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Patterns in adolescent cannabis use predict the onset and symptom structure of schizophrenia-spectrum disorder

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ABSTRACT

This study investigated adolescent cannabis use as a risk factor for schizophrenia spectrum disorder (SSD). Motives for early cannabis use and resulting usage patterns were examined alongside clinical measures of SSD onset and symptomatology.

Participants (N = 178) were recruited for two samples, 1: healthy controls (HC) with cannabis use, 2: schizophrenia patients (SSD) with cannabis use. Structured interviews of participants and family informants were used to obtain diagnostic and biographical information.

Factor-analysis of reported motives for initiating cannabis use produced four groups; sedation, stimulation, social pressure, and recreation. Regression analyses revealed significant relationships between these groups and SSD. Most notably, reason group factor scores predict SSD risk as well as schizotypal symptom severity. Findings also indicate that these factors follow a hierarchical structure, which explains their relative involvement in increased SSD risk.

We suggest that adolescent cannabis use both hastens the onset and amplifies the severity of SSD. In response we propose a model for identifying at risk individuals, predicting the onset and severity of SSD, and potentially mitigating the associated psychiatric impairments.

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1. Introduction

1.1. Background

Cannabis is one of the most widely used illicit substances globally (UNODC, 2017), and among psychotic individuals (Kavanagh et al., 2004). A meta-analysis of 35 studies found that adults with schizophrenia had a lifetime prevalence of a cannabis use disorder of 27.1% in contrast to 8% of the general population (Koskinen et al., 2010). These high rates of consumption are especially concerning among adolescents and young adults at prodromal or early stages of a psychosis given the number of potential influences cannabis has on the development and severity of psychiatric illness. Recent literature has not only found that the prevalence of psychosis and schizotypal personality disorder increased with greater cannabis use (Davis et al., 2013), but also that cannabis misuse leads to higher relapse rates (Malla et al., 2008), more frequent psychiatric hospitalization and suicide (Sayers et al., 2005), increased rates of housing instability and homelessness (Tsuang and Fong, 2004), more frequent instances of violent behavior (Hodgins and Klein, 2017) and more frequent and severe medical problems (Jones et al., 2004; (Dixon, 1999) including HIV, hepatitis B/C, obesity and obesity related cancer, and tardive dyskinesia (Leucht et al., 2007; (Miller et al., 2005).

Several studies have suggested that cannabis is a risk factor for schizophrenia spectrum disorder (SSD; reviewed in Volkow et al., 2016). It is widely held that adolescent cannabis usage is associated with an earlier onset of psychotic symptoms (Galvez-Buccollioni et al., 2012) and a worsened prognosis thereafter (Manrique-Garcia et al., 2014). Although the mechanism(s) for this interaction are not fully understood (van Winkel and Kuepper, 2014) they appear predominantly in individuals with an elevated family risk of SSD (Proal et al., 2014; Henquet et al., 2005).

Despite the evidence for a causal relationship between cannabis use and SSD, little has been done to model the heterogeneity of cannabis usage behaviors. Just as not all SSD patients have similar clinical presentations, not all cannabis users adhere to similar patterns of drug consumption. This variance, we suggest, contains information that signals and predicts several features of SSD prior to the emergence of

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identifiable symptoms. Accordingly, we aim to generate a model for better understanding the relationship between adolescent cannabis use and SSD risk and morbidity.

1.2. Hypotheses

We propose a model to categorize the heterogeneity of motives behind first cannabis use during adolescence using factor analysis [Hypothesis I]. We test whether such model can predict features of cannabis consumption behaviors and SSD symptomatology [Hypothesis II]. We additionally suggest that these motives follow a predictable, hierarchical structure in their contribution to SSD severity as measured by The Structured Interview for Schizotypy [Hypothesis III].

2. Methods

2.1. Sample

Subjects were between the ages of 18 and 40, and were recruited from New York City and the metropolitan Boston area. Criteria for SSD patient eligibility included a current diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder, or psychosis not otherwise specified (see Proal et al., 2014 for details of methods). This study was approved by the institutional review boards (IRBs) for each medical center where patients originated and subjects were recruited.

Subjects reporting a lifetime use of recreational drugs other than cannabis >5 times, or any medical condition that could compromise ability to participate or give informed consent were excluded from the study. The overall sample was divided into two cohorts. All subjects meeting the above criteria were included.

