Psychological Medicine (2012), **42**, 149–159. © Cambridge University Press 2011
doi:10.1017/S0033291711000973

ORIGINAL ARTICLE

Replication in two independent population-based samples that childhood maltreatment and cannabis use synergistically impact on psychosis risk

M. Konings[1,2], N. Stefanis[3], R. Kuepper[2], R. de Graaf[4], M. ten Have[4], J. van Os[2,5], C. Bakoula[6] and C. Henquet[2,7]*

[1] *Department of Psychiatry and Neuropsychology, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht University Medical Centre, The Netherlands*
[2] *Department of Psychiatry, GGZ Eindhoven, The Netherlands*
[3] *University of Mental Health Research Institute (UMHRI) and Department of Psychiatry, National and Kapodistrian University of Athens, Greece*
[4] *Netherlands Institute of Mental Health and Addiction, Utrecht, The Netherlands*
[5] *Department of Psychosis Studies, Institute of Psychiatry, King's College London, King's Health Partners, London, UK*
[6] *First Department of Pediatrics, Athens University Medical School, 'Aghia Sophia' Children's Hospital, Athens, Greece*
[7] *PsyQ Heerlen, Mondriaan, Zuid-Limburg, The Netherlands*

Background. There may be biological plausibility to the notion that cannabis use and childhood trauma or maltreatment synergistically increase the risk for later development of psychotic symptoms. To replicate and further investigate this issue, prospective data from two independent population-based studies, the Greek National Perinatal Study ($n=1636$) and The Netherlands Mental Health Survey and Incidence Study (NEMESIS) ($n=4842$), were analyzed.

Method. Two different data sets on cannabis use and childhood maltreatment were used. In a large Greek population-based cohort study, data on cannabis use at age 19 years and childhood maltreatment at 7 years were assessed. In addition, psychotic symptoms were assessed using the Community Assessment of Psychic Experiences (CAPE). In NEMESIS, the Composite International Diagnostic Interview (CIDI) was used to assess psychotic symptoms at three different time points along with childhood maltreatment and lifetime cannabis use.

Results. A significant adjusted interaction between childhood maltreatment and later cannabis use was evident in both samples, indicating that the psychosis-inducing effects of cannabis were stronger in individuals exposed to earlier sexual or physical mistreatment [Greek National Perinatal Study: test for interaction $F(2, 1627)=4.18$, $p=0.02$; NEMESIS: test for interaction $\chi^2(3)=8.08$, $p=0.04$].

Conclusions. Cross-sensitivity between childhood maltreatment and cannabis use may exist in pathways that shape the risk for expression of positive psychotic symptoms.

Received 16 September 2010; Revised 13 May 2011; Accepted 17 May 2011; First published online 16 June 2011

Key words: Cannabis, childhood trauma, interaction, psychosis, schizophrenia.

Introduction

Cannabis use increases the risk for psychotic outcomes in a dose–response manner (Henquet *et al*. 2005; Semple *et al*. 2005; Moore *et al*. 2007). Only a minority of cannabis users develops psychosis, suggesting that cannabis may act as a component cause, impacting on psychosis risk in co-dependence with other factors. Gene–environment or environment–environment interactions may underlie this association (Henquet *et al*. 2008), where, for example, individuals at increased genetic risk (a patient or a first-degree relative of a patient) or psychometric risk (the existence of subthreshold psychotic experiences) show increased sensitivity to the psychosis-inducing effects of cannabis (van Os *et al*. 2002; Verdoux *et al*. 2003*b*; D'Souza *et al*. 2005; Henquet *et al*. 2005; GROUP, 2011). Similarly, methodologically strong studies, including prospective studies, have demonstrated associations between childhood trauma, childhood maltreatment and childhood adversity on the one hand and psychotic symptoms/psychotic disorder on the other (Whitfield *et al*. 2005; Wicks *et al*. 2005; Lataster *et al*. 2006; Spauwen *et al*. 2006; Scott *et al*. 2007; Shevlin *et al*. 2007; Kelleher *et al*. 2008; Shevlin *et al*. 2008; Freeman & Fowler, 2009; Read *et al*. 2009; Schreier *et al*. 2009; Elklit & Shevlin, 2010; Fisher *et al*. 2010; Mackie *et al*. 2010; Arseneault *et al*. 2011). The pathway through

* Address for correspondence: Dr C. Henquet, Department of Psychiatry and Neuropsychology, Maastricht University Medical Centre, PO Box 616 (Vijverdal), 6200 MD Maastricht, The Netherlands.
(Email: cecile.henquet@sp.unimaas.nl)

which trauma causes psychosis is the subject of increasing investigation (Read *et al*. 2009). In a prospective study, Cougnard *et al*. (2007) suggested that trauma, urbanicity and cannabis do not reflect the same environmental risk in bringing about abnormal persistence of developmental subclinical expression of psychosis because of the synergistic action of these factors. More recent evidence also indicates that joint exposure to cannabis and childhood trauma occasions more-than-additive effects; Houston *et al*. (2008) showed that early sexual trauma increased the risk for psychosis only in individuals who had been exposed to cannabis before the age of 16 years. In a recent study with adolescents, the same evidence for interaction between childhood trauma and cannabis use and psychotic symptoms was found (Harley *et al*. 2010).

