Does cannabis use predict psychometric schizotypy via aberrant salience?

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Abstract

Cannabis can induce acute psychotic symptoms in healthy individuals and exacerbate pre-existing psychotic symptoms in patients with schizophrenia. Inappropriate salience allocation is hypothesised to be central to the association between dopamine dysregulation and psychotic symptoms. This study examined whether cannabis use is associated with self-reported salience dysfunction and schizotypal symptoms in a non-clinical population. 910 University students completed the following questionnaire battery: the cannabis experience questionnaire modified version (CEQmv); schizotypal personality questionnaire (SPQ); community assessment of psychic experience (CAPE); aberrant salience inventory (ASI). Mediation analysis was used to test whether aberrant salience mediated the relationship between cannabis use and schizotypal traits. Both frequent cannabis consumption during the previous year and ASI score predicted variation across selected positive and disorganised SPQ subscales. However, for the SPQ subscales 'ideas of reference' and 'odd beliefs', mediation analysis revealed that with the addition of ASI score as a mediating variable, current cannabis use no longer predicted scores on these subscales. Similarly, cannabis use frequency predicted higher total SPQ as well as specific Positive and Disorganised subscale scores, but ASI score as a mediating variable removed the significant predictive relationship between frequent cannabis use and 'odd beliefs', 'ideas of reference', 'unusual perceptual experiences', 'odd speech', and total SPQ scores. In summary, cannabis use was associated with increased psychometric schizotypy and aberrant salience. Using self-report measures in a non-clinical population, the cannabis-related increase in selected positive and disorganised SPQ subscale scores was shown to be, at least in part, mediated by disturbance in salience processing mechanisms.

Keywords: aberrant salience; cannabis; schizotypy

1. Introduction

Substance misuse is the primary comorbidity in schizophrenia, with cannabis being the most commonly misused illicit substance (Adan et al., 2017; Hunt et al., 2018). Cannabis use has also been implicated as an independent risk factor in the development of psychotic illness (Marconi et al., 2016). Genetic and psychometric risk for psychosis, as well as age and lifetime history of cannabis exposure, are significant factors in relation to later risk for developing psychosis following cannabis exposure (Stefanis et al., 2004). Cannabis (or Δ9-tetrahydrocannabinol [THC], the primary psychoactive ingredient of cannabis) can induce acute psychotic symptoms in healthy individuals (Bhattacharyya et al., 2009), exacerbate pre-existing psychotic symptoms in patients with schizophrenia (D'Souza et al., 2005), and might increase risk of schizophrenia after long-term use (Marconi et al., 2016).

Some authors have emphasised the role of mesostriatal dopaminergic activity in assigning salience to environmental stimuli, and their potential relevance to the development of psychotic symptoms (Kapur, 2003; Winton-Brown et al., 2014). The key role for "aberrant salience" in precipitating the emergence of psychotic symptoms has been supported by empirical studies showing that expression of psychosis-like symptoms is associated with salience misattribution in both patients with schizophrenia (Roiser et al., 2009) and healthy controls with increased psychometric risk for psychosis (Stefanis et al., 2013). THC administration in healthy individuals also has a significant impact on salience processing, and these changes are accompanied by alterations in striatal dopaminergic function (Bossong et al., 2009; Wijayendran et al., 2018).

Aberrant salience has been measured using both performance-based and self-report instruments (Cicero et al., 2010; Roiser et al., 2009). The aberrant salience inventory (ASI) is

a questionnaire designed to measure salience disturbance and has been validated across diverse population samples (Cicero et al., 2010; Raballo et al., 2017). ASI scores are associated with increased psychometric risk for psychosis (Cicero et al., 2010, 2013). Lifetime exposure to psychosocial stressors implicated in schizophrenia has been associated with increased ASI scores (Gaweda et al., 2019; McCutcheon et al., 2019). Additionally, frequent cannabis use was associated with higher ASI scores in a university student sample (Bernardini et al., 2018).

Schizophrenia is conceptualised as a heterogeneous disorder, with clinically defined psychotic illness existing on a continuum with normal behaviour (Van Os et al., 2009). This dimensional view proposes that "schizotypal" traits map onto a continuum of psychosis proneness from subclinical psychotic ideation through to florid psychotic symptoms such as delusions and hallucinations (Linscott and van Os, 2013; Raballo et al., 2017; Gaweda et al., 2019; Grant et al., 2018). As individuals with heightened levels of schizotypy may be at greater risk for later development of a schizophrenia-spectrum disorder, studies employing schizotypal participants provide an opportunity to examine factors that might precede the onset of illness. Schizotypal traits have also been shown to be higher in cannabis users (see Szoke et al., 2014 for review of studies), hence schizotypal characteristics may be conceptualised as a consequence of early and heavy cannabis use, or a predictor of the psychotogenic effects of cannabis exposure (Bailey and Swallow, 2004). Alternatively, it has been proposed that other variables, which may include putative psychological mechanisms underlying psychotic experiences, may mediate the influence the relationship between cannabis use and the development of schizotypal traits (Dumas et al., 2002).