2.1.1. Sample 1 (N = 92)

Controls with no history of psychotic illness, and a history of significant adolescent cannabis use during adolescence, but no other drug use. 105 participants were recruited and enrolled. After evaluation, 7 subjects were excluded for not meeting cannabis use criteria, 6 were excluded for having used other drugs >5 times in their lifetime.

2.1.2. Sample 2 (N = 86)

Individuals with a history of chronic schizophrenia and significant adolescent cannabis use prior to the onset of psychosis. 91 participants were recruited and enrolled. One was excluded for not meeting diagnostic criteria for Axis 1 psychotic disorder, two were excluded for not meeting cannabis use criteria, two were excluded for having used other drugs >5 times in lifetime (Additional demographic information is available in Table 1).

2.2. Measures

The Diagnostic Interview for Genetic Studies (DIGS, version IV; Nurnberger et al., 1994) was used to interview subjects and evaluate the onset, pattern, course, comorbidity, and chronology of psychotic, mood and substance abuse symptoms. Lifetime incidence of SSD was defined as having a history of clinically observed psychotic symptoms resulting in a formal SSD diagnosis. Age at onset of psychosis, defined as the age at which an individual first experienced delusions, hallucinations, disorganized speech, disorganized or catatonic behavior was assessed as part of this standardized instrument. Age at onset of psychosis, age at onset of cannabis use, and lifetime duration of cannabis use were recorded in years.

During the structured interviews, raters asked subjects to list their motives for first using cannabis. These qualitative responses were recorded and coded into 36 total items (Table 2). Each subject independently received a binary score of 0 or 1 for each item based on their given reasons for initial cannabis use (0 = Item not referenced as motive for first use; 1 = Item referenced as motive for first use). The wording of this measure was intentionally left ambiguous to avoid influencing subjects' responses, thereby controlling recall and rater bias (Hassan, 2006).

The Structured Interview for Schizotypy (SIS) measured schizotypal symptom severity among subjects (Kendler et al., 1989). This instrument assessed several signs and symptoms relating to "the hypothesized personality-like expression of a schizophrenia genotype" (Kendler et al., 1989) with a focus on "global" composite scores which assessed both individual symptoms as well as symptom clusters. In total, 19 individual symptoms and 4 rater indicated signs were recorded for each participant. The SIS was preferred due to findings that schizotypal symptoms are significantly more prevalent in relatives of patients with schizophrenia (Appels et al., 2004) and that such symptoms share some of the same genetic underpinnings (Fanous et al., 2007) and social deficits (Dickey et al., 2005) as schizophrenia. All measurements were taken and recorded by experienced clinical investigators.

2.3. Data analysis

In order to evaluate the hypothesized factor-structure of cannabis use motives, a principal components factor analysis was conducted on the 36 subject-reported reasons for introductory use of cannabis using accepted procedural guidelines (Floyd and Widaman, 1995). All items correlated at least .48 with at least one other item which suggested reasonable factorability; the Kaiser-Meyer-Olkin measure of sampling adequacy was 0.75; and Bartlett's test of sphericity was highly significant ($\chi 2\,(630) = 1526.16$, $p < .01$). Criteria for retained factors was an eigenvalue >1 and confirmation by a scree test. The initial eigenvalues assigned 17.8% of the variance to Factor 1, 13.9% of the variance to Factor 2, 12.6% of the variance to Factor 3, and 12.3% of the variance to Factor 4. The remaining factors had eigenvalues below one and each accounted for <4% of the variance. The four-factor solution, which explained 56.7% of the variance, was preferred because of its previous theoretical support (Simons et al., 1998; Schofield et al., 2006), the use of a 'cut off' threshold of Eigenvalues below one, and the insufficient number

Table 1
Demographic data of total sampled population arranged by cohort.

Mean	Total (N = 178)	HC cohort (N = 92)	SSD cohort (N = 86)	X^2	F	p-Value
Age in years (SD)	23.9 (4.84)	22.21 (2.76)	25.71 (5.59)	–	32.18	<.001
Gender N (%)						
Female	122 (43.7%)	48 (52.2%)	17 (19.8%)	14.87	-----	<.001
Male	157 (56.3%)	44 (47.8%)	69 (80.2%)			
Psychosis onset age (SD)	21.14 (3.18)	-----	21.22 (2.73)	-----	-----	-----
Cannabis onset age (SD)	15.55 (2.32)	15.82 (2.20)	15.45 (2.45)	-----	1.20	.274
Education years (SD)	15.95 (13.92)	14.10 (1.88)	12.70 (2.21)	–	.705	.402

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