Psychiatry Research 218 (2014) 180–186

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

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

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ARTICLE INFO

Article history:
Received 16 September 2013
Received in revised form
11 February 2014
Accepted 29 March 2014
Available online 5 April 2014

Keywords:
Attenuated psychotic symptoms
Psychosis
Anxiety
Clinical high risk
Prodromal

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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http://dx.doi.org/10.1016/j.psychres.2014.03.040
0165-1781/

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

whether any of the potential mediators that were supported in tests of Predictions 1 and 2 mediated the relation between cannabis use and APPS, as this technique has been deemed the most valid approach to mediation analyses (Hayes, 2012). Significance of mediation was determined by examination of the 95% bias-corrected bootstrap confidence interval (CI). There are no *p*-values associated with this method, and significant mediation was declared if the CI did not include zero. Preacher and Hayes SPSS indirect bootstrapping macro for mediation was used, which has been considered the most appropriate test for mediation with a single mediator (Preacher and Hayes, 2008).

5. In exploratory analyses, the same relations will hold for those meeting the aforementioned D-APPS criteria compared to those endorsing a low frequency of distressing symptoms: anxiety and depressive symptoms will mediate the relation between cannabis use and D-APPS status. Analyses for Predictions 1–4 were repeated with the dependent variable D-APPS, logistic regression was conducted to determine if cannabis use was associated with increased likelihood of meeting D-APPS status, and ANOVAs were used in place of Pearson correlations. Similarly, bootstrapping analyses of indirect effects were conducted to determine if any of the potential mediators that were supported in tests of Predictions 1 and 2 mediated the relation between cannabis use and D-APPS.

For descriptive purposes (to examine the magnitude of coefficient change), multiple regressions (APPS as dependent variable) and logistic regressions (D-APPS as dependent variable) were conducted with and without potential mediators/covariates (see Table 3). All tests were two-tailed and considered significant if $p < 0.05$.

3. Results

3.1. Sample characteristics

See Table 1 for demographic data and mean scores for all self-report scales. Five participants were removed from analyses given that their ages were greater than three standard deviations above the mean age (i.e., greater than 38 years old; age range 38–53 years) and were past the typical age of onset for schizophrenia (age range 17–35 years; American Psychological Association, 2000). The APPS variable was not normally distributed (skewness = 1.3, kurtosis = 1.4) and was log transformed, and subsequently normally distributed, for all analyses. As Table 2 indicates, there were no differences in D-APPS status by gender or age and APPS was not related to gender ($p = 0.692$) or age ($p = 0.528$).

Table 1
Demographic characteristics of the sample.

	Overall sample ($n = 674$)
Demographics	
Male, *n* (%)	195 (28.9)
Age (years), mean (S.D.) [range]	20.5 (2.3) [17–35]
Race, *n* (%)	
Non-hispanic white	393 (58.31)
African–American	84 (12.50)
Asian/Pacific Islander	96 (14.24)
Hispanic/Latino	27 (4.01)
Biracial/Multiracial	34 (5.04)
Other	40 (5.90)
Receiving or seeking treatment, *n* (%)	85 (12.6)
CES-D score, mean (S.D.) [range]	7.5 (5.0) [0–26]
STAI score, mean (S.D.) [range]	11.8 (4.4) [7–28]
SPS score, mean (S.D.) [range]	13.2 (12.5) [0–70]
Amphetamine use, *n* (%)	59 (8.8)
Cannabis use frequency, *n* (%)	
Never used	416 (61.7)
Once or twice	100 (14.8)
Several times per month	72 (10.7)
Several times per week	35 (5.2)
Daily	51 (7.6)
PQ score, mean (S.D.) [range]	
Total APPS endorsed	8.8 (7.4) [0–37]
High D-APPS[a]	13.0 (4.6) [8–27]
Low D-APPS[b]	0.9 (1.1) [0–3]

[a] Endorsement of eight or more distressing attenuated positive symptoms ($n = 88$).
[b] Endorsement of three or fewer distressing attenuated positive symptoms ($n = 466$).