There is some biological evidence to support this association. Both stressful experiences and delta-9-tetrahydrocannabinol (THC, the main psycho-active constituent of cannabis) have been found to increase dopaminergic signaling in the mesolimbic system (Voruganti *et al*. 2001; Soliman *et al*. 2008; Bossong *et al*. 2009) and prefrontal cortex (Stokes *et al*. 2010). Hyperdopaminergia may be associated with psychosis (Kapur, 2003) and the interaction between early life adversity and cannabis may increase risk for psychosis by bringing about enduring sensitization to dopamine agonists (Kuepper *et al*. 2010). Indications for this biological mechanism come from animal and human research showing that early life stress may result in an altered behavioral response to dopamine agonists in adulthood (Engert *et al*. 2009; Rodrigues *et al*. 2011). The aim of the current study was to further investigate the interaction between different kinds of childhood adversities and later cannabis use, assessed at different time points, ensuring independent exposure assessment, and to establish whether early experience of maltreatment moderates the association between later cannabis use and psychotic outcomes in a dose–response fashion, using two longitudinal population-based studies. In addition, correlation between childhood maltreatment and later cannabis use was investigated to establish whether interaction may point to underlying moderation (one factor influencing the effect of the other) or mediation (one factor influencing the occurrence of the other).

Method

Samples

The Greek National Perinatal Study

The Greek National Perinatal Survey is a prospective cohort study of all individuals who were born in Greece between 1 and 30 April 1983 ($n = 11\,048$) (Tzoumaka-Bakoula, 1987; Stefanis *et al*. 2004). Data were collected at three different time points. After birth (T0), data on the children's health and on socio-economic factors of the parents were collected by the obstetrician and/or the midwife who was responsible for or present at the delivery. In 1990, at age 7 years (T1), questionnaires were sent to the primary school teachers who then invited the parents to complete further questionnaires (parental questionnaire). A total of 6594 questionnaires were completed by parents or caregivers (60% response rate). In 2001, when subjects were 19 years old (T2), 4675 questionnaires were sent to the parents and to the subjects (parental and subject self-report questionnaires), which yielded completed questionnaires on 3500 subjects (75% response rate). The Greek study sought and received approval, as required, from both the National Hellenic Research Foundation (NHRF) Institute of Biological Research and Biotechnology (IBRB) and the National Privacy Principles Board. Written parental informed consent was obtained at T0; at T2, subjects also provided written informed consent (Stefanis *et al*. 2004).

The Netherlands Mental Health Survey and Incidence Study (NEMESIS)

NEMESIS is a prospective study on the incidence, course and consequences of psychiatric disorders in the Dutch general population (aged 18–64 years) (Bijl *et al*. 1998*a*, *b*; Cougnard *et al*. 2007). Subjects were interviewed at home at three different time points: baseline (T0, 1996), T1 (1997, assessing the period between T0 and T1) and T2 (1999, assessing the period between T1 and T2). NEMESIS is based on a multistage, stratified, random sampling procedure in 90 municipalities. First, a sample of 90 Dutch municipalities was drawn. Second, a sample of private households within each municipality was selected and members with the most recent birthday within each household who were sufficiently fluent in Dutch were selected (Bijl *et al*. 1998*a*, *b*). A total of 7076 individuals provided written informed consent and were interviewed at T0 (response rate of 70%); 5618 subjects (79% of baseline sample) participated at T1; and 4848 subjects (69% of baseline sample) were assessed at T2. Attrition was largely non-selective (de Graaf *et al*. 2000). Ethical approval was obtained from the ethics committee of the Netherlands Institute of Mental Health and Addiction.

Measures

The Greek National Perinatal Study

Childhood maltreatment at T1. At T1 (at age 7 years), childhood maltreatment was defined using a question

from the parental questionnaire where parents could indicate the frequency of physical punishment in the form of spanking. The question was phrased as follows: 'Quite frequently, parents will resort to "spanking" as a way of "punishing" the child. How often has this happened with this particular child before the child went to school?' Categories were 'never', 'occasionally' or 'often'.

Cannabis use at T2. At T2 (at age 19 years), frequency of lifetime cannabis use was assessed (never, once, 2–4 times, $\geqslant$5 times and regular use). Guided by a previous study using this sample and this measure (Stefanis *et al*. 2004), cannabis use was dichotomized as 'never' *versus* 'at least once'. Lifetime use of other drugs was similarly dichotomized as 'never' *versus* 'at least once'.

Psychosis outcome at T2. At T2, subjects completed the Community Assessment of Psychic Experiences (CAPE), a self-report questionnaire developed to measure lifetime psychotic experiences in the positive, negative and depressive symptom dimensions of psychosis in the general population (Konings *et al*. 2006), based on the Peters *et al*. Delusions Inventory (PDI; Peters *et al*. 1996). The CAPE measures frequency and also distress of experiences on a four-point scale from 'never' (1), 'sometimes' (2), 'often' (3) to 'nearly always' (4). The CAPE has been shown to be reliable (Verdoux *et al*. 2003*a*; Konings *et al*. 2006; Brenner *et al*. 2007) and displays discriminative validity across diagnostic groups and individuals from the general population (Hanssen *et al*. 2003), in addition to concurrent validity with clinical interview measures of psychosis proneness (Konings *et al*. 2006; Konings & Maharajh, 2006). For the current analyses, the total score of the frequency items of positive psychotic experiences was used, expressed in units standard deviation (hereafter: psychosis, a continuous variable).