A better understanding of the mechanistic basis underlying the cannabis-psychosis association is dependent upon further research focusing on changes in salience processing as a principal outcome related to long-term cannabis use (Wijayendran et al., 2018). It is

hypothesised that increased aberrant salience, assessed using the ASI, mediates the association between cannabis use and psychometric liability for psychosis, as measured by schizotypy scales and self-reported experience of psychotic symptoms and daily life stress experiences. In the current study we investigated whether cannabis use parameters were associated with self-reported abnormality in salience processing and whether this is associated with higher schizotypy.

2. Methods

All participants were volunteers who provided informed consent according to procedures approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals.

2.1 Participants

Participants were undergraduate and postgraduate students of University College Cork (UCC) and Cork Institute of Technology (CIT). The sample consisted of 910 students (from a total eligible sample of 16,200, corresponding to a response rate of 5.6%), with no declared history of neurological disorder or any formal psychiatric diagnosis during their life. Participants were recruited through distribution, via email, of a link to the questionnaire battery, hosted on surveymonkey.com [Portland, Oregon, USA]. No incentive to participate in this study was offered to students.

2.2 Measures

The following questionnaires were employed in this study: ASI (Cicero et al., 2010), Schizotypal Personality Questionnaire (SPQ; Raine, 1991), Community Assessment of Psychic Experiences (CAPE; Hanssen et al., 2003) and the Cannabis Experience Questionnaire modified version (CEQmv; Di Forti et al., 2009). The latter questionnaire also

measured a number of socio-demographic characteristics including age, sex, nationality, and education level.

The ASI is a 29-item self-report measure of aberrant salience. Each item requires a 'yes' or 'no' response in relation to lifetime experiences. The ASI yields a total score calculated as number of positive responses and has the following five subscales: Increased significance; Senses sharpening; Impending understanding, Heightened emotionality; Heightened cognition. The ASI has been shown to have good reliability and validity for measuring aberrant salience in patients with a psychosis history as well as in non-clinical samples (Cicero et al., 2010).

The SPQ is a 72-item index of schizotypy, based on DSM-IIIR criteria for schizotypal personality disorder, that can be measured in the general population. The SPQ comprises nine subscales that form three dimensions: (a) Cognitive-perceptual/Positive (including the four subscales 'ideas of reference', 'odd beliefs', 'unusual perceptual experiences', 'paranoid ideation'); (b) Interpersonal (including the four subscales 'excessive social anxiety', 'no close friends', 'constricted affect', 'paranoid ideation'); and (c) Disorganised (including the two subscales 'odd or eccentric', 'odd speech') (Raine et al., 1994). The SPQ uses a dichotomous response format. A total SPQ score was based on the sum of all nine subscale scores.

The CAPE is a 42-item self-report scale developed to assess the frequency of clinical symptoms and severity of symptom-related distress in the general population (Stefanis et al., 2002). It evaluates three symptom clusters observed in severe cases of psychiatric illness: positive, negative, and depressive. The CAPE uses a 4-point Likert scale (0-3) to indicate frequency of symptoms ("Never", "Sometimes", "Often", and "Nearly always"), and a 4-point scale to demonstrate degree of distress experienced as a result of symptoms if present ("Not distressed", "A bit distressed", "Quite distressed", "Very distressed").

The CEQmv was administered to collect data on consumption of cannabis (and of other drugs of abuse). This questionnaire explores cannabis consumption in detail, including: age at first use, lifetime cannabis consumption, current cannabis consumption (defined as frequent use of cannabis consumption during the previous 12 months), frequency of use, consumption of other drugs. Previous studies have compared participants that never used cannabis with those who did use cannabis ("ever vs. never"), as well as participants that used cannabis at the time of the study relative to participants that did not use cannabis at that time ("current" vs. "other" comparison) (see Szoke et al., 2014, for review). Definitions of "current" use vary across studies, but several have defined it as frequent intake during the preceding year (e.g. van Gastel et al., 2012). The present study categorised cannabis use as (a) lifetime use ("ever vs. never"), (b) current use (frequent use during previous year, yes/no), or (c) cannabis use frequency (5-level ordinal variable; every day, more than once a week, a few times each month, a few times each year, only once or twice (ever)).

2.3 Data Analysis

All univariate statistical analyses were performed using SPSS Version 24 (IBM Corporation, Armonk, NY) with an alpha level set at $p \leq 0.05$ (two-tailed) for all outcomes. Kolmogorov-Smirnov analysis conducted on ASI, SPQ, and CAPE values revealed that these data were not normally distributed. Therefore, the Mann-Whitney U test or Kruskal Wallis analysis of variance were conducted to compare variation across measures between two groups (e.g. gender) or greater than two groups (e.g. cannabis use frequency), respectively. The Cliff's delta (|d|) statistic was used to study effect size. Pearson's Chi-square test was used to test relationships between categorical variables. Correlation analysis was carried out using Spearman's rho where the Holm-Bonferroni adjustment for multiple comparisons was used.

