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Effects of cannabis and psychosis vulnerability in daily life: an experience sampling test study

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ABSTRACT

Background. Epidemiological findings suggest that cannabis use is a risk factor for the emergence of psychosis, and that the induction of psychotic symptoms in the context of cannabis use may be associated with a pre-existing vulnerability for psychosis. This study investigated in a non-clinical population the interaction between cannabis use and psychosis vulnerability in their effects on psychotic experiences in daily life.

Method. Subjects ($N = 79$) with high or low levels of cannabis use were selected among a sample of 685 undergraduate university students. Experience sampling method (ESM) was used to collect information on substance use and psychotic experiences in daily life. Vulnerability to develop psychosis was measured using a clinical interview assessing the level of psychotic symptoms. Statistical analyses were performed using multilevel linear random regression models.

Results. The acute effects of cannabis are modified by the subject's level of vulnerability for psychosis. Subjects with high vulnerability for psychosis are more likely to report unusual perceptions as well as feelings of thought influence than subjects with low vulnerability for psychosis, and they are less likely to experience enhanced feelings of pleasure associated with cannabis. There is no evidence that use of cannabis is increased following occurrence of psychotic experiences as would be expected by the self-medication model.

Conclusion. Cannabis use interacts with psychosis vulnerability in their effects on experience of psychosis in daily life. The public health impact of the widespread use of cannabis may be considerable.

INTRODUCTION

Cannabis use has dramatically increased in adolescents and young adults over the last decades (Webb *et al.* 1996; Perkonigg *et al.* 1999; Smart & Ogborne, 2000). Since a large percentage of subjects from the general population is now exposed to this drug, even a small increase in the risk of adverse effects may have significant deleterious consequences for the health of the population (Rose, 1992). A stringent evaluation of the impact of cannabis on mental health is therefore warranted (Hall & Solowij, 1997; Johns, 2001).

Cross-sectional epidemiological studies have shown that individuals with psychosis use cannabis more often than other individuals in the general population (Regier *et al.* 1990; Degenhardt & Hall, 2001). This association is apparent in the early course of the disorder (Linszen *et al.* 1994; Hambrecht & Hafner, 1996; Rabinowitz *et al.* 1999), and the deleterious prognostic impact of persistent cannabis use on the course of psychosis has been demonstrated by several studies (Kovasznay *et al.* 1997; Addington & Addington, 1998; Verdoux *et al.* 1999*a*). Converging findings from prospective population-based cohort studies

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indicate that increased levels of cannabis use predate the onset of illness in subjects with psychosis, thereby suggesting that cannabis use may play an aetiological role in the emergence of the disorder (Andreasson *et al*. 1987; Van Os *et al*. 2002; Weiser *et al*. 2002). However, the nature of the link between cannabis use and psychosis is far from clear, and it is difficult to conclude, using currently available evidence, whether cannabis use is a cause rather than a consequence of psychosis. It has been suggested that the induction of psychotic symptoms in the context of cannabis use may be associated with a pre-existing vulnerability for psychosis (McGuire *et al*. 1995). If this were true, one would expect differential effects of cannabis exposure in individuals with and without pre-existing psychosis vulnerability. A limited number of studies have explored the links between psychosis vulnerability and cannabis use in non-clinical populations (Williams *et al*. 1996; Skosnik *et al*. 2001). Although these studies have reported that subjects who used cannabis were more likely to present with higher scores on schizotypal personality questionnaires, they were unable to assess the degree to which cannabis exposure and psychosis vulnerability dynamically interact to produce psychotic symptoms. This limitation is due in part to the fact that the potential association of cannabis use to psychotic symptoms is likely to be restrained to a brief time period (such as a few hours), and therefore difficult to detect using standard prospective assessment techniques over longer time intervals. As a result, studies of the expression of psychosis vulnerability as a function of cannabis use should not only be examined in vulnerable individuals before the full expression of the disorder but also through the application of data collection techniques that are more capable of capturing the relatively brief period of this interaction.

