are associated with psychotic symptoms in the general population (Wigman et al., 2012), and (3) are associated with increases in cannabis use (Wittchen et al., 2007; Buckner et al., 2012). With regards to the latter, evidence suggests that social anxiety disorder may be a risk factor for cannabis dependence (Buckner et al., 2012) and that major depression predicts increased rates of cannabis use and dependence (Wittchen et al., 2007). Similarly, one study reported that social anxiety moderated the relationship of schizotypy symptoms and frequent cannabis use, and that depression

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and trait anxiety moderated the relationship between positive schizotypy traits and cannabis use frequency (Najolia et al., 2012). Therefore, it is possible that the association between cannabis use and psychotic symptoms may be related, at least in part, to premorbid and/or prodromal mood and anxiety symptoms. One study suggesting that heavy cannabis use is associated with the development of psychotic symptoms in a non-clinical sample controlled for diagnoses of anxiety and depression, rather than subthreshold anxiety/depressive symptoms (Fergusson et al., 2003). However, individuals experiencing APPS may not have yet developed a clinical disorder; therefore, mood and anxiety symptoms may be better represented using a dimensional approach (Wigman et al., 2012). Further, previous studies have not specifically examined mood and anxiety disorders as potential mediators of the relation between cannabis use and APPS.

The aim of the present study was to determine whether depression and anxiety symptoms mediate the relation between cannabis use and increases in APPS on a dimensional scale. APPS experienced by the general population may have relevance for individuals at risk for psychotic disorders (Kaymaz et al., 2012; van Os and Linscott, 2012). An extended psychosis phenotype, whereby APPS reported by non-help seeking individuals has been linked to risk for developing clinical psychosis, is supported by findings suggesting that subclinical and clinical psychosis share many of the same risk factors (van Os et al., 2009; van Os and Linscott, 2012), and that those endorsing APPS are at 3.5 times increased risk of developing a psychotic disorder (Kaymaz et al., 2012), demonstrating the utility of assessing psychotic experiences dimensionally. We predicted that frequent cannabis use would be associated with significant increases in APPS, and that symptoms of depression and anxiety would mediate the relationship between cannabis use and APPS. A secondary aim was to determine whether the aforementioned relationship existed when examining individuals who may be at higher clinical risk for psychosis compared to individuals at lower risk. We viewed these secondary analyses as exploratory as our clinical high risk measure has only been associated with clinical high risk for psychosis in clinical samples (Loewy et al., 2005). We predicted that symptoms of depression and anxiety would mediate the relationship between frequent cannabis use and higher clinical risk for psychosis.

2. Methods

2.1. Participants

The protocol was approved by the Institutional Review Board (IRB) at Temple University. Written informed consent was obtained from participants and a Certificate of Confidentiality was obtained from the National Institutes of Health (NIH) to protect identifiable research information from forced disclosure. Participants were 674 undergraduate students recruited via an online subject recruitment website. All participants received course credit for their participation and were at least 17 years of age; however, our sample only includes one 17-year-old subject due to mid-study IRB changes that now restrict subject recruitment to 18 and older.

2.2. Measure and procedures

All participants completed a set of questionnaires at computer stations in the laboratory. The Prodromal Questionnaire (PQ; Loewy et al., 2005, 2007) was administrated, which is a 92-item questionnaire that measures subthreshold psychotic symptoms experienced in the past month in the absence of substance or medication use and has been validated against semi-structured interviews that assess emerging and frank psychosis, such as the Structured Interview for Prodromal Symptoms (SIPS; Miller et al., 2002; Kline et al., 2012). Each item endorsed was rated as either distressing or not distressing by the participant. The present study used the positive symptoms subscale scores and summed the presence or absence of endorsed symptoms (45 items total). The two dependent variables were (1) total number of positive symptoms endorsed (APPS) and (2) endorsement of eight or more distressing APPS (D-APPS) compared to three or fewer distressing APPS (the mean of APPS distressing symptoms in our sample), a dichotomous variable. Endorsing eight or more D-APPS has achieved 90% sensitivity and 49% specificity in correctly classifying clinical high risk for psychosis cases identified using the SIPS in clinical samples (Loewy et al., 2005), and 2% of an undergraduate sample met this criterion (corresponding to approximate rates of those at risk for psychosis in the general population) (Loewy et al., 2007, 2012). We chose this cutoff value in order to maximize sensitivity and to reduce our chance of type II error, at the possible cost of type I error. The use of two dependent variables for psychosis, one of which is exploratory (i.e., D-APPS), allowed us to determine whether our mediation hypothesis applied to only the continuum of APPS in the general population, or was relevant to potentially more clinically-relevant symptoms.