3.2. Attenuated positive psychotic symptoms, cannabis use, mood and anxiety scores

Scores on APPS endorsed and APPS endorsed as distressing by cannabis use frequency are shown in Fig. 1 for descriptive purposes. The Spearman's rho revealed a statistically significant relationship between cannabis use and APPS ($rs = 0.23$, $p < 0.0001$) and APPS ($rs = 0.15$, $p < 0.0001$) endorsed as distressing. Similarly, the number of APPS endorsed was significantly positively associated with symptoms of depression ($r = 0.50$, $p < 0.0001$), social anxiety ($r = 0.44$, $p < 0.0001$), and trait anxiety ($r = 0.53$, $p < 0.0001$). Table 2 indicates differences between low and high cannabis users on self-reported mood and anxiety symptoms and APPS. There were no differences on CES-D and SPS scores between low and high cannabis users, but high cannabis users had significantly higher STAI scores compared to low cannabis users. There also were significantly higher APPS scores among higher cannabis users compared to low cannabis users (see Table 2).

3.3. Mediation analyses: APPS

Only STAI scores were examined as a potential mediator as it was the only anxiety/mood scale that differed between high and low cannabis users. Bootstrapping analyses for indirect effects indicated that STAI scores mediated the relationship between cannabis use frequency and number of APPS endorsed, as indicated by the CI not including zero (Bias Corrected CI: 0.0070–0.0917). Further, these results held after adding amphetamine use to models. The decrease in the magnitude of cannabis use on APPS after adding STAI into the model is shown in Table 3.

3.4. Exploratory analyses: D-APPS

Similarly, the independent, dependent and potential mediator (STAI) variables were significantly associated with one another, permitting performance of mediation analyses. As Table 2 indicates, individuals in the D-APPS group endorsed significantly more symptoms of depression, social anxiety, and trait anxiety compared to the low D-APPS group. Logistic regression indicated that higher cannabis use was associated with increased odds of being classified as D-APPS (see Table 3). Bootstrapping analyses for indirect effects suggested that STAI scores mediated the relationship between cannabis use frequency and D-APPS, indicated by the CI not including zero (Bias Corrected CI: 0.0347–0.8817), which was consistent when amphetamine use was added into the model. This relation also was seen descriptively in logistic regression models, in which cannabis use was associated with significantly increased odds of D-APPS, which became non-significant after adding STAI to the models with and without adjusting for amphetamine use (see Table 3). All mediation relationships between STAI, cannabis use, and D-APPS remained when amphetamine use was added into the model.

4. Discussion

To the best of our knowledge, this is the first study to directly examine whether mood and anxiety symptoms account for the increased prevalence of cannabis use among individuals who endorse APPS. The results of the present analyses indicate that the relationship between cannabis use and subthreshold psychotic

Table 2
Demographics, questionnaire scores, and cannabis use by risk for psychosis; questionnaire scores by cannabis frequency.

	Low D-APPS ($n=466$[a])	High D-APPS ($n=88$[a])	F	d.f.	p-Value
Demographics					
Male, n (%)	141 (30.3)	21 (23.9)			0.227
Age (years), mean (S.D.)	20.5 (2.4)	20.5 (2.4)			0.993
Receiving or seeking treatment, n (%)	41 (8.8)	26 (29.5)			
CES-D score, mean (S.D.)	6.0 (4.0)	13.2 (5.7)	207.99	553	< **0.0001**
STAI score, mean (S.D.)	10.5 (3.5)	17.0 (4.7)	232.16	553	< **0.0001**
SPS score, mean (S.D.)	10.2 (10.4)	26.8 (15.3)	158.27	553	< **0.0001**
Cannabis use frequency					
Low use or never, n (%)	418 (89.7)	70 (79.5)			**0.007**
High use, n (%)	48 (10.3)	18 (20.5)			
	Low frequency of cannabis use ($n=588$)	High frequency of cannabis use ($n=86$)			
CES-D score, mean (S.D.)	7.4 (4.9)	8.3 (5.2)	2.30	673	0.130
STAI score, mean (S.D.)	11.7 (4.4)	12.8 (4.6)	5.20	673	**0.023**
SPS score, mean (S.D.)	13.1 (12.5)	14.0 (12.6)	0.37	673	0.541
APPS score[b], mean (S.D.)	8.1 (7.1)	13.3 (7.8)	39.36	673	< **0.001**

[a] Exploratory analyses that dichotomized risk status were conducted on a sample size of 554.
[b] APPS mean and S.D. based on non-transformed variable, F, d.f., and p-value based on log-transformed variable prior to controlling for amphetamine use.

Table 3
Unadjusted and adjusted regression and logistic regression models examining the relation between cannabis use and APPS/D-APPS.