In the current study, we examined the interaction between cannabis use and psychosis vulnerability in a non-clinical population using a prospective experience sampling design. We used the experience sampling method (ESM) to assess onset of psychotic experiences in response to cannabis use in daily life. ESM is a structured diary technique that allows for a series of random momentary assessments in the stream of daily life (Delespaul, 1995; Swendsen & Norman, 1998; Swendsen *et al*. 2000; Myin–Germeys *et al*. 2001). The interpretation of findings obtained using repeated measures prospectively collected in daily life situations is not constrained by the limitations of retrospective evaluations, by evaluations within single environmental contexts, or by assessments using wider time intervals that do not directly capture the temporal relations among these variables, and as such may yield more valid data in the measurement of person–environment interactions.

Vulnerability to develop psychosis was measured using a clinical interview that assessed the level of psychotic symptoms (Verdoux *et al*. 1998*b*; Yung *et al*. 1998; Poulton *et al*. 2000; Van Os *et al*. 2001). The specific objectives of this investigation were: (*i*) to determine if cannabis use is associated with increased occurrence of psychotic experiences; and (*ii*) to examine if the impact of cannabis varies between subjects with and without a psychosis vulnerability.

METHOD

Subjects

Baseline screening

The method has been outlined in detail in previous work (Verdoux *et al*. 2002). Briefly, undergraduate university students in psychology were invited to participate in a study on daily life behaviour and experiences. All subjects gave written informed consent to participate in the investigation. A standardized self-report questionnaire was used to collect information on demographic characteristics, substance use and psychosis proneness. Subjects were asked to specify the frequency of use over the last month (ranging from 1, 'never in the past 30 days' to 7, 'several times a day') concerning diverse substances including cannabis.

Psychosis proneness was assessed using the Community Assessment of Psychic Experiences (CAPE) (Stefanis *et al*. 2001; Verdoux *et al*. 2002), a 42-item (final version) self-report questionnaire derived from the Peters *et al*. Delusions Inventory (PDI-21) (Peters *et al*. 1999). Based upon our previous studies using the PDI-21 in non-clinical populations (Verdoux *et al*. 1998*a*, *b*), we have excluded or reformulated ambiguous

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FIG. 1. Selection procedure of subjects included in the experience sampling (ESM) assessment phase. (THC, Cannabis use; PP, psychosis proneness; M, male; F, female.)

items, and added items exploring hallucinations. Each item explores the frequency of the experience on a four-point scale of 'never', 'sometimes', 'often' and 'nearly always'. In the present study, the 'CAPE-pos' score was defined as the sum of the 20 items assessing positive symptoms (range 0–80). The CAPE also includes 14 items exploring negative symptoms derived the SENS (Selten *et al*. 1998), and eight cognitive symptoms discriminating between depressive and negative symptoms (Kibel *et al*. 1993).

Selection of the ESM group

The baseline sample included all students attending an information meeting on course organization at the beginning of the new university year. Of the 685 subjects invited to participate in the survey, 649 fully completed the self-report screening questionnaire. The sample included 586 females and 63 males, as expected by the skewed gender distribution of students in psychology. The 649 subjects had a mean age of 20 (S.D. = 3) years; most of them ($N = 619$, 95·7%) were single. Nearly one in three subjects ($N = 194$, 29·91%) had used cannabis over the last month (once in the past month, $N = 46$; two or three times/month, $N = 46$; once a week, $N = 26$; two or three times/week, $N = 33$; once a day, $N = 22$; more than once a day, $N = 21$). The median (InterQuartile Range, IQR) CAPE-pos score was 29 (26–33).

A stratified random sample depending on cannabis (tetrahydrocannabinol (THC)) consumption and CAPE-pos scores was selected for the ESM phase of the investigation (Fig. 1). In order to maximize the probability of observing sufficient variance in THC use in daily life, THC consumption over the last month was categorized into 'high THC' (use at least 2/3 times a week) and 'low THC' (no use over the past month). In order to select subjects representative of the overall distribution of psychosis proneness (PP) in the baseline sample, we categorized the CAPE-pos scores into tertile groups to randomly select approximately equal numbers of subjects with 'low PP' (0–27), 'medium PP' (28–33), or 'high PP' (34–76) within each THC group. Since the baseline sample included < 10% males, we randomly selected a higher proportion of male subjects within each THC/PP group in order to include a higher proportion (30%) of males in the ESM sample. Research psychologists blind to the selection criteria telephoned subjects selected according to this stratification method, and those agreeing to participate in the other phases of the study received financial compensation (€75). Of the 88 subjects invited to participate in the ESM phase of the study, seven declined to participate and two were excluded at

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the completion of the study due to deviations from the established procedures. There were no significant differences with regard to demographic and clinical variables between these subjects and those included in the ESM phase.