Based on univariate analyses that examined the relationships between cannabis use and SPQ and CAPE scores (Table 3), mediation analysis was used to test the hypothesis that aberrant salience (i.e. ASI score) mediates the association between cannabis use and SPQ scores, controlling for gender. To assess the mediating role of ASI, two regression models were conducted: the first baseline model (model 1) containing SPQ total or SPQ sub-scale as the outcome, current cannabis use or cannabis use frequency as the main predictor, and gender as a control variable; the second mediation model (model 2) repeated this process with ASI as a potential mediator variable. To assess mediation, we focused on the reduction in co-efficient of cannabis use from the baseline model (assuming a significant prediction at the baseline model level) to the mediation model, and whether ASI is a significant predictor of SPQ score. These models were also compared with Likelihood ratio tests, and both Akaike information criterion (AIC) and Bayesian information criterion (BIC) were presented as goodness of fit measures. As the outcome variable of SPQ total and its subscales were both non-normally distributed and on an ordinal scale, linear regression was deemed inappropriate. Instead, a Poisson distribution was used which more accurately approximated the SPQ distributions. Additionally, as there were "0" counts in the data across all outcomes (participants scoring "0") a zero-inflated Poisson (ZIP) model was adopted for our analyses, with the data for both model components presented in the summary tables. These components are two individual regressions that form a single statistical: A Poisson component aiming to explain variance in SPQ scores 1 and above (i.e., without "0" values) and a Zero component which contrasts those that score exactly "0" and those that scores 1 or above (i.e., a binary logistic regression). Therefore, model performance statistics (e.g., AIC, BIC, etc.) refer to both these components simultaneously. The analysis focuses primarily on the first Poisson component for interpretability due to the large number of analyses. Two exceptions are the zero components for SPQ total for current cannabis use and cannabis use frequency (Table 6).

Only six 0 scores for SPQ total were observed meaning the "0" was severely smaller than the comparison group, leading to inflated standard errors. This is especially prominent for cannabis use frequency, as some cross tabulations did not include an observation. The subscales however had higher levels of 0 values ranging from 82 for 'excessive social anxiety' up to 352 for 'odd beliefs'; meaning this approach was more appropriate. However, these Zero components are reported for transparency but not considered for interpretation. Confidence intervals were bootstrapped (10000 replications) and extracted using the BCa method. As traditional R_2 is primarily appropriate for simple linear regression, pseudo-R_2 is instead used here. This was calculated as the squared correlation between actual and predicted model values. This value was also adjusted for multiple predictors. These analyses were conducted in R Studio (RStudio Team, 2015, version 3.6.0) using the "pscl" package.

3. Results

Table 1 and Supplementary Table 1 present the socio-demographic and cannabis use characteristics of the study sample. No sex differences were observed for lifetime cannabis use ($\chi_2 = 1.25$, $P = 0.29$), but male respondents were more likely to be current cannabis users at the time of the study ($\chi_2 = 8.15$, $P = 0.003$) and were more frequent cannabis users ($\chi_2 = 14.75$, $P = 0.005$). Family history of mental illness was associated with increased likelihood of lifetime cannabis use ($\chi_2 = 17.03$, $P < 0.001$) and current cannabis use ($\chi_2 = 4.70$, $P = 0.02$). Neither family history of neurological illness nor highest education level achieved were associated with any cannabis use parameter (all $P > 0.05$).

Summary scores for the ASI, SPQ, and CAPE scales are presented in Supplementary Table 2. Females displayed higher values for the following SPQ subscales: 'odd beliefs' ($U = 85207$, $z = 3.93$, $P < 0.001$, $|d| = 0.13$), 'excessive social anxiety' ($U = 80067$, $z = 5.03$, $P < 0.001$, $|d| =$

0.15). Males showed higher scores for the 'constricted affect' subscale (U = 88076, z = 2.97, P = 0.003, |d| = 0.12). No statistically significant effects of sex were observed for ASI and CAPE scores. Respondents reporting a family history of mental illness demonstrated significantly higher total ASI (U = 73156, z = 4.03, P < 0.001, |d| = 0.17) scores. While family history of mental illness had no effect on CAPE frequency or distress scores, family history was associated with increased scores across the following sub-scales scores: 'unusual perceptual experiences' (U = 74113, z = 3.94, P < 0.001, |d| = 0.16), 'excessive social anxiety' (U = 74591, z = 3.76, P < 0.001, |d| = 0.15), 'odd or eccentric' (U = 73559, z = 4.10, P <0.001, |d| = 0.16), and 'paranoid ideation' (U = 73637, z = 4.04, P < 0.001, |d| = 0.16). For both sex and family history variables, the effect sizes for all outcome variables was either negligible (|d| < 0.17) or small (0.147 ≤ |d| < 0.33).

Results of correlational analysis across the ASI, SPQ, and CAPE instruments are presented in Table 2. Total ASI score demonstrated significant positive correlations with all SPQ scores (total, dimension and subscales); magnitude of correlation coefficients ranged from 0.20-0.68. No significant correlation was observed between ASI and any CAPE measure.