	APPS (log transformed)					D-APPS status			
	β[a]	B[a]	Lower CI[b]	Upper CI[b]	p Value	OR	Lower CI	Upper CI	p Value
Unadjusted models									
Step 1									
Cannabis	0.238	0.262	0.220	0.304	< 0.001	2.239	1.231	4.071	0.008
Step 2									
Cannabis	0.199	0.220	0.183	0.257	< 0.001	1.899	0.903	3.990	0.091
STAI	0.487	0.041	0.038	0.044	< 0.001	1.390	1.302	1.482	< 0.001
Adjusted models									
Step 1									
Cannabis	0.222	0.245	0.201	0.289	< 0.001	1.849	0.970	3.521	0.042
Amphetamine	0.057	0.075	0.023	0.127	0.151	1.898	0.921	3.913	0.082
Step 2									
Cannabis	0.196	0.216	0.178	0.254	< 0.001	1.774	0.783	4.016	0.169
STAI	0.486	0.041	0.038	0.044	< 0.001	1.388	1.301	1.481	< 0.001
Amphetamine	0.013	0.017	−0.028	0.062	0.715	1.220	0.473	3.145	0.681

Bootstrapping results suggested significant mediation for both models of APPS and D-APPS status.
[a] β (standardized coefficients) and B (unstandardized coefficients) reflect the coefficients for regressions with the log transformed APPS variable as the dependent variable.
[b] Confidence Intervals (CIs) for the unstandardized (B) coefficients.

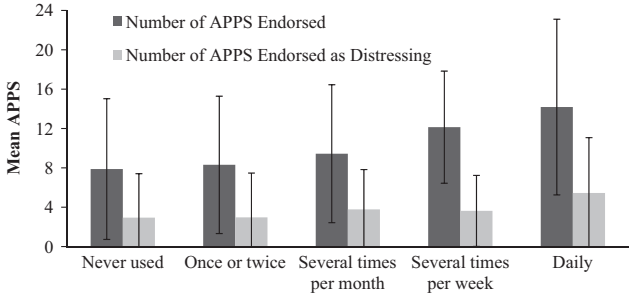

Fig. 1. Attenuated positive psychotic symptoms by cannabis use. Mean APPS and mean APPS distressing items by cannabis use frequency, ranging from never used to daily use. Error bars represent the standard deviation. APPS scores, for both APPS and D-APPS, increase as frequency of cannabis consumption increases.

symptoms is mediated by trait anxiety symptoms. Further, our exploratory analyses suggest that trait anxiety symptoms mediate the relationship between cannabis use and higher risk of psychosis, as measured by endorsement of D-APPS, a potentially more clinically relevant construct. While the current results echo those measuring schizotypy symptoms in an undergraduate sample, in which trait anxiety moderated the relationship between cannabis use frequency and positive schizotypy traits, the present study did not find a role of social anxiety and depression in this relationship, as with previous schizotypy findings (Najolia et al., 2012). The current findings point to the importance of considering trait anxiety symptoms in analyzing the association between cannabis use and psychosis. Additional research is warranted to determine whether these findings extend to clinical high risk, prodromal, and other non-clinical samples.

There are multiple potential explanations for our findings. First, it is plausible that increases in cannabis use in those who experience APPS may be a form of self-medication for anxiety. Indeed, self-medication is prevalent in approximately 24% of individuals with mood disorders in the general population (Bolton et al., 2009), and self-medication for generalized anxiety disorder (GAD) may be more likely than for other anxiety disorders (Robinson et al., 2009). It has been theorized that individuals with GAD, compared to social phobia, may experience

anxiety-provoking situations with greater frequency, and are therefore more likely to utilize self-medication rather than avoidance (Robinson et al., 2009). This may partially explain the similar depressive and social anxiety symptoms, but not trait anxiety symptoms, between the cannabis frequency groups in the present study. However, the present study does not directly address the potential self-medicating role of cannabis, and the aforementioned study referred to self-medication with alcohol, not cannabis (Robinson et al., 2009). Further, some studies have found that cannabis use may not be a critical factor in the development of psychosis (Phillips et al., 2002; Yung et al., 2004; Auther et al., 2012), possibly suggesting that it is instead a behavioral response to the emergence of psychotic symptoms. Others have found that anxiety may be a stronger predictor of regular cannabis use and cannabis-related problems, even compared to depression and psychosis (Van Dam et al., 2012).