ESM procedure

ESM is an ambulatory self-assessment method designed to collect information on subjective experience occurring in naturalistic settings (Delespaul, 1995; Swendsen & Norman, 1998; Swendsen *et al*. 2000; Myin-Germeys *et al*. 2001). Responding to randomly programmed signals from portable electronic devices, subjects were asked to describe their present experience by answering a brief questionnaire several times a day over consecutive days. Subjects participated in a training session concerning the ESM procedures in which they were instructed on how to complete each item of the ESM form at each signal of a multi-alarm wristwatch. Subjects were then studied in their daily living environment. Over seven consecutive days, the watch emitted an alarm signal at randomized moments over each of the following time periods: 8.00 to 11.00 a.m.; 11.00 a.m. to 2.00 p.m.; 2.00 to 5.00 p.m.; 5.00 to 8.00 p.m.; and 8.00 to 11.00 p.m.

The ESM form collected information on substance use and psychotic experiences for the period between the current and previous signals (corresponding on average to the previous 3 h). Substance use was explored by the question 'Over the last period, did you use some substances?' (Yes/No), followed by an open question 'if, yes, which substance(s) did you use?'. Psychotic experiences were explored by four questions formulated in order to be as acceptable as possible for repeated measurements during daily activities (Myin-Germeys *et al*. 2001). Subjects were asked to rate on 7-point Likert scales the following questions: (1) 'How would you describe the social ambience and the persons you met?' (1, very friendly/7, very hostile); (2) 'Did you have the impression that something strange happened to you or around you that you could not explain?' (1, nothing strange/7, very strange); (3) 'Did you have unusual sensorial or perceptual experiences?' (1, not at all/7, very often); (4) 'Did you have the impression that your thoughts or emotions could be read or influenced?' (1, not at all/7, very often).

Assessment of psychosis vulnerability using clinical interviews

At the end of the ESM phase, the subjects were interviewed using the Mini-International Neuropsychiatric Interview (MINI, 4.4 version) (Lecrubier *et al*. 1997), by research psychiatrists blind to both the risk status of subjects (psychosis proneness or cannabis use) as well as with regard to their ESM data. The MINI is a short diagnostic interview designed to be used in non-clinical populations that includes a 'psychotic' section with nine items exploring psychotic symptoms. Of these items, two are rated on the basis of clinical observation and seven are questions eliciting answers that are rated as 'bizarre' or 'non-bizarre' psychotic symptoms. Psychosis vulnerability was defined in the present study by the MINI criteria for identifying possible psychotic condition among subjects from the general population (Amorin *et al*. 1998); (*i*) at least one bizarre psychotic symptom over the last month; or (*ii*) at least two non-bizarre psychotic symptoms over the last month.

Statistical method

Statistical analyses were conducted using STATA software (StataCorp, 2001). Multilevel linear random regression models were used to estimate the effect of the independent variable (cannabis use) on the dependent variables (psychotic experiences). ESM data can be conceptualized as two-level (or hierarchical) data, with repeated observations (ESM signal level) being nested within a given person (subject level). Multilevel or hierarchical linear modelling techniques are a variant of the more often used unilevel linear regression analyses. The advantages of these methods are that the dependency of repeated measures within the same person is taken into account, and that it can accommodate non-informative missing values (Golstein, 1987). Since the observations from a given subject that are temporally close may be more similar than those further apart, the variance explained by autocorrelation was taken into account by including the autoregression factor in the model (STATA XTREGAR procedure). 'B' is the fixed regression coefficient of the predictor in the multilevel model and can be interpreted identically to the estimate in a unilevel linear

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regression analysis. All the models were *a priori* adjusted for gender and age. Interactions between independent variables were assessed by the Wald test (Clayton & Hills, 1993).