NEMESIS

Subjects were interviewed using the Composite International Diagnostic Interview (CIDI version 1.1, computerized version). The CIDI is a fully standardized, structured interview developed by the World Health Organization (WHO) to be used by trained health professionals for the assessment of mental disorders according to the definition and diagnostic criteria of the DSM-IV and ICD-10 (Smeets, 1993). It is intended for use in epidemiological studies and clinical trials. CIDI assessment at T0 yielded lifetime ratings; assessments at follow-up were interval ratings referring to the period between T0 and T1 and between T1 and T2 respectively.

Childhood maltreatment at T0. At T0, childhood maltreatment was assessed. Subjects were asked, using a semi-structured self-constructed interview, whether they had experienced any kind of emotional, physical, psychological or sexual abuse before the age of 16 years. This semi-structured interview with four questions was also used in the study by Janssen *et al*. (2004). Subjects were also asked to indicate the frequency of the abuse on a scale from 1 to 6, with 1 = never, 2 = once, 3 = sometimes, 4 = regular, 5 = often and 6 = very often. Consistent with a previous study analyzing the association between maltreatment and psychosis in this sample (Janssen *et al*. 2004), the sum of answers of the four items (scale 1–6) was coded '0' when the score was 4, '1' when the total score was 5–9 (defined as 'mild'), '2' when the total score was 10–14 (defined as 'moderate') and '3' when the total score was 15–24 (defined as 'severe'). A composite score as opposed to more specific forms of trauma was used to increase statistical power required to calculate interaction between trauma and cannabis, and because no specific hypothesis regarding interaction between cannabis and a specific kind of trauma was apparent.

Cannabis use at T0 and follow-up. At T0, lifetime cannabis use was assessed using the CIDI-L section on substance use. Consistent with a previous study using NEMESIS data (van Os *et al*. 2002), T0 lifetime cannabis use was dichotomized as 'never' *versus* 'at least once'. T0 lifetime use of other drugs was similarly categorized as 'never' *versus* 'at least once'. Cannabis use over the follow-up period was combined into a single variable, defined as 'no use' *versus* 'use at least once at T1 or T2', consistent with previous analyses (Henquet *et al*. 2006) and hereafter referred to as 'T1/T2 cannabis use'.

Psychosis outcome over the follow-up period (*T1 and T2*). At T1 and T2, data on the psychosis outcome were collected using the psychosis section (G) of the CIDI. This section consists of 17 items concerning delusions (13 items) and hallucinations (four items), which correspond to classic psychotic symptoms such as persecution, thought interference, auditory hallucinations and passivity phenomena. Each item was scored on a scale from 1 to 6 with 1 = no symptom, 2 = psychotic symptom present but not clinically relevant, 3 = psychotic symptom is the result of drug use, 4 = psychotic symptom is the result of a somatic disease, 5 = true psychotic symptom, and 6 = interviewer is in doubt because there is a plausible explanation for

what seems to be a psychotic symptom. Conforming with previous work, individuals with at least one positive rating on any of the CIDI psychosis items (a score of >1 on at least one item) at either T1 or T2, irrespective of the type of rating (2–6), were considered as having psychotic symptoms at follow-up (hereafter: T1/T2 psychosis) (Henquet *et al*. 2006). The psychosis outcome at T0 was used to assess a possible association between T0 psychotic symptoms and later T1/T2 cannabis use.

Analyses

Analyses were carried out using Stata version 10.0 (Stata Corporation, USA). The dependent variable in the analyses of both the Greek study and NEMESIS was psychosis (Greek study: continuous T2 CAPE psychosis outcome; NEMESIS: dichotomous CIDI T1/T2 psychosis). Independent variables for main and interactive effects were early childhood maltreatment and later cannabis use (Greek study: three-level continuous childhood maltreatment variable at T1 and dichotomous cannabis use at T2; NEMESIS: four-level continuous childhood maltreatment at T0 and dichotomous T1/T2 cannabis use). Associations were tested using regression [Greek data: multiple regression yielding *B* effect size of continuous standardized psychosis outcome variable; NEMESIS: logistic regression of dichotomous psychosis outcome yielding odds ratios (ORs)]. To test whether the association between cannabis use and the psychosis outcome would differ as a function of childhood maltreatment, maltreatment × cannabis interaction terms were fitted. In case of significant interaction, cannabis effect sizes for the different maltreatment levels (Greek data: three levels; NEMESIS: four levels) were calculated by making the appropriate linear combinations derived from the model containing the interaction, using the Stata LINCOM routine. Statistical significance was assessed by the Wald test. In both studies, all analyses were *a priori* adjusted for sex, urbanicity and other drug use. In line with previous studies using NEMESIS data, NEMESIS analyses were additionally adjusted for age (10-year groups), ethnic group (0, subject and both parents born in The Netherlands; 1, other), dichotomous single marital status, experience with discrimination (four levels of severity) and dichotomous unemployment (van Os *et al*. 2002). In addition, for both studies, analyses were carried out investigating whether individuals with a history of childhood maltreatment were more likely to start using cannabis compared to individuals with no childhood maltreatment, using logistic regression analysis of dichotomous cannabis use as the dependent variable. To assess self-medication effects (psychosis causing cannabis use), the association between psychotic symptoms at T0 and cannabis use at follow-up was calculated in NEMESIS only (as no prospective data for this association were available in the Greek study).