Table 3 presents a summary and comparison of ASI (total and subscale), SPQ (total, subscale and dimension) and CAPE scores between current cannabis users and their controls. Lifetime cannabis use, was not associated with any statistically significant variation in ASI, SPQ or CAPE scores (all P > 0.05; Supplementary Table 3). Current cannabis use was associated with significantly increased ASI total and all subscale scores (Table 3). Additionally, current cannabis users showed increased scores across the Positive (U = 43555, z = -2.95, P = 0.002) and Disorganised (U = 40603, z = 4.13, P < 0.001) SPQ dimensions, as well as the SPQ subscales 'ideas of reference' (U = 43364, z = 3.05, P = 0.002) and 'odd or eccentric' (U = 40016, z = 4.44, P < 0.001). Analysis based on cannabis use frequency revealed that frequent consumption was associated with higher scores across the Disorganised SPQ dimension (χ^2 =

23.52, P < 0.001), as well as the following subscales: ‘odd or eccentric’ (χ^2 = 26.90, P < 0.001); ‘unusual perceptual experiences’ (χ^2=12.66, P=0.01); ‘odd speech’ (χ^2 = 12.51, P = 0.01). Higher consumption frequency was also associated with higher ASI scores (χ^2 = 10.72, P = 0.03).

Age at first use of cannabis was negatively correlated with scores on the SPQ Positive dimension (r_s = -0.14, P = 0.002), but no other ASI, SPQ or CAPE measure. When asked to quantify level of cannabis consumption up to the age of sixteen, no significant differences were observed across ASI, SPQ and CAPE scores between participants who consumed less than one cannabis joint per day relative to participants who used between one and four joints per day (all P > 0.05). No significant relationships were observed between frequency of cannabis use up to the age of sixteen and any ASI, SPQ and CAPE measure (all P > 0.05).

For the mediation analysis the Poisson components were compared between baseline and mediation models. For analyses with current cannabis use, “yes” was treated as the reference category, with a negative regression coefficient in the Poisson component representing those who do *not* use cannabis have a lower SPQ score and vice versa for a positive coefficient. However, a positive coefficient for the zero component predicts that those *not* currently using cannabis are more likely to score “0” relative to scoring 1 or above. Inspection of the Poisson components showed that *not* currently using cannabis was a significant predictor of lower SPQ total score (log(odds) = -0.134 [-0.221, -0.046.], P < 0.001; Supplementary Table 4), ‘odd or eccentric’ (log(odds) = -0.145 [-0.270, -0.015], P = 0.014; Supplementary Table 5) , ‘ideas of reference’ (log(odds) = -0.150 [-0.270, -0.021], P = 0.004; Table 4), and marginally, ‘odd beliefs’ (log(odds) = -0.189 [-0.407, 0.046], P = 0.05; Table 5) and ‘odd speech’ (log(odds) = -0.083 [-0.189, 0.025], P = 0.07; Supplementary Table 6) subscale scores, in the baseline models. Therefore, only the marginally and statistically significant models (SPQ

total, ‘odd or eccentric’, ‘ideas of reference’, ‘odd beliefs’, and ‘odd speech’) were carried forward for mediation analysis.

In these mediation models, ASI total score was found to significantly predict SPQ total score (log(odds) = 0.04 [0.038, 0.047], P < 0.001), but cannabis remained a significant independent predictor (log(odds) = -0.055 [-0.129, 0.02], P = 0.001), despite showing a 59% reduction in its effect following the inclusion of ASI. Similarly, ASI independently predicted ‘odd or eccentric’ (log(odds) = 0.029 [0.022, 0.037], P < 0.001), with cannabis continuing to be a significant predictor (log(odds) = -0.119 [-0.238, 0.007], P = 0.04), with a 17.9% reduction in log(odds). ASI total score was also found to significantly predict ‘ideas of reference’ (log(odds) = 0.046 [0.039, 0.052], P < 0.001), but current cannabis was reduced to a marginal predictor on this subscale (log(odds) = -0.100 [-0.211, 0.017], P = 0.056; Table 4), demonstrating a 33% reduction in its effect. For the SPQ subscale analyses, where current cannabis use was a marginal predictor, ASI was a significant predictor in ‘odd speech’ (log(odds) = 0.035 [0.029, 0.040], P < 0.001) with current cannabis use becoming non-significant predictor (log(odds) = -0.037 [-0.136, 0.062], P = 0.44). For ‘odd beliefs’, ASI was also a significant predictor (log(odds) = 0.049 [0.039, 0.060], P < 0.001), with cannabis use again becoming non-significant (log(odds) = -0.131 [-0.332, 0.085], P = 0.177; Table 5).

In all cases the mediation models were a better fit to the data than the baseline models, evidenced through significant Likelihood ratio tests (all P < 0.001) and lower AIC and BIC indices; suggesting the addition of ASI improved the model.