We first examined: (*i*) the effect of cannabis on psychosis outcome, defined as occurrence of psychotic experiences within the same ESM assessment period; (*ii*) the effect of psychosis vulnerability on psychosis outcome; (*iii*) the interaction between cannabis and psychosis vulnerability on psychosis outcome. In order to characterize the temporal sequence between cannabis and psychotic experiences, we subsequently explored whether cannabis use during a given time period in the day was associated with increased occurrence of psychotic experiences for the next ESM assessment that same day, or conversely, whether the occurrence of psychotic experiences during a given time period was associated with increased cannabis use for the subsequent ESM assessment. Finally, we explored whether use of other illicit drugs may have an impact on the associations between cannabis and psychotic experiences.

RESULTS

Subjects

The 79 subjects (24M/55F) included in the ESM phase had a mean age of 22·1 years (S.D. = 5·3). Sixteen subjects fulfilled MINI criteria for psychosis (at least one bizarre psychotic symptom, or two non-bizarre psychotic symptoms). There was good agreement between risk status identified by the self-report questionnaire and by the structured diagnostic interview. None of the 'low PP' subjects, four (13·3%) of the 'middle PP' subjects, and 12 (52·2%) of the 'high PP' subjects fulfilled MINI criteria for psychosis, respectively.

Of the 41 subjects identified as 'high cannabis users' by the self-report questionnaire, 30 (73·2%) fulfilled MINI criteria of cannabis abuse ($N = 12$) or dependence ($N = 18$) *versus* only one individual (2·6%) among subjects identified as 'low cannabis users'. Only three (3·8%) subjects fulfilled the MINI criteria of other illicit substance abuse/dependence reflecting psychostimulants ($N = 3$) or opiates ($N = 1$); all three subjects also fulfilled MINI criteria for cannabis abuse/dependence. Of the subjects with and without MINI criteria for psychosis, six (37·5%) and 25 (39·7%) fulfilled MINI criteria of cannabis use, respectively.

ESM measures

Out of 2765 ESM assessments, there were 2546 (92·1%) valid (i.e. no missing information) ESM substance reports, including 375 (14·7%) reports of cannabis use by 40 (50·1%) subjects, and seven reports of other drugs use (ecstasy $N = 5$; cocaine $N = 1$; heroine $N = 1$) by four (5·1%) subjects. There were 2510 (90·8%) valid ESM reports for 'perceived hostility' (mean 2·7, S.D. = 1·3), 2548 (92·2%) for 'strange impressions' (mean 1·4, S.D. = 1), 2541 (91·9%) for 'unusual perceptions' (mean 1·2, S.D. = 0·8), and 2549 (92·2%) for 'thought influence' (mean 1·5, S.D. = 1·1). There were no large or significant differences in the frequencies of missing data according to demographic characteristics or risk status of the sample (cannabis use or psychosis proneness).

Effect of cannabis use and psychosis vulnerability on psychosis outcome

The main effects of cannabis use or psychosis vulnerability on the occurrence of psychotic experiences in daily life are presented in Table 1. Regarding the main effect of cannabis use on psychosis outcome, a negative association was found between perceived hostility and cannabis use, indicating that subjects were significantly less likely to report perceived hostility, i.e. they were more likely to find the atmosphere and the people friendly, in the periods marked by cannabis use than without cannabis use. There was a positive association between unusual perceptions and cannabis use, indicating that subjects were significantly more likely to experience unusual perceptions in the periods marked by cannabis use than without cannabis use. Regarding the main effect of psychosis vulnerability on psychosis outcome, subjects with high psychosis vulnerability (MINI criteria for psychosis) were more likely to report perceived hostility, strange impressions or unusual perceptions over the ESM assessment, than subjects without such a vulnerability. In order to assess whether cannabis use and psychosis vulnerability independently predicted the occurrence of psychotic experiences, the two

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Table 1. *Effect of cannabis use and psychosis vulnerability on ESM psychosis outcome*