Synergism refers to the situation where the combined effect of two or more factors is greater than the sum (additive model) or the product (multiplicative model) of their solitary effects. It has been shown that the true degree to which two factors co-participate in producing an outcome can be estimated from the additive statistical interaction that comes closer to, but is not the same as, biological synergism or the proportion of those exposed to the two factors that have the outcome because of the specific combined action of the two factors (Darroch, 1997; van Os & Sham, 2003). This method is commonly used in psychiatric research, showing synergy between proxy measures of genetic risk on the one hand and traumatic head injury (Corcoran & Malaspina, 2001), cannabis use (van Os *et al*. 2002), prenatal maternal infection (Clarke *et al*. 2009) and urbanicity (van Os & Sham, 2003; van Os *et al*. 2004; Spauwen *et al*. 2006) on the other, and also as between trauma and cannabis use (Harley *et al*. 2010). In line with these previous publications, the additive interaction was calculated between early maltreatment and later cannabis use, in models of psychotic symptoms.

Results

The Greek National Perinatal Study

The final sample consisted of subjects whose parents had completed questionnaires on childhood maltreatment at T1 and who had completed the self-report CAPE questionnaire and questions on cannabis use at T2. This yielded a risk set of 1636 subjects (45% male). At T1, maltreatment was reported to occur 'sometimes' in 940 subjects (58%) and 'often' in 196 (12%) of children. At T2, at age 19 years, 96 of the adolescents (6%) reported cannabis use.

Main effects of childhood maltreatment and cannabis use on psychosis outcome

Exposure to T1 childhood maltreatment, after adjustment, was positively associated with T2 psychosis outcome [adjusted *B* linear trend over three levels = 0.11, 95% confidence interval (CI) 0.03–0.18, $p = 0.006$], with evidence of dose–response (*B* 'sometimes': 0.08, 95% CI −0.3 to 0.18, $p = 0.151$; *B* 'often': $B = 0.23$, 95% CI 0.07–0.39, $p = 0.005$). The association between childhood maltreatment and psychosis outcome remained statistically significant after further

Table 1. *Mean T2 positive symptom scores (CAPE) by T1 childhood maltreatment and T2 cannabis use in the Greek National Perinatal Study*

T1 maltreatment	T2 CAPE score Mean (S.D.)	Unadjusted T2 cannabis effect size			Adjusted T2 cannabis effect size[a]		
		β	95% CI	p	β	95% CI	p
Never							
T2 Cannabis− ($n=481$)	−0.08 (0.93)	0.48	0.05–0.93	0.032	0.55	0.11–0.99	0.015
T2 Cannabis+ ($n=19$)	0.41 (0.85)						
Occasionally							
T2 Cannabis− ($n=874$)	−0.04 (0.99)	0.51	0.27–0.75	<0.001	0.55	0.30–0.81	<0.001
T2 Cannabis+ ($n=66$)	0.47 (0.89)						
Often							
T2 Cannabis− ($n=185$)	0.06 (1.00)	1.34	0.75–1.93	<0.001	1.46	0.87–2.06	<0.001
T2 Cannabis+ ($n=11$)	1.40 (1.05)						

CAPE, Community Assessment of Psychic Experiences; CI, confidence interval; S.D., standard deviation.
[a] Adjusted effects sizes, *a priori* adjusted for sex, urbanicity and other drug use.

adjustment for cannabis use (B linear trend = 0.10, 95% CI 0.01–0.02, $p=0.01$).

T2 cannabis use was associated with T2 psychosis outcome after adjustment ($B=0.65$, 95% CI 0.44–0.86, $p=0.000$). The association between cannabis and psychosis outcome remained significant after further adjustment for childhood maltreatment ($B=0.65$, 95% CI 0.44–0.86, $p=0.000$).

Cannabis use × childhood maltreatment interaction

There was a significant adjusted interaction between T1 three-level continuous childhood maltreatment and T2 dichotomous cannabis use in the model of T2 psychosis [test for interaction: $F(2, 1627)=4.18$, $p=0.016$]. An extra-linear relationship was observed, the psychosis-inducing effects of cannabis being elevated only in those with the highest level of physical punishment ('often') in childhood (Table 1). For these individuals, the adjusted effect of cannabis on psychosis outcome was much stronger ($B=1.46$, 95% CI 0.87–2.06, $p<0.001$), compared to those with physical punishment rated 'occasionally' ($B=0.55$, 95% CI 0.30–0.81, $p<0.001$) or 'never' ($B=0.55$, 95% CI 0.11–0.99, $p=0.015$). There was no evidence that T1 childhood maltreatment was associated with increased risk of T2 cannabis use (OR 1.21, 95% CI 0.85–1.74, $p=0.29$).

NEMESIS

The final sample consisted of subjects who (i) completed the CIDI at T1 and (ii) at T2 and (iii) completed the questions on childhood maltreatment at T0. This yielded a risk set of 4842 subjects (47% male). The mean age at T0 was 41.2 years (S.D. = 11.9). Moderate to severe maltreatment was reported by 8.5% of the sample and 9.5% reported T1/T2 cannabis use.