However, the self-medication hypothesis has been challenged by longitudinal evidence indicating that substance use precedes onset of positive psychotic symptoms (van Os et al., 2002). Also challenging the self-medication hypothesis is evidence that anxiety may not be predictive of cannabis use (Osuch et al., 2013), along with longitudinal studies suggesting no association between cannabis use and anxiety disorders (van Laar et al., 2007; Wolitzky-Taylor et al., 2012). However, subclinical symptoms of anxiety are infrequently considered in the relationship between psychosis and cannabis use, and this omission may have masked the relationships of interest. Regardless of the role of cannabis use in the manifestation of APPS, the present results highlight the importance of considering mood and anxiety symptoms when analyzing the relationship between cannabis and psychosis.

Another possibility, albeit not supported by the present correlational data, is that symptoms of trait anxiety may be a first indicator of progression towards psychosis following cannabis use. Support for this possibility comes from studies that have found increases in anxiety following cannabis use, as well as individual differences in severity of anxiety responses to cannabis, suggesting a potential genetic vulnerability that may overlap with vulnerability to psychosis (see Johns, 2001; Patton et al., 2002). In this case, cannabis use would still be considered a risk factor for psychosis, but it may also increase risk for trait anxiety symptoms, which may or may not emerge prior to or concurrently with APPS. Practically, determining whether one of these possibilities (or some other variation) is correct would be difficult and would be limited by ethical constraints, but this effort should be considered in future research, especially longitudinal studies of those at risk for psychosis.

The present results indicate the importance of considering affective and mood-related factors, particularly trait anxiety symptoms, in interpreting the relationship between cannabis use and psychotic symptoms (see Macleod et al., 2004). Other studies have utilized diagnostic rather than dimensional approaches to symptoms (Fergusson et al., 2003; Anglin et al., 2012), whereas those with increased APPS may have more diffuse anxiety and mood symptoms that are better represented by a dimensional approach (Wigman et al., 2012). Further, the present study was designed to examine anxiety and depression in a mediational role, in contrast to past studies that controlled for these symptoms to minimize variance.

Among the strengths of the current study was the use of a dimensional measure of APPS. Psychotic symptoms constitute a continuum of unusual thinking, delusions, and hallucinations, of which only the most debilitating or frequent are considered to be of diagnostic relevance (van Os et al., 2009). However, constraining the definition of psychotic symptoms to only those of diagnostic relevance could under-represent the contribution of these symptoms to the liability for psychotic disorders. In contrast, the systematic study of APPS in non-clinical samples could provide new insights into risk factors. Further, our sample included a substantial number of participants at an age when psychosis tends to emerge from a non-treatment seeking sample, which contrasts with many existing studies that utilize help-seeking individuals. Although it is possible that an undergraduate sample may reduce generalizability, the institution from which the participants were recruited is large (approximately 38,000 students) and the student body is drawn from diverse socioeconomic and demographic backgrounds, making the present sample likely to be generalizable to same-aged peers. Further, there are shared mechanisms between clinical and non-clinical psychosis, pointing to the importance of utilizing non-clinical populations in determining risk factors for psychosis (Kelleher and Cannon, 2011).

Despite these strengths, the limitations of this study include the exploratory nature of the analyses with the D-APPS variable. The D-APPS variable has not been validated in a non-clinical sample, and although the cut-off score of 8 or more distressing positive symptoms has been validated in clinical samples (Loewy et al., 2007), its ability to identify individuals at risk for psychosis in other populations is unclear. Our utilization of D-APPS indicated that 13% of our sample met this criterion, whereas it captured 2% of an undergraduate sample in Loewy et al. (2007). The discrepancy between rates may be explained by differences in the demographic characteristics of the two undergraduate samples, along with the likelihood that our rate includes a number of false positives. Individuals captured in the D-APPS category may represent those experiencing/at risk for other psychological disorders (i.e., anxiety disorders) who may still experience subthreshold psychotic-like symptoms but do not meet criteria for a psychotic disorder. Nevertheless, risk of conversion to a psychotic disorder after one year has been found to be 3.5 times higher in those who experience APPS in a general, non-help seeking population, indicating that our findings may have relevance to risk for psychotic disorders (Kaymaz et al., 2012). Further, the D-APPS group clearly was experiencing more clinically meaningful symptoms, as approximately 13% of the entire sample and 30% of the D-APPS sample either sought or received treatment in the past month (see Tables 1 and 2), providing support for the assertion that the D-APPS participants represent a more clinically meaningful group that may be at risk for a variety of mental disorders, including psychosis.