	Perceived hostility		Strange impressions		Unusual perceptions		Thought influence	
	Yes	No	Yes	No	Yes	No	Yes	No
Cannabis use								
Mean (S.D.)	2·2 (1·1)	2·8 (1·3)	1·6 (1·2)	1·3 (1)	1·2 (0·8)	1·1 (0·8)	1·4 (1)	1·5 (1·2)
B* (95%CI)	−0·42 (−0·55, 0·28)		0·08 (−0·02, 0·19)		0·11 (0·01, 0·20)		0·02 (−0·10, 0·14)	
P	0·0001		0·13		0·03		0·75	
Psychosis vulnerability†								
Mean (S.D.)	3 (1·6)	2·6 (1·2)	1·7 (1·3)	1·3 (0·9)	1·4 (1·2)	1·1 (0·6)	1·7 (1·3)	1·4 (1·1)
B* (95%CI)	0·46 (0·05, 0·86)		0·44 (0·13, 0·75)		0·25 (0·09, 0·41)		0·25 (−0·11, 0·61)	
P	0·03		0·005		0·003		0·18	
Independent effects‡ of								
Cannabis use (B*; 95%CI)	−0·42 (−0·55, −0·28)		0·09 (−0·02, 0·2)		0·11 (0·02, 0·21)		0·02 (−0·10, 0·14)	
P	0·0001		0·10		0·02		0·73	
Psychosis vulnerability (B*; 95%CI)	0·43 (0·02, 0·83)		0·44 (0·14, 0·75)		0·26 (0·10, 0·4)		0·25 (−0·11, 0·62)	
P	0·04		0·004		0·002		0·17	

* Regression coefficient adjusted for age and sex.
† MINI psychosis criteria.
‡ Cannabis use and psychosis vulnerability in the same model.

variables were entered in the same model. The associations between cannabis use and psychosis outcome over the ESM assessment were unchanged after adjustment for psychosis vulnerability. These findings indicate that in daily life, psychosis vulnerability and cannabis use are independent predictors of the occurrence of unusual perceptual experience and of strange impressions (at trend level for cannabis use), and have an opposite and independent impact on perceived hostility feelings.

Interaction between cannabis use and psychosis vulnerability on psychosis outcome

Significant interactions were found between psychosis vulnerability and cannabis use in the association with the daily life experience of perceived hostility ($\chi^2 = 4{\cdot}4$, df = 1, $P = 0{\cdot}04$), unusual perceptions ($\chi^2 = 4{\cdot}4$, df = 1, $P = 0{\cdot}04$), and thought influence ($\chi^2 = 5{\cdot}3$, df = 1, $P = 0{\cdot}02$). No interaction was found between psychosis vulnerability and cannabis use in the association with strange impression ($\chi^2 = 0{\cdot}03$; df = 1, $P = 0{\cdot}86$). These findings indicate that the effects of cannabis on the daily life experience of perceived hostility, unusual perceptions and thought influence are modified by the level of psychosis vulnerability. Thus, we performed stratified analyses in order to assess the associations between cannabis use and psychotic experiences within each level of psychosis vulnerability (Table 2). Subjects with low psychosis vulnerability were more likely to find the atmosphere friendly in periods with cannabis use, but that effect was not found in subjects with high psychosis vulnerability. Conversely, subjects with high psychosis vulnerability were at trend level more likely to experience unusual perceptions or thought influence in periods with cannabis use, however such effects were not found in subjects with low psychosis vulnerability.

Temporality of the associations between cannabis use and psychotic experiences

The previous analyses demonstrate the existence of cross-sectional associations between cannabis use and psychotic experiences in daily life, i.e. subjects with cannabis use within a given 3 h period are more likely to report psychotic experiences within the same ESM assessment period. In order to characterize better the temporal association between cannabis use and psychosis symptom outcome, we explored the relation between psychotic experiences and cannabis use across sequential assessment periods within the same day. The models were adjusted for cannabis use within the current ESM assessment, MINI psychosis criteria, sex and age. The only significant finding was a negative association at trend level between perceived hostility for a given ESM assessment on the day and can-

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Table 2. *Effect of cannabis use on ESM psychosis outcome by level of vulnerability for psychosis*

	Perceived hostility		Unusual perceptions		Thought influence	
	Yes	No	Yes	No	Yes	No
High psychosis vulnerability*						
Cannabis use						
Mean (S.D.)	2·1 (1·2)	3·1 (1·6)	1·6 (1·3)	1·4 (1·1)	1·8 (1·2)	1·7 (1·3)
B† (95%CI)	−0·02 (−0·39, 0·35)		0·34 (−0·02, 0·7)		0·33 (0, 0·7)	
P	0·91		0·07		0·06	
Low psychosis vulnerability*						
Cannabis use						
Mean (S.D.)	2·2 (1·1)	2·7 (1·2)	1·2 (0·7)	1·1 (0·6)	1·4 (1)	1·4 (1·1)
B† (95%CI)	−0·47 (−0·62, −0·33)		0·06, (−0·02, 0·2)		−0·04 (0·16, 0·09)	
P	0·0001		0·12		0·58	