Main effects of childhood maltreatment and cannabis use on psychosis

Exposure to T0 childhood maltreatment, after adjustment, was positively associated with T1/T2 psychosis outcome (OR linear trend over four levels 1.96, 95% CI 1.73–2.20, $p=0.000$), and this association remained statistically significant after further adjustment for cannabis use (OR 1.93, 95% CI 1.71–2.18, $p=0.000$). T0 cannabis use was associated, after adjustment, with T1/T2 psychosis (OR 1.73, 95% CI 1.24–2.42 $p=0.001$), and this association remained significant after further adjustment for T0 childhood maltreatment (OR 1.45, 95% CI 1.03–2.03, $p=0.034$). T0 childhood maltreatment was associated with a significantly increased risk of T1/T2 cannabis use (OR 1.57, 95% CI 1.33–1.86, $p<0.001$). There was no large or significant association between T0 psychotic symptoms and later cannabis use (T1: OR 1.22, 95% CI 0.84–1.78, $p=0.31$; T2: OR 1.27, 95% CI 0.84–1.93, $p=0.25$).

Cannabis × maltreatment interaction

There was a significant interaction between childhood maltreatment and T1/T2 cannabis use in the model of T1/T2 psychosis [$\chi^2(3)=8.08$, $p=0.04$]. Again, an extra-linear relationship was observed (Table 2). Thus, the effect of cannabis in the group with severe maltreatment exposure was much higher [adjusted risk difference (RD) 30.5%, 95% CI 9.4–51.7, $p=0.005$] than those with moderate (adjusted RD 4.6%, 95% CI −8.9 to 18.1, $p=0.50$) or mild maltreatment exposure (adjusted RD 4.8%, 95% CI −0.7 to 10.3, $p=0.09$).

Table 2. *T1/T2 psychosis outcome by T0 childhood maltreatment and T1/T2 cannabis use in NEMESIS*

T0 maltreatment	No. without T1/T2 psychosis	No. with T1/T2 psychosis	% T1/T2 psychosis	% Unadjusted risk difference (95% CI)	% Adjusted risk difference (95% CI)[a]
Never					
T1/T2 Cannabis− ($n=3017$)	2873	144	4.8	4.4 (0.5 to 8.4)	1.2 (–2.3 to 4.6)
T1/T2 Cannabis+ ($n=217$)	197	20	9.2		
Mild					
T1/T2 Cannabis− ($n=1026$)	945	81	7.9	7.9 (2.2 to 13.6)	4.8 (–0.7 to 10.3)
T1/T2 Cannabis+ ($n=171$)	144	27	15.8		
Moderate					
T1/T2 Cannabis− ($n=239$)	189	50	20.9	9.1 (−4.6 to 22.8)	4.6 (–8.9 to 18.1)
T1/T2 Cannabis+ ($n=50$)	35	15	30.0		
Severe					
T1/T2 Cannabis− ($n=98$)	72	26	26.5	36.0 (14.7–57.2)	30.5 (9.4–51.7)
T1/T2 Cannabis+ ($n=24$)	9	15	62.5		

NEMESIS, The Netherlands Mental Health Survey and Incidence Study; CI, confidence interval.

[a] Adjusted difference in risk, *a priori* adjusted for sex, urbanicity, other drug use, age, ethnicity, urbanicity, single marital status, discrimination and unemployment.

Discussion

This study, using two independent population-based samples, has shown that experience of childhood maltreatment moderates the association between cannabis and psychosis. Even maltreatment sometimes considered less severe, such as spanking, displayed main effects if it was 'often', and interacted with cannabis use. These findings are in accordance with two earlier studies (Houston *et al*. 2008; Harley *et al*. 2010). The current study adds strength to these results because of its longitudinal design and because it has shown that maltreatment moderates the effects of cannabis in a dose-dependent, extra-linear fashion, more severe maltreatment being associated with the greatest effect of cannabis in later expression of psychosis. Furthermore, the findings indicate that self-medication (people using cannabis to self-medicate their psychotic symptoms or the traumatizing effects of early adversities) (Shevlin *et al*. 2009) is unlikely to account for the interaction between childhood maltreatment and cannabis exposure because only in NEMESIS was an association between childhood maltreatment and later cannabis use present, and also in NEMESIS, psychosis at baseline did not predict future cannabis use.

Interaction between environmental factors

There is accumulating evidence that cannabis use and maltreatment in childhood or early adolescence play a role in the pathway to psychotic symptoms. The current results add credence to the suggestion that these environmental factors may act synergistically on the same final common pathway, as evidenced by the more-than-additive interaction. Interpretation of interaction of risk factors is difficult because correlation needs to be taken into account as well, as simulations show that environment–environment interaction (one environmental factor controlling sensitivity to the other) may be confounded by environment–environment correlation (one environmental factor controlling exposure to the other). The current results are inconsistent with respect to correlation between maltreatment and cannabis because only in NEMESIS, and not in the Greek survey, do early maltreatment predisposed individuals start using cannabis later in life. Because this association was only present in NEMESIS and was absent in the Greek survey, it suggests that there may be a small amount of gene–environment correlation in addition to gene–environment interaction. In the earlier study by Harley *et al*. (2010), the possible correlation between early cannabis use and childhood maltreatment was also calculated, showing that subjects who had experienced childhood maltreatment were five times more likely to use cannabis, confirming the hypothesis that environment–environment correlation cannot be ruled out. The occurrence of both interaction and correlation for the same risk factor at the same time was shown before in depression: the genetic liability for depression acts in part by increasing the sensitivity to stressful life events (Kendler *et al*. 1995) but the same genes also influence the probability that individuals will experience stressful life events in the

first place (Kendler & Karkowski-Shuman, 1997). The same may hold for perinatal adversity and risk for schizophrenia: the genes predisposing for schizophrenia may not only render an individual more sensitive to the risk-increasing effect of perinatal adversity but also increase the risk for perinatal adversity itself (Marcelis *et al*. 1998).

