



## Brief report

## Total exposure duration and proximity of cessation of cannabis use predict severity of sub-clinical psychotic symptoms among former users

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## ABSTRACT

In a non-clinical military enrolment setting, former cannabis users ( $N=81$ ), compared to substance-naïve controls ( $N=132$ ), endorsed markedly elevated rates of schizotypy subscale scores on the Schizotypal Personality Questionnaire (SPQ). Total duration of exposure and proximity of cessation of cannabis use also had an important impact on the severity of psychosis-like symptoms.

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## 1. Introduction

Early cannabis use may increase the risk for psychotic symptoms (Stefanis et al., 2004a) and repeated exposure to cannabis may sensitise individuals who are genetically at risk for psychosis (Henquet et al., 2008). A dose–response relation between cannabis use and psychosis has been shown both in terms of frequency of symptoms and established psychotic disorders among current users (Zammit et al., 2002; Stefanis et al., 2004a). However, complete elimination of  $\Delta^9$ -tetrahydrocannabinol (THC) may take up to 30 days (Ashton, 2001). To our knowledge, the present study is the first to directly examine a plausible dose–response relation between sub-clinical psychotic symptoms (SPS) and cannabis exposure with the drug-free interval at least 30 days or longer.

Experimental reversibility (Hill, 1965) lends support for a putative association between exposure and outcome. To date, there has not been a study that examines SPS as a possible outcome following cessation of cannabis use. In this investigation, we compared severity of SPS among healthy former users vs. substance-naïve controls in the same military enrolment setting. We examined the relationship of former cannabis use on different dimensions of SPS, as well as between SPS and total duration of cannabis exposure (Td), and between

SPS and the duration of last cannabis-free interval at the time of assessment (dCFI).

## 2. Methods

The study was approved by the university and the military hospital ethics boards. The participants were male military conscripts who boarded at the same military training school between January and March 2008 in western Turkey. Psychiatric and substance-use histories were obtained as part of a routine medical examination at 1 month after recruitment that enabled a 'wash-out' period for exposure. As ascertained from the military records, all participants were in good health without medical or psychiatric co-morbid conditions.

Based on the Munich Composite International Diagnostic Interview (Wittchen et al., 1995), our definition of former use required exposure "on at least five independent occasions" with use of a joint (alone or shared) at each event. Of the total 168 eligible index subjects, eight refused to participate, and 65 were excluded ( $n=8$ , history of psychosis;  $n=11$ , antipsychotic use;  $n=15$ , psychotic disorder in a first-degree relative;  $n=11$ , cocaine, hallucinogen, or opiate abuse;  $n=20$ , and/or regular ecstasy abuse). To ensure the reliability of participant's self-reports, the remaining 95 conscripts were further assessed using a semi-structured interview for a detailed history of cannabis abuse including: age of first use (AoFU), methods and reasons for use, the frequency of use, intervals of regular use and cannabis-free periods. The reports for 14 subjects were found to be inconsistent with their self-report at study inception. The remaining 81 subjects were evaluated for SPS.

The controls were cannabis-naïve conscripts whose military numbers were subsequent to former cannabis users. Twenty-nine of the 160 controls were excluded (history of prior psychotic disorder,  $n=4$ ; antipsychotic use,  $n=3$ ; psychotic disorder in a first-degree relative,  $n=18$ ; and cocaine abuse,  $n=4$ ). The remaining 131 controls were evaluated for SPS.

The SPS scores were assessed by the Turkish version of the Schizotypal Personality Questionnaire (SPQ), shown to be a reliable and valid instrument for studies among young adults (Sener et al., 2006). Cronbach's alpha coefficient for the overall scale is

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0.91 with coefficients for subscales ranging from 0.66 to 0.83 (Sener et al., 2006). Factor analysis of the SPQ (Raine, 2006) reveals cognitive–perceptual and disorganised schizotypy factors that correspond to positive schizotypy and an interpersonal schizotypy factor (i.e., social anxiety, constricted affect and lack of close friendships) that corresponds to negative schizotypy. The SPQ has also been used for the identification of risk factors for susceptibility to psychosis (Vollema et al., 2002) as well as severity of psychosis-like experiences (Stefanis et al., 2004b).

Total duration of cannabis exposure (Td) was determined as the sum total (in months) of former cannabis use intervals established by the semi-structured interviews. Duration of the last cannabis-free interval at the time of assessment (dCFI) was measured in months. The mean Td was  $47.8 \pm 25.8$  months and the mean dCFI was  $3.5 \pm 3.1$  months. Mean AoFU was  $14.47 \pm 1.31$ .

Analyses included *t*-tests to assess severity of SPS between groups. Spearman correlation coefficients were calculated among former cannabis users to assess the effect of AoFU, Td and dCFI with SPS scores. We applied stepwise linear regression tests with SPQ-positive, SPQ-negative and SPQ-total scores as the dependent and the Td as well as the dCFI as independent variables.

### 3. Results

Cannabis users were younger than controls ( $t = 2.43$ ,  $P < 0.05$ ) but did not differ significantly in educational level ( $t = 1.65$ ,  $P = 0.1$ ). Compared to substance-naïve controls, former cannabis users had higher levels of total, positive and negative schizotypy (Table 1).

Td was positively correlated with SPQ-positive scores ( $r = 0.221$ ,  $P < 0.05$ ) but not with SPQ-total and SPQ-negative scores. The dCFI was negatively correlated with SPQ-total ( $r = -0.512$ ,  $P < 0.001$ ), SPQ-positive ( $r = -0.492$ ,  $P < 0.001$ ) and SPQ-negative ( $r = -0.449$ ,  $P < 0.001$ ) scores. AoFU was not correlated with the SPQ scores (SPQ-total;  $r = -0.14$ ,  $P = 0.22$ , SPQ-positive;  $r = -0.203$ ,  $P = 0.07$ , SPQ-negative; and  $r = -0.042$ ,  $P = 0.71$ ).