The frequency of substance use was measured using the Drug Use Frequency measure (DUF; O'Farrell et al., 2003). The DUF has established concurrent validity with the well-validated Timeline Followback measure (Sobell and Sobell, 1996) and with collateral informants (O'Farrell et al., 2003). The questionnaire assessed use of various substances, but for the present study only cannabis use and amphetamine use within the past 3 months were analyzed, as use of other substances linked to psychosis were not specifically asked about (e.g. cocaine) and opiate use occurred at too low of a frequency in our sample. Substance use was measured on a Likert-type scale that included values of (1) never, (2) once or twice, (3) several times a month, (4) several times a week, and (5) daily. The frequency of cannabis use was dichotomized for analyses: "low use" (never, once or twice, or several times a month) and "high use" (several times a week or daily). Dichotomization was based on comparisons of each of the cannabis frequency groups on APPS score. The three low frequency use categories were each significantly different from the two higher frequency use categories when compared on APPS (data available upon request). Further, the two higher frequency use categories were not significantly different from each other on APPS (data available upon request). In addition, amphetamines, which act as dopamine agonists, may induce acute paranoid psychosis (Bell, 1973), and as individuals who frequently use cannabis are more likely to use other drugs, such as amphetamines, amphetamines have been hypothesized to explain the association between cannabis use and schizophrenia (Hall and Degenhardt, 2000). Therefore, amphetamine use was included as a covariate and was recoded into two categories: "never" and "any use."

Symptoms of depression were evaluated with the brief version of the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977; Kohout et al., 1993), which ascertained the presence and severity of depressive symptoms that occurred over the past week. The CES-D is reliable across samples (Radloff, 1977; Roberts, 1980, 1989) and has demonstrated concurrent and construct validity (Radloff, 1977). The range of scores is 0–30 and scores equal to or greater than 10 are thought to represent significant depressive symptomatology (Andresen et al., 1994). The State-Trait Anxiety Inventory, Trait Form, Anxiety Subscale (STAI; Spielberger et al., 1983) assessed symptoms of generalized (trait) anxiety, using a version that contained only items that loaded highly on an anxiety factor and excluded items that loaded predominantly on a depression factor, so as to exclude overlapping symptoms and provide a purer measure of generalized anxiety (Bieling et al., 1998). The STAI-trait has good construct validity (Smeets et al., 1997), discriminant and convergent validity (Spielberger et al., 1983), and test-retest reliability (Rule and Traver, 1983). The seven items were scored on a scale that required participants to rate how frequently they experience a particular anxiety symptom. Potential scores range from 7 to 28, and individuals with a clinical diagnosis of an anxiety disorder typically score greater than or equal to 16 (Bieling et al., 1998). Finally, social anxiety symptoms were evaluated using the Social Phobia Scale (SPS; Mattick and Clarke, 1998). The SPS has established convergent and discriminant validity, and test-retest reliability (Mattick and Clarke, 1998). Scores on the SPS may range from 0 to 80, and scores equal to or greater than 24 indicate a potential diagnosis of social anxiety disorder (Heimberg et al., 1992). Responses on all questionnaires were summed and higher scores indicated greater symptom severity.

2.3. Statistical analyses

Normality of the main dependent variable, APPS, was explored by examination of kurtosis and skewness values, as well as visual inspection of the distribution. Age and sex were explored as potential covariates by determining whether they were related to the main dependent variables.

Statistical analyses addressed the following predictions:

1. APPS scores will be positively correlated with scores on the CES-D, STAI, and SPS, as tested via Pearson correlations.
2. Individuals using cannabis at a higher frequency will demonstrate higher scores on the CES-D, STAI, and SPS, compared to individuals with a lower frequency of cannabis use, as tested via Analyses of Variance (ANOVAs).
3. Individuals using cannabis at a higher frequency will endorse a greater number of APPS compared to individuals with a lower frequency of cannabis use, as tested via ANOVA.
4. CES-D, STAI, and SPS scores will mediate the relationship between frequent cannabis use and increases in APPS, tested via bootstrapping analyses of indirect effects. Bootstrapping analyses of indirect effects were used to test

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