Cross-sensitization between maltreatment and cannabis

Exposure to cannabis increases risk for psychosis outcomes in a dose–response fashion (Henquet *et al*. 2005; Zammit *et al*. 2007), suggesting an underlying process of sensitization. Evidence for this hypothesis comes from animal studies: rats that were pretreated with increasing doses of THC showed a greater behavioral response to a THC challenge after a 14-day washout period than did THC-naïve rats (Cadoni *et al*. 2001, 2008). The current finding suggests that the psychosis-inducing effects of cannabis are moderated by early experience of maltreatment, suggesting cross-sensitization between stress and cannabis in shaping risk of psychotic outcomes. Sensitization involving dopaminergic signaling has been proposed as a possible mechanism by which environmental factors such as stress or cannabis use impact on psychosis risk (Collip *et al*. 2008). Animal studies have shown fairly consistently that both stress and THC lead to increased release of dopamine, particularly striatal regions (Abercrombie *et al*. 1989; Tidey & Miczek 1996; French *et al*. 1997; Tanda *et al*. 1997; Cheer *et al*. 2004), although evidence for this in humans is less clear (Bossong *et al*. 2009; Stokes *et al*. 2009; Kuepper *et al*. 2010). Few studies have examined possible cross-sensitization between THC and stress. Rats living under normal conditions (i.e. access to water and food), that were exposed to THC, showed only minor behavioral changes and no change in dopaminergic neurotransmission (MacLean & Littleton, 1977). By contrast, under stressful housing conditions (i.e. isolation and food deprivation), THC administration had marked behavioral consequences. Furthermore, it also resulted in significantly increased dopamine uptake (MacLean & Littleton, 1977). Similarly, Mokler *et al*. (1987) showed that, in rat pups, pretreatment with THC altered the stress-induced dopamine response in the hypothalamus and frontal cortex. Exposure to traumatic experiences during childhood similarly may occasion enduring neurobiological effects with over-reactivity of the hypothalamus and the hypothalamic–pituitary–adrenal (HPA) axis, abnormalities in neurotransmitter systems and structural brain changes (Read *et al*. 2001).

Limitations

Childhood maltreatment, cannabis use and psychosis outcome measures were assessed using different instruments across NEMESIS and the Greek study. Childhood maltreatment in NEMESIS was specified as any kind of emotional, physical, psychological or sexual abuse whereas in the Greek study, childhood maltreatment was limited to physical punishment. The question that arises is what degree of spanking may be considered a traumatic experience. Nevertheless, it has been shown that repeated slapping or spanking is associated with increased lifetime rates of psychiatric disorder (MacMillan *et al*. 1999). Similarly, a longitudinal birth cohort study in New Zealand showed that those exposed to 'harsh or abusive' treatment during childhood were at greater risk of later mental health problems (Fergusson & Lynskey, 1997). In addition, several studies have shown that the same biological mechanism that is thought to underlie the association between trauma and psychosis may also be relevant for moderate levels of stress, as studies suggest that even small stressors occasion increases in dopamine levels in the brain (Davis *et al*. 1991; Glenthoj, 1995; Laruelle, 2000; Myin-Germeys *et al*. 2005). The current study is the first to demonstrate that even non-severe physical mistreatment can interact with cannabis on psychosis risk. No data on continuation of childhood maltreatment were available in the Greek study. However, there is little doubt that these smaller stressors occur more frequently during childhood than major traumatic experiences, and as such could impact on the aforementioned process of sensitization in a cumulative way.

Another limitation is that, in the Greek National Perinatal Study, the measure of childhood maltreatment relied on parental information, which may have resulted in under-reporting and underestimation of effect sizes. Nevertheless, the results were consistent across studies, and the Greek data are unique in that maltreatment was assessed prospectively. The measurement of childhood maltreatment relied on self-report. This type of assessment is acceptable, is associated with a high response rate and yields rates that are comparable to face-to-face interviews (Dill *et al*. 1991; Wurr & Partridge, 1996; Read *et al*. 1997; Janssen *et al*. 2004).

In both studies, psychotic symptoms rather than psychotic illness were assessed in non-clinical samples. Psychotic symptoms are more prevalent in the general population than psychotic illness yet are associated with the same environmental risk factors as psychotic illness (van Os & Kapur 2009; Polanczyk *et al*. 2010) and predict psychotic disorder over time