This process was repeated for current cannabis use frequency which was treated as a categorical variable, as the levels of frequency were not equally spaced (e.g., “a few times each year”, “a few times each month”, “more than once a week”, etc.). For this analysis, the first category of “only once or twice” was used as the reference category with all coefficients

representing the change in SPQ when moving from this reference category to another category (e.g., “only once or twice” vs. “a few times each month”). Therefore, a positive coefficient represents an increase in SPQ score between categories. Each cannabis frequency level was a significant predictor of SPQ total score over “only once or twice” (Table 6, all $P < 0.001$) in the baseline model. For the other two subscales that were significant using current cannabis use, ‘ideas of reference’ saw an increase in score only for “a few times each month” (log(odds) = 0.177 [-0.045, 0.393], P = 0.033; Supplementary Table 7), while ‘odd or eccentric’ was significant at “every day” use only (log(odds) = 0.262 [0.004, 0.511], P = 0.036; Supplementary Table 8). For the subscales that were previously marginally significant, ‘odd beliefs’ reported an increase in score at “more than once a week” (log(odds) = 0.498 [0.108, 0.86], P = 0.002; Supplementary Table 9), while ‘odd speech’ showed an increase at “a few times each year” (log(odds) = 0.141 [-0.026, 0.312], P = 0.042) and “a few times each month” (log(odds) = 0.161 [-0.033, 0.353], P = 0.031; Supplementary Table 10). One major difference between these approaches was that significant increases in scores were found for ‘no close friends’ at “every day” cannabis use (log(odds) = 0.223 [-0.087, 0.477], P = 0.039; Supplementary Table 11), and ‘unusual perceptual experiences’ at ‘more than once a week’ (log(odds) = 0.355 [0.091, 0.616], P = 0.001; Supplementary Table 12), which were not significant in the currently use cannabis models. The remaining scales saw no significant differences in the baseline Poisson components.

In the mediation model, ASI total score was found to significantly predict SPQ total score and all nine subscales ($P < 0.001$), but cannabis use remained a significant predictor of SPQ total scores for all frequency categories (all $P < 0.05$) with exception of ‘> once a week’ (log(odds)= -0.017 [-0.153, 0.11], P = 0.608; Table 6). For ‘odd or eccentric’, the significant difference at “every day” remained, with a 4.2% reduction. For ‘ideas of reference’ the significant prediction of “a few times each month” was no longer significant (log(odds) =

0.081[-0.107, 0.26], P = 0.333). ‘Odd beliefs’ saw both significant predictions return as non-significant (P > 0.05, reduction: 37.2% - 49.6%) while ‘odd speech’ similarly returned no significant cannabis predictors (P > 0.05, reduction: 34.8% - 38.5%). ‘No close friends’ saw the prediction at “every day” reduced to marginal (log(odds) = 0.192 [-0.122, 0.447], P = 0.077). For ‘unusual perceptual experiences’, cannabis use (‘more than once a week’) no longer predicted scores (log(odds) = 0.164 [-0.041, 0.375], P = 0.127), showing a reduction of 19%. As the remaining subscales saw no prediction from any cannabis frequency mediation are not reported here. Again, all mediation models were a better fit to the data than the baseline models.

4. Discussion

In the present study, frequent cannabis users reported higher scores across Positive and Disorganised schizotypal domains and aberrant salience measures than light users, who in turn reported more than those who had minimal cannabis exposure. This apparent ‘dose–response’ relationship mirrors the relationship between cannabis use and psychotic disorders in clinical populations (Henquet et al., 2008), supporting further the association between cannabis use and psychosis.

Current cannabis use (frequent use during the preceding year) was associated with higher scores across the Positive and Disorganised SPQ dimensions, and related subscales (i.e. ‘ideas of reference’, ‘odd or eccentric’). Previous studies have found that cannabis use is associated with higher rates of Positive and Disorganised, but not Interpersonal (negative), schizotypy traits (Bailey & Swallow, 2004; Schiffman et al., 2005; Earleywine, 2006; Cohen et al., 2011; Eren et al., 2017). The present results are consistent with previous reports that regular cannabis users on average display more cognitive and perceptual distortions, as well

as disorganization, but not interpersonal deficits. In agreement with our hypothesis, while current cannabis use and aberrant salience independently predicted variation in selected Disorganised ('odd or eccentric', 'odd speech') or Positive dimensions ('ideas of reference', 'odd beliefs'), the cannabis-schizotypy association for the 'ideas of reference', 'odd beliefs', and 'odd speech' (where the initial cannabis association was marginal), was explained by the effect of the drug on aberrant salience processing. A similar profile was observed for self-reported frequent cannabis use. Core symptoms of schizophrenia and related disorders, as well as psychosis proneness, have been proposed to reflect a disturbance in salience-based information processing (Kapur, 2003; Howes & Kapur, 2009). It has been suggested that misattribution of salience to irrelevant stimuli might represent one such marker of vulnerability to progression to psychosis among high cannabis users (Bernardini et al., 2018). Others have suggested that misattribution of significance to otherwise neutral stimuli may trigger the phenotypic expression of Positive schizotypal traits (Raballo et al., 2019). The present results demonstrate that aberrant salience principally accounts for the effects of frequent cannabis use on Positive schizotypal traits, as indexed by scores on the 'ideas of reference' and 'odd beliefs' SPQ sub-scales, while exerting a reduced or non-existent mediating influence on cannabis-affected Disorganised sub-scales, as well as global SPQ score.