Regression analyses revealed similar relationship patterns for the total, positive and negative schizotypy scores and cannabis-related parameters. The dCFI was included in the model that explained 27% of the variance in the SPQ-total ( $R^2 = 0.272$ ,  $Beta = -0.53$ , S.D. = 1.67,  $t = -5.52$ ,  $P < 0.001$ ) and 20% of the variance in the SPQ-negative ( $R^2 = 0.202$ ,  $Beta = -0.45$ ,  $t = -4.44$ ,  $P < 0.001$ ) scores. Regarding the SPQ-positive scores, a model that consisted of both the dCFI ( $Beta = -0.5$ ,  $t = -5.29$ ) and Td ( $Beta = 0.21$ ,  $t = 2.21$ ) explained 30% of the variance in the SPQ-positive scores ( $R^2 = 0.309$ ,  $P < 0.001$ ).

### 4. Discussion

Our findings suggest that the severity of all dimensions of SPS decline after cessation of cannabis use. Regression analyses revealed that dCFI was a stronger predictor of SPS than Td among former cannabis users. Cessation of cannabis use after the first psychotic episode among subjects with established psychosis contributes to a clear improvement in symptoms, suggesting experimental reversibility (González-Pinto et al.,

2011). To our knowledge, the present study is the first to show an association between proximity of cannabis cessation and the severity of SPS among healthy subjects. We found that the duration of exposure, as well as proximity of its cessation, may have an important impact on SPS. The findings support a possible biological gradient for emergence of sub-clinical symptoms of psychosis.

Williams et al. (1996) showed that current and former cannabis users with exposure prior to 30 days had higher schizotypy scores than cannabis-naïve participants. Skosnik et al. (2001) showed that former users with exposure prior to 45 days before the SPQ assessments demonstrated fewer SPS than current users but were not different from substance-naïve controls. Dumas et al. (2002) found that a combined group of occasional and past users (with an indefinite cessation period) had higher SPQ scores than never users. We found that former cannabis users do have a marked degree of elevation on SPQ scores compared to substance-naïve controls. We excluded subjects with family history of psychosis that would otherwise interact and confound the expression of SPS. The severity of SPS scores was negatively correlated with the time elapsed after last use, and discrepancies between studies may be due to different cessation periods.

With respect to the association of Td and SPS dimensions, our results are parallel to studies involving current users (Dumas et al., 2002; Fridberg et al., 2011). Td was correlated with positive but not with negative schizotypy dimensions. Such a relationship may either be explained by direct pharmacological effects of cannabis leading to SPS or pre-existing schizotypal traits leading to abuse (Dumas et al., 2002). The presence of SPS among former users in our study may not be explained by a direct biochemical effect of cannabis as dCFI is minimum 1 month. Although dopamine sensitisation (Henquet et al., 2008) may still be operational in subsequent effects of former cannabis use on positive SPS, negative dimensions of SPS may be intrinsic to psychosis and might represent a trait rather than a state, and hence be less sensitive to effects of exposure.

Among our study limitations, first and foremost, is that it is difficult to disentangle the direction of associational effects due to the cross-sectional design. The SPQ scale does not measure the onset of symptoms, and negative schizotypy may precede cannabis exposure. Second, we relied on self-reports for classification of cannabis exposure and symptoms outcomes. It would not have been feasible, or appropriate, to confirm exposure levels by biological means in the military setting, which would have almost certainly annulled the feasibility of the study, as it would not have been approved as a matter of public policy. Third, we recognise that under-reporting may be an important biasing factor, but its direction would have been mitigated by the same recruitment context and any differential under-reporting by the index group would have reduced the likelihood of detection of group differences. An important strength of the study is its non-clinical military enrolment setting for both groups comparable in all regards including their restricted living circumstances with theoretically no possibility of exposure to cannabis during the 30 days prior to assessments.

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**Table 1**  
Comparison of the two groups for socio-demographic variables, SPQ total and subscale scores.

	Cannabis group (n = 81)	Control group (n = 131)	
Age (mean ± S.D.)	20.7 ± 1.1	21.3 ± 2.2	$t = 2.43$ , $P < 0.05^*$
Education (years) (mean ± S.D.)	7.8 ± 2.6	8.5 ± 3.7	$t = 1.65$ , $P = 0.1$
SPQ-Total Score (mean ± S.D.)	37.3 ± 15.9	16.9 ± 11.1	$t = 10.93$ , $P < 0.01^*$
Positive schizotypy (mean ± S.D.)	24.3 ± 11.6	9.7 ± 7.6	$t = 11.06$ , $P < 0.01^*$
Cognitive perceptual schizotypy (mean ± S.D.)	16.3 ± 7.6	6.9 ± 5.5	$t = 10.33$ , $P < 0.01^*$
Disorganized schizotypy (mean ± S.D.)	8.1 ± 4.4	2.8 ± 2.9	$t = 10.48$ , $P < 0.01^*$
Interpersonal (Negative) schizotypy (mean ± S.D.)	17.5 ± 7.3	9.3 ± 6.2	$t = 8.77$ , $P < 0.01^*$

Independent samples *t*-test (2-tailed) was used for analysis. SPQ: Schizotypal Personality Questionnaire, S.D.: Standard deviation, \*: Statistically significant.

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