* MINI psychosis criteria.
† Regression coefficient adjusted for age and sex.

nabis use at the previous ESM assessment that same day (B = −0·15, 95%CI −0·31, 0, *P* = 0·07), i.e. subjects were more likely to find the ambiance friendly if they have used cannabis in the previous ESM period. There was no increased risk of other psychotic experiences for a given ESM assessment if cannabis was consumed during the previous assessment period. There was no evidence that cannabis use was increased in the periods following occurrence of any of the psychotic experiences.

Impact of psychostimulant use on the associations between cannabis use and psychotic experiences

Although there were few ESM reports of use of illicit drugs other than cannabis, we explored whether the associations between cannabis and psychotic experiences could be at least in part explained by these additional substances. In models adjusted for age, sex, and psychosis vulnerability, psychostimulant use (ecstasy or cocaine) in daily life was associated with a greater likelihood to report unusual perceptions (B = 1·2, 95%CI 0·5, 1·8, *P* = 0·0001) or thought influence (B = 1·03, 95%CI 0·29, 1·76, *P* = 0·006). The associations between cannabis use and psychotic experiences were not modified after adjustment for psychostimulant use (perceived hostility B = −0·42, 95%CI −0·55, −0·28, *P* = 0·0001; strange impressions B = 0·09, 95%CI −0·02, 0·20, *P* = 0·10; unusual perceptions B = 0·11, 95%CI 0·02, 0·21, *P* = 0·02; thought influence B = 0·02, 95%CI −0·10, 0·14, *P* = 0·76). These findings indicate that the effects of cannabis use on psychosis outcome are not explained by concomitant use of psychostimulants.

DISCUSSION

Our findings demonstrate that cannabis use is a risk factor for the acute occurrence of psychotic experiences in daily life, and that the effects of cannabis are modified by the subject's level of vulnerability for psychosis. Subjects with high psychosis vulnerability are more likely to report unusual perceptions and feelings of thought influence in periods with cannabis use, and less likely to experience the enhanced feelings of pleasure associated with cannabis, than subjects with low vulnerability for psychosis. The effects of cannabis are time-limited and are restricted to the 3 h surrounding its consumption, with no evidence that use of cannabis is increased following occurrence of psychotic-like experiences.

Methodological limitations

We have little motive to suspect a selection bias in this sample, since the rate of participation to the survey was satisfactory, with only 5% incomplete questionnaires at the baseline screening, and < 10% refusals to participation in the ESM phase. Students may differ with regard to several characteristics from subjects from the general population, as for example the prevalence of substance use disorders. However, this does not hamper the generalizability of our

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findings, since it is unlikely that these differences might have modified the direction and the strength of the associations between cannabis use and psychotic experiences.

Psychosis vulnerability was defined using MINI criteria for identifying possible psychotic condition. The MINI psychotic section has been designed to rule out probable psychotic disorders, and for identification of possible psychotic condition in subjects from the general population (Amorin *et al.* 1998). Thus, MINI psychotic items are aimed at identifying occurrence of psychotic experiences, but do not include any assessment of distress or disability, or symptom duration. Validity of self-reported psychotic symptoms in subjects from the general population may be questioned in that over-reporting can occur due to misinterpretation of some questions (Eaton *et al.* 1991; Verdoux *et al.* 1998*a*). However, the clinically-based distinction between 'true' (or clinically relevant) and 'false' psychotic symptoms may be misleading, since these two kinds of experiences or beliefs, which are associated with similar risk factors (Verdoux *et al.* 1998*b*; Van Os *et al.* 2000), more probably lie on a continuum. As there was a phenomenological overlap between the measure of psychosis vulnerability and the outcome measure, we cannot rule out that different findings would have been obtained using a different measure of psychosis vulnerability, as for example familial morbid risk for psychosis. It would be of interest to investigate the association between cannabis use and occurrence of psychotic experiences in high-risk subjects with a familial vulnerability for psychosis.