Current cannabis users showed higher total ASI scores, but lifetime cannabis use was not associated with any increase in ASI scores. These results contrast with those of Bernardini et al. (2018), where both lifetime and current cannabis users demonstrated higher ASI scores relative to non-users. In agreement with studies using ASI or performance-based measures such as SAT (Bloomfield et al., 2016; Bernardini et al., 2018), higher cannabis use frequency was associated with higher levels of aberrant salience.

No effect of either lifetime (i.e. 'ever vs. never') or current cannabis use was observed on positive, negative or depressive frequency or distress dimensions of the CAPE, a measure of recent psychotic-like experiences; these findings contrast with those reported previously for CAPE (Schubart et al., 2011; Skinner et al., 2011; Bernardini et al., 2018). This may in part be explained by the observation that cannabis effects on SPQ score in the present analyses particularly reflects highly significant effects on Disorganised dimension sub-scales. While the CAPE has two dimensions for reporting psychotic experiences (positive, negative), it does not contain a Disorganisation factor. Additionally, it should be noted that a non-linear relationship between regular cannabis use and CAPE scores has been reported previously, with the presence of positive and negative symptoms similarly observed in very regular cannabis users and non-cannabis users relative to a group of moderate cannabis users (Brañas et al., 2016).

Research that has investigated the direction of the association between cannabis use and development of psychosis has consistently shown that cannabis use precedes the emergence of psychotic symptoms (Henquet et al., 2005; Stefanis et al., 2013). Similarly, Hjorthoj et al. (2018) demonstrated that conversion from schizotypal disorder to schizophrenia was significantly higher among those with cannabis use disorder. The current study design precludes conclusions about whether schizotypal traits predispose individuals to use cannabis (Wijayendran et al., 2018), or whether cannabis use is associated with an increase in schizotypal traits, or indeed whether chronic cannabis use may increase phenotypic expression of schizotypal traits in individuals harbouring the latent schizotypy construct (Lenzenweger, 2018). Future research could address this issue by following participants longitudinally to establish the temporal precedence of cannabis exposure and aberrant salience before the development of psychotic-like experiences. Additionally, such studies might also incorporate complementary testing on laboratory-based cognitive measures such

as the salience attribution test (SAT) (Roiser et al., 2009), although achieving large sample sizes necessary to probe such complex relationships can prove challenging in these circumstances.

In conclusion, we report that aberrant salience is an important mediating variable underlying the relationship between current cannabis use and the increase in psychometrically-defined positive schizotypy. Further research is required to investigate not only the biological substrates underlying the relationship between cannabis use and the development of schizophrenia-spectrum symptoms, but also the impact of psychological and psychosocial factors modulating the strength of this relationship. This will ultimately inform the development of more targeted and effective interventions for individuals with schizophrenia-spectrum disorders.

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Table Legends

Table 1 Characteristics of the sample population (n=910)

Table 2 Correlations between ASI and both SPQ and CAPE scores

Table 3 Comparison of ASI, SPQ, and CAPE scores between current cannabis users and nonusers

Table 4 Mediation analysis results predicting SPQ 'ideas of reference' subscale scores based on current cannabis use

Table 5 Mediation analysis results predicting SPQ 'odd beliefs' subscale scores based on current cannabis use

Table 6 Mediation analysis results predicting total SPQ score based on cannabis use frequency

Table 1 Characteristics of the sample population (*n*=910)

Characteristic	*n*	*%*
Sex		
Female	515	(56.6%)
Male	386	(42.4%)
Not specified	9	(1.0%)
Nationality		
Irish/British	787	(86.5%)
Other European	71	(7.8%)
North American	14	(1.5%)
Asian	13	(1.4%)
Other/Not specified	25	(2.8%)
Highest level of education		
Secondary level	355	(39.0%)
Post-secondary level	122	(13.4%)
Primary degree	328	(36.0%)
Masters degree	70	(7.7%)
Doctoral degree	3	(0.3%)
Other/Not specified	32	(3.5%)
Family history of mental illness		
Yes	290	(31.9%)
No	608	(66.8%)
Not specified	12	(1.3%)
Lifetime cannabis use		
Yes	469	(51.5%)
No	365	(40.1%)
Not specified	76	(8.4%)
Current cannabis use		
Yes	181	(19.9%)
No	563	(61.9%)
Not specified	166	(18.2%)
Age at first cannabis use		
Mean age (SD)	17.6	(2.7%)
Range	7-28	
Frequency of cannabis use		
Every day	34	(3.7%)
Greater than once a week	60	(6.6%)
A few times each month	96	(10.5%)
A few times each year	123	(13.5%)
Only once or twice	163	(17.9%)
Not specified	434	(47.7%)

Figures presented are number (%) unless stated otherwise.