(Poulton *et al*. 2000; Hanssen *et al*. 2005). The current results confirm earlier findings that both cannabis and adversity not only affect psychotic illness but also impact on the broader extended psychosis phenotype in the general population, which represents behavioral expression of liability to psychotic disorder. The results do not, however, provide information about to what degree the interaction between cannabis and maltreatment contributes to the onset of new psychotic symptoms or to the persistence of existing symptoms (Dominguez *et al*. 2010). A further limitation of the current study is that self-reported cannabis use was not confirmed by urinalysis. Lifetime prevalence of cannabis use in the Greek National Perinatal Study was low (6%) compared to other that in European countries (20–31%) (Wone *et al*. 2004; Kokkevi *et al*. 2006). However, in other Greek studies, comparable prevalence rates of 4–8.6% have been reported (Kokkevi *et al*. 2007; Menti *et al*. 2007). NEMESIS was conducted in The Netherlands, where cannabis is sold and consumed legally in coffee shops, which makes under-reporting unlikely. In addition, false negatives would probably have contributed to a more, rather than a less, conservative result. Cannabis use in the current study was dichotomously defined; however, frequency and duration of use, and also the potency of cannabis consumed, were not specified. Given recent findings that different types of cannabis affect mental health differentially (Di Forti *et al*. 2009; Morgan *et al*. 2010), future research should take into account differences in potency of cannabis in addition to duration of exposure (Henquet *et al*. 2010). The samples included in this study were not sufficiently genetically sensitive to allow examination of underlying gene–environment interaction or gene–environment correlation. It is unlikely, however, that the reported interactions between cannabis and childhood adversities are reducible to gene–environment interplay. If genes predisposing to schizophrenia also contribute to exposure to both adversity and cannabis use, an interaction between these two factors would not be expected.

Appendix

NEMESIS trauma questionnaire

The following questions are about forms of childhood trauma to which you may have been exposed before the age of 16 years.

(1) Do you think that there was any kind of emotional neglect?
(*This means, for example, that people at home didn't listen to you, that your problems were ignored, that you had the feeling of not receiving attention, care or support by the people in your house*)

(2) Do you think there was any kind of psychological abuse?
(*This means, for example, being sworn at, brothers or sisters who were being favored, unjust punishment, blackmail*)

(3) Do you think there was any kind of physical abuse?
(*That is, were you ever beaten, kicked, punched or did you experience any other kind of physical abuse?*)

(4) Were you ever approached sexually against your will?
(*This means: had you ever been touched sexually by anyone against your will or forced to touch anybody; were you ever pressurized into sexual contact against your will?*)

Acknowledgements

C. Henquet received support from the Dutch Medical Research Council (VENI grant). The research leading to these results has received funding from the European Community's Seventh Framework Program under grant agreement HEALTH-F2-2009-241909 (Project EU-GEI).

Declaration of Interest

J. van Os is a speaker or grant holder with Lilly, BMS, Lundbeck, Organon, Janssen-Cilag, GSK, Otsuka and Astra-Zeneca.

References

Abercrombie ED, Keefe KA, DiFrischia DS, Zigmond MJ (1989). Differential effect of stress on in vivo dopamine release in striatum, nucleus accumbens, and medial frontal cortex. *Journal of Neurochemistry* **52**, 1655–1658.

Arseneault L, Cannon M, Fisher HL, Polanczyk G, Moffitt TE, Caspi A (2011). Childhood trauma and children's emerging psychotic symptoms: a genetically sensitive longitudinal cohort study. *American Journal of Psychiatry* **168**, 65–72.

Bijl RV, Ravelli A, van Zessen G (1998*a*). Prevalence of psychiatric disorder in the general population: results of The Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Social Psychiatry and Psychiatric Epidemiology* **33**, 587–595.

Bijl RV, van Zessen G, Ravelli A, de Rijk C, Langendoen Y (1998*b*). The Netherlands Mental Health Survey and Incidence Study (NEMESIS): objectives and design. *Social Psychiatry and Psychiatric Epidemiology* **33**, 581–586.

Bossong MG, van Berckel BN, Boellaard R, Zuurman L, Schuit RC, Windhorst AD, van Gerven JM, Ramsey NF, Lammertsma AA, Kahn RS (2009). Delta 9-tetrahydrocannabinol induces dopamine release in the human striatum. *Neuropsychopharmacology* **34**, 759–766.

Brenner K, Schmitz N, Pawliuk N, Fathalli F, Joober R, Ciampi A, King S (2007). Validation of the English and French versions of the Community Assessment of Psychic Experiences (CAPE) with a Montreal community sample. *Schizophrenia Research* **95**, 86–95.

Cadoni C, Pisanu A, Solinas M, Acquas E, Di Chiara G (2001). Behavioural sensitization after repeated exposure to Delta 9-tetrahydrocannabinol and cross-sensitization with morphine. *Psychopharmacology* (*Berlin*) **158**, 259–266.

Cadoni C, Valentini V, Di Chiara G (2008). Behavioral sensitization to delta 9-tetrahydrocannabinol and cross-sensitization with morphine: differential changes in accumbal shell and core dopamine transmission. *Journal of Neurochemistry* **106**, 1586–1593.

Cheer JF, Wassum KM, Heien ML, Phillips PE, Wightman RM (2004). Cannabinoids enhance subsecond dopamine release in the nucleus accumbens of awake rats. *Journal of Neuroscience* **24**, 4393–4400.

Clarke MC, Tanskanen A, Huttunen M, Whittaker JC, Cannon M (2009). Evidence for an interaction between familial liability and prenatal exposure to infection in the causation of schizophrenia. *American Journal of Psychiatry* **166**, 1025–1030.

Collip D, Myin-Germeys I, van Os J (2008). Does the concept of 'sensitization' provide a plausible mechanism for the putative link between the environment and schizophrenia? *Schizophrenia Bulletin* **34**, 220–225.

Corcoran C, Malaspina D (2001). Traumatic brain injury and schizophrenia. *International Journal of Mental Health* **30**, 17–33.