We cannot exclude under-reporting of cannabis use. However, there is little stigmatization of cannabis use in this kind of population due to the widespread use of this substance, and the prevalence in the whole student population was comparable to that reported in similar samples. Furthermore, this bias, if any, would have attenuated rather than increased the strength of the associations between cannabis and psychosis.

As cannabis users included in the ESM phase were selected on the basis of regular cannabis use over the past month, the MINI interview may have identified psychotic symptoms induced by cannabis intoxication over the same period. Thus, we cannot exclude that the criteria for psychosis vulnerability used in the present study selected subjects with a specific vulnerability for cannabis-induced psychotic symptoms, making the findings at least in part tautological. There is no available evidence supporting or excluding the fact that such a specific vulnerability may exist. As differentiating 'spontaneous' psychotic symptoms from those induced by cannabis in cannabis users raise complex methodological problems, this issue could only be clarified by experimental studies exploring in cannabis non-users the effects of this substance according to level of psychosis vulnerability.

The finding that psychostimulant use is associated with increased occurrence of psychotic experiences, independently from concomitant cannabis use, is in accordance with previous case reports suggesting that such substances may induce psychotic syndromes (McGuire & Fahy, 1991; McGuire *et al.* 1994; Poole & Brabbins, 1996; Vaiva *et al.* 2001). However, this last finding is drawn from a limited number of reports and must be interpreted with caution.

Interpretation of findings

Our study provides direct evidence that cannabis interacts with psychosis vulnerability in the induction of psychotic experiences, supporting the hypothesis that exposure to cannabis may precipitate or exaggerate psychotic experiences in subjects with existing psychosis vulnerability. Concerning the temporal sequence between cannabis use and psychotic experiences, the reports of the present sample are consistent with the estimated duration of the pharmacological effects of cannabis (Ashton, 2001). By contrast, the inability of psychotic symptoms to predict later cannabis use does not support the self-medication model hypothesizing that cannabis is a consequence, rather than a cause, of psychotic symptoms. This lack of prospective relationship is also notable in that previous investigations have demonstrated the capacity of ambulatory monitoring techniques to predict substances consumption, including when self-medication is implicated (Shiffman & Prange, 1988; Swendsen *et al.* 2000). However, as there was a 3 h window between two ESM assessments, we cannot definitely exclude that subjects presenting with psychotic experiences are at increased risk of immediately using cannabis

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when having such experiences. This issue has to be further explored in studies using shorter intervals between ESM assessments.

Another finding was that subjects with psychosis vulnerability do not apparently 'benefit' from certain 'desirable' effects of cannabis, such as more positive or friendly feelings concerning social ambience. Although this finding adds further evidence against the self-medication hypothesis, possible mediating factors, such as the fact that psychosis vulnerable individuals might be more likely to consume cannabis alone than with friends, have to be further explored.

Regarding the interpretation of causality, the present study only explored the interaction between the acute effects of cannabis and the vulnerability for psychosis in the induction of psychotic experiences. As a result, we can only speculate that there is a continuum between the short-term and the long-term effects of cannabis in the interaction with psychosis vulnerability. Cumulative exposure to cannabis may induce persistent psychotic symptoms in vulnerable subjects, and the subsequent course of these symptoms may become, at least in part, independent of the exposure to cannabis.

The brain mechanisms underlying the interaction between psychotic vulnerability and cannabis exposure have to be clarified. THC modifies dopaminergic transmission (Tanda *et al*. 1997), and may thus interact with a pre-existing genetically or environmentally determined vulnerability for dopaminergic system dysregulation. Abnormalities of cannabinoid receptors or endogenous cannabinoid compounds may also be implicated in the pathophysiology of psychosis (Dean *et al*. 2001), and exposure to exogenous cannabinoid drugs may reveal or exacerbate pre-existing dysfunctions of cannabinoid system.

Our findings may have public health implications that merit consideration. If further studies confirm that cannabis is a risk factor for psychosis, its impact on the mental health of the population may not be negligible considering the growing number of adolescents exposed to this risk factor (Rose, 1992). Since adolescence and early adulthood is the peak period for incidence of psychosis, reducing exposure to cannabis in this high-risk age group may contribute to the avoidance of some incident cases of psychosis.

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