Table 2 Correlations between ASI and both SPQ and CAPE Scores

Scale	*Parameter*	r_s	*P-value* [a]
SPQ	Total	0.60	< 0.001
	Ideas of reference	0.55	< 0.001

	Excessive social anxiety	0.27	< 0.001
	Odd beliefs	0.47	< 0.001
	Unusual perceptual experiences	0.63	< 0.001
	Odd or eccentric	0.46	< 0.001
	No close friends	0.20	< 0.001
	Odd speech	0.49	< 0.001
	Constricted affect	0.31	< 0.001
	Paranoid ideation	0.50	< 0.001
	Cognitive Perceptual	0.68	< 0.001
	Interpersonal	0.38	< 0.001
	Disorganised	0.54	< 0.001
CAPE	Total frequency	-0.01	0.71
	Positive dimension	0.03	0.43
	Positive dimension distress	-0.04	0.20
	Negative dimension	-0.04	0.21
	Negative dimension distress	-0.05	0.18
	Depressive dimension	-0.03	0.35
	Depressive dimension distress	-0.04	0.21

[a] α value adjusted for multiple comparisons

Table 3 Comparison of ASI, SPQ, and CAPE scores between current cannabis users and nonusers

Scales	***Parameters***	***Current cannabis nonusers (n=563)***		***Current cannabis users (n=181)***		***P*** [a]	***Cliff's |d|***	***95% CI for Cliff's |d| (Upper, Lower)***
		Mean	***SD***	***Mean***	***SD***			
ASI	Total	9.29	7.51	11.11	7.33	0.002 *	0.15	(0.062, 0.244)
	Increased significance	2.60	2.23	3.16	2.22	0.002 *	0.15	(0.055, 0.239)
	Senses sharpening	1.37	1.42	1.70	1.55	0.009	0.12	(0.029, 0.216)
	Impending understanding	1.64	1.65	1.90	1.59	0.025	0.11	(0.017, 0.197)
	Heightened emotionality	2.41	1.81	2.82	1.68	0.004	0.14	(0.050, 0.232)
	Heightened cognition	1.15	1.32	1.38	1.39	0.032	0.10	(0.008, 0.192)
SPQ	Total	23.29	14.24	26.27	13.15	0.004	0.14	(0.050, 0.231)
	Ideas of reference	2.74	2.39	3.36	2.50	0.002 *	0.15	(0.054, 0.241)

	Excessive social anxiety	3.96	2.67	4.02	2.74	0.78	0.01	(-0.083, 0.110)
	Odd beliefs	1.12	1.45	1.26	1.57	0.397	0.04	(-0.053, 0.131)
	Unusual perceptual experiences	2.04	1.95	2.43	2.00	0.01	0.12	(0.029, 0.215)
	Odd or eccentric	1.99	2.03	2.77	2.41	< 0.001 *	0.21	(0.121, 0.304)
	No close friends	3.08	2.58	2.96	2.40	0.76	-0.02	(-0.110, 0.079)
	Odd speech	3.29	2.61	3.90	2.53	0.004	0.14	(0.050, 0.234)
	Constricted affect	2.33	1.99	2.57	2.00	0.106	0.08	(-0.015, 0.172)
	Paranoid ideation	2.74	2.34	2.98	2.15	0.084	0.08	(-0.007, 0.175)
	Cognitive	8.64	6.56	10.04	6.23	0.002 *	0.15	(0.051, 0.237)
	Perceptual							
	Interpersonal	12.11	7.84	12.54	7.51	0.402	0.04	(-0.053, 0.135)
	Disorganised	5.29	4.11	6.67	4.03	< 0.001 *	0.20	(0.109, 0.293)
CAPE	Total	1.62	0.02	1.66	0.03	0.150	0.09	(-0.190, 0.201)
	Positive dimension	1.23	0.30	1.25	0.34	0.391	0.05	(-0.051, 0.143)
	Positive dimension distress	2.23	1.58	2.12	1.31	0.490	-0.03	(-0.130, 0.062)
	Negative dimension	1.94	0.51	1.94	0.55	0.085	0.00	(-0.096, 0.100)
	Negative dimension distress	2.05	1.78	2.24	3.36	0.659	0.02	(-0.074, 0.117)
	Depressive dimension	5.11	4.69	5.60	5.05	0.665	0.07	(-0.030, 0.163)
	Depressive dimension distress	1.82	0.50	1.87	0.53	0.122	0.08	(-0.022, 0.175)

[a] *α value adjusted for multiple comparisons; CI, confidence interval; SD, standard deviation*

Table 4 Mediation analysis results predicting SPQ 'ideas of reference' subscale scores based on current cannabis use

Model		Variable	Log(odds)	95% CI	SE	OR	z	*P*	*GVIF*	R^2_{pseudo}
Model 1 Baseline	Ideas of Reference - Poisson	intercept	1.257	[1.133, 1.371]	0.049	3.515	25.47	0.000		
		Cannabis (NO)	-0.15	[-0.270, -0.021]	0.051	0.861	-2.914	0.004	1.02	
		Gender	0.131	[0.016, 0.25]	0.048	1.14	2.74	0.006	1.02	
	Ideas of Reference -ZIP	intercept	-2.203	[-2.829, -1.637]	0.303	0.11	-7.281	0.000		
		Cannabis (NO)	0.58	[-0.019, 1.252]	0.306	1.786	1.896	0.058	1.01	
		Gender	0.072	[-0.413, 0.578]	0.240	1.075	0.3	0.764	1.01	7.015%
Model 2 Mediation	Ideas of Reference - Poisson	intercept	0.647	[0.497, 0.796]	0.067	1.91	9.71	0.000		
		Cannabis (NO)	-0.100	[-0.211, 0.017]	0.052	0.905	-1.915	0.056	1.03	
		Gender	0.142	[0.035, 0.246]	0.049	1.153	2.916	0.004	1.02	
		ASI	0.046	[0.039, 0.052]	0.003	1.047	15.004	0.000	1	
	Ideas of Reference	intercept	-1.199	[-2.25, -0.336]	0.441	0.301	-2.717	0.007		