Our sample was approximately 70% females, and this may limit generalizability. Specifically, cannabis use disorders (CUD) are more prevalent in males, and women with CUD are more likely to receive mood and anxiety disorder diagnoses (Khan et al., 2013) and to have more severe positive psychotic symptoms (Thorup et al., 2007). Although there were no sex differences in cannabis use or APPS in the present study and males did constitute a significant portion of the sample, future studies should examine potential gender issues further. Future studies should also (1) utilize cannabis assessments that extend beyond use in the past 3 months, (2) examine use at various developmental periods in order to understand whether using cannabis confers a greater risk at certain neurodevelopmental periods, and (3) analyze cannabis use dimensionally. Other drugs that have been associated with psychotic symptoms, such as opiates and cocaine, were not examined in this study due to limitations with our measure and low frequency of opiate use in our sample (see Van Dam et al., 2008; Smith et al., 2009), but should be explored in future studies. Our measurement of amphetamines inquired about use of "uppers, speed," and is therefore ambiguous as to use of other stimulants, so future studies may benefit from additionally listing prescription psychostimulants as examples, especially given the widespread use of these medications.

Additional limitations include the self-report nature of the measures, which depends on the veracity of an individual's responses and may be liable to bias. However, the CES-D, SPS, and

STAI are widely used measures with established construct validity (Roberts, 1980; Mattick and Clarke, 1998; Bieling et al., 1998) and have been linked to various biological constructs (Furmark et al., 2002; Lang et al., 2005). Further, while some results find higher rates of cannabis use in same-aged peers who are not in college compared to college students (White et al., 2005), our rate of daily cannabis use in past three months (7.6%) corresponded to daily use in past month among individuals aged 12 or older according to a national survey (7.6%) (Substance Abuse and Mental Health Services Administration, 2013). Nevertheless, it would be useful for our results to be replicated in other college population samples (e.g. private institutions) and non-college populations. Additionally, the cross-sectional design of the study does not allow us to make conclusions regarding the causal nature of the relationships under investigation, and the mediation model may be more complicated or in a different direction than hypothesized. For example, cannabis use may mediate the relation between anxiety and APPS. Further, it is likely that anxiety does not completely explain the relation between cannabis use and APPS/D-APPS. Indeed, while the present results suggest significant mediation, cannabis use remained significantly associated with APPS (but not D-APPS) after adding trait anxiety symptoms to the model, even though the magnitude of this relation was significantly decreased. Thus, future studies should explore other potential mediators that may contribute to the cannabis-APPS relation. Nonetheless, this is the first study to demonstrate that the relationship between trait anxiety symptoms and APPS was stronger than the relationship between cannabis use and APPS, raising the possibility that the role of anxiety symptoms in this context is an important contributor to the APPS-psychosis association.

The results of this study indicate the importance of considering overall premorbid and prodromal functioning in assessing the relationship between cannabis use and APPS. Further, the study underscores the utility of employing a dimensional approach to psychosis, as complementary results were found when analyzing individuals with more clinically relevant symptoms (D-APPS). Our findings reflect those of other studies (Phillips et al., 2002; Yung et al., 2004; Auther et al., 2012), and this may indicate that the mechanisms underlying APPS also have relevance for clinical psychosis (Kelleher and Cannon, 2011). Additional research is necessary to determine whether the present findings are generalizable to prodromal samples and individuals at clinical high risk for psychosis. The present data indicate that symptoms of trait anxiety may play a role in the relationship between cannabis use and APPS, and may provide preliminary support for a potential target of future treatment studies. Also critical to note is that the relationship between genetic and/or neurocognitive vulnerability to the development of psychosis and the symptom-potentiating mechanisms of cannabis is highly complex and not well understood. Overall, our study provides preliminary evidence for the importance of considering trait anxiety symptoms when examining associations between cannabis use and psychosis, which may have implications for future studies that explore how cannabis use operates in the neurodevelopmental course of psychosis.

Conflict of interest

All authors declare that they have no conflicts of interest.

Acknowledgments

The study was supported by College of Liberal Arts Research Award, Temple University, Philadelphia, PA (L. Ellman), and a start up grant awarded to L. Ellman.

The authors thank Heather Mayer and Rebecca Wolfe for their assistance with data collection.

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