- ZIP	Cannabis (NO)	0.365	[-0.416, 1.437]	0.400	1.441	0.912	0.362	1	
	Gender	0.219	[-0.419, 0.956]	0.318	1.245	0.689	0.491	1.02	
	ASI	-0.162	[-0.258, -0.1]	0.032	0.85	-5.054	0.000	1.02	62.448 %

Note: Model 1: AIC=3259, BIC=3286.6, % change Poisson=33.3%, Model 2: AIC=2944.5, BIC=2981.3, % change Zero=37.1%, LR test, X2(2) =318.53, P < 0). CI, confidence interval. GVIF, generalized variance inflation factor. OR, odds ratio. SE, standard error.

Table 5 Mediation analysis results predicting SPQ 'odd beliefs' subscale scores based on current cannabis use

Model		Variable	Log(odds)	95% CI	SE	OR	z	*P*	*GVIF*	R^2_{pseudo}
Model 1 Baseline	Odd Beliefs - Poisson	intercept	0.553	[0.344, 0.76]	0.094	1.738	5.902	0.000		
		Cannabis (NO)	-0.189	[-0.407, 0.046]	0.097	0.828	-1.942	0.052	1.07	
		Gender	0.309	[0.084, 0.536]	0.096	1.362	3.221	0.001	1.07	
	Odd Beliefs -ZIP	intercept	-0.441	[-0.877, 0.011]	0.222	0.643	-1.986	0.047		
		Cannabis (NO)	0.024	[-0.462, 0.546]	0.234	1.024	0.101	0.920	1.05	
		Gender	-0.155	[-0.604, 0.362]	0.221	0.856	-0.699	0.485	1.05	3.631%
Model 2 Mediation	Odd Beliefs - Poisson	intercept	-0.242	[-0.508, 0.036]	0.135	0.785	-1.79	0.000		
		Cannabis (NO)	-0.131	[-0.332, 0.085]	0.097	0.877	-1.351	0.177	1.08	
		Gender	0.353	[0.135, 0.563]	0.096	1.423	3.676	0.000	1.08	
		ASI	0.049	[0.039, 0.06]	0.006	1.05	8.857	0.000	1.01	
	Odd Beliefs	intercept	0.766	[0.032, 1.456]	0.365	2.151	2.098	0.036		

- ZIP	Cannabis (NO)	-0.352	[-1.023, 0.358]	0.321	0.703	-1.098	0.272	1.11	
	Gender	-0.095	[-0.762, 0.645]	0.314	0.909	-0.301	0.763	1.07	
	ASI	-0.142	[-0.193, -0.097]	0.024	0.868	-6.006	0.000	1.07	37.187 %

Note: Model 1: AIC=2174.7, BIC=2202.3, % change Poisson=30.7%, Model 2: AIC=1957.4, BIC=1994.2, reduction Zero=1566.7%, LR test, X2(2) =221.26, P < 0). CI, confidence interval. GVIF, generalized variance inflation factor. OR, odds ratio. SE, standard error.

Table 6 Mediation analysis results predicting total SPQ total score based on cannabis use frequency

Model		Variable	Log(odds)	95% CI	SE	OR
Model 1 Baseline	SPQ - Poisson	intercept	3.053	[2.923, 3.175]	0.022	21.179
		Cannabis: a few times each year	0.171	[0.04, 0.308]	0.025	1.186
		Cannabis: a few times each month	0.174	[0.019, 0.33]	0.027	1.19
		Cannabis: More than once a week	0.149	[-0.008, 0.308]	0.032	1.161
		Cannabis: Every day	0.208	[-0.009, 0.435]	0.038	1.231
		Gender	0.01	[-0.094, 0.117]	0.019	1.01
Model 2 Mediation	SPQ - Poisson	intercept	2.643	[2.528, 2.763]	0.025	14.055
		Cannabis: a few times each year	0.077	[-0.039, 0.184]	0.025	1.08
		Cannabis: a few times month	0.074	[-0.049, 0.194]	0.027	1.077
		Cannabis: > than once a week	-0.017	[-0.153, 0.11]	0.032	0.983
		Cannabis: Every day	0.078	[-0.1, 0.229]	0.038	1.081
		Gender	0.027	[-0.058, 0.114]	0.019	1.027
		ASI	0.042	[0.037, 0.047]	0.001	1.043

Note: Model 1: AIC=5841.9, BIC=5891.6, Model 2: AIC=4646.6, BIC=4704.7, LR test, X2(2) =1199.3, P < 0). CI, confidence interval. GVIF, generalized variance inflation factor. OR, odds ratio. SE, standard error.