Cougnard A, Marcelis M, Myin-Germeys I, De Graaf R, Vollebergh W, Krabbendam L, Lieb R, Wittchen HU, Henquet C, Spauwen J, van Os J (2007). Does normal developmental expression of psychosis combine with environmental risk to cause persistence of psychosis? A psychosis proneness-persistence model. *Psychological Medicine* **37**, 513–527.

Darroch J (1997). Biologic synergism and parallelism. *American Journal of Epidemiology* **145**, 661–668.

Davis KL, Kahn RS, Ko G, Davidson M (1991). Dopamine in schizophrenia: a review and reconceptualization. *American Journal of Psychiatry* **148**, 1474–1486.

de Graaf R, Bijl RV, Smit F, Ravelli A, Vollebergh WA (2000). Psychiatric and sociodemographic predictors of attrition in a longitudinal study: The Netherlands Mental Health Survey and Incidence Study (NEMESIS). *American Journal of Epidemiology* **152**, 1039–1047.

Di Forti M, Morgan C, Dazzan P, Pariante C, Mondelli V, Marques TR, Handley R, Luzi S, Russo M, Paparelli A, Butt A, Stilo SA, Wiffen B, Powell J, Murray RM (2009). High-potency cannabis and the risk of psychosis. *British Journal of Psychiatry* **195**, 488–491.

Dill DL, Chu JA, Grob MC, Eisen SV (1991). The reliability of abuse history reports: a comparison of two inquiry formats. *Comprehensive Psychiatry* **32**, 166–169.

Dominguez MD, Wichers M, Lieb R, Wittchen HU, van Os J (2010). Evidence that onset of clinical psychosis is an outcome of progressively more persistent subclinical psychotic experiences: an 8-year cohort study. *Schizophrenia Bulletin* **37**, 84–93.

D'Souza DC, Abi-Saab WM, Madonick S, Forselius-Bielen K, Doersch A, Braley G, Gueorguieva R, Cooper TB, Krystal JH (2005). Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biological Psychiatry* **57**, 594–608.

Elklit A, Shevlin M (2010). Female sexual victimization predicts psychosis: a case-control study based on the Danish Registry System. *Schizophrenia Bulletin*. Published online: 20 May 2010. doi:10.1093/schbul/sbq048.

Engert V, Joober R, Meaney MJ, Hellhammer DH, Pruessner JC (2009). Behavioral response to methylphenidate challenge: influence of early life parental care. *Developmental Psychobiology* **51**, 408–416.

Fergusson DM, Lynskey MT (1997). Physical punishment/maltreatment during childhood and adjustment in young adulthood. *Child Abuse and Neglect* **21**, 617–630.

Fisher HL, Jones PB, Fearon P, Craig TK, Dazzan P, Morgan K, Hutchinson G, Doody GA, McGuffin P, Leff J, Murray RM, Morgan C (2010). The varying impact of type, timing and frequency of exposure to childhood adversity on its association with adult psychotic disorder. *Psychological Medicine* **40**, 1967–1978.

Freeman D, Fowler D (2009). Routes to psychotic symptoms: trauma, anxiety and psychosis-like experiences. *Psychiatry Research* **169**, 107–112.

French ED, Dillon K, Wu X (1997). Cannabinoids excite dopamine neurons in the ventral tegmentum and substantia nigra. *Neuroreport* **8**, 649–652.

Glenthoj BY (1995). The brain dopaminergic system. Pharmacological, behavioural and electrophysiological studies. *Danish Medical Bulletin* **42**, 1–21.

GROUP (2011). Evidence that familial liability for psychosis is expressed as differential sensitivity to cannabis: an analysis of patient-sibling and sibling-control pairs. *Archives of General Psychiatry* **68**, 138–147.

Hanssen M, Bak M, Bijl R, Vollebergh W, van Os J (2005). The incidence and outcome of subclinical psychotic experiences in the general population. *British Journal of Clinical Psychology* **44**, 181–191.

Hanssen M, Peeters F, Krabbendam L, Radstake S, Verdoux H, van Os J (2003). How psychotic are individuals with non-psychotic disorders? *Social Psychiatry and Psychiatric Epidemiology* **38**, 149–154.

Harley M, Kelleher I, Clarke M, Lynch F, Arseneault L, Connor D, Fitzpatrick C, Cannon M (2010). Cannabis use and childhood trauma interact additively to increase the risk of psychotic symptoms in adolescence. *Psychological Medicine* **40**, 1627–1634.

Henquet C, Krabbendam L, de Graaf R, ten Have M, van Os J (2006). Cannabis use and expression of mania in the general population. *Journal of Affective Disorders* **95**, 103–110.

Henquet C, Krabbendam L, Spauwen J, Kaplan C, Lieb R, Wittchen HU, van Os J (2005). Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *British Medical Journal* **330**, 11.

Henquet C, Di Forti M, Morrison P, Kuepper R, Murray RM (2008). Gene-environment interplay between cannabis and psychosis. *Schizophrenia Bulletin* **34**, 1111–1121.

Henquet C, van Os J, Kueper R, Delespaul P, Smits M, Campo JA, Myin-Germeys I (2010). Psychosis reactivity to

cannabis use in daily life: an experience sampling study. *British Journal Psychiatry* **196**, 447–453.

Houston JE, Murphy J, Adamson G, Stringer M, Shevlin M (2008). Childhood sexual abuse, early cannabis use, and psychosis: testing an interaction model based on the National Comorbidity Survey. *Schizophrenia Bulletin* **34**, 580–585.

Janssen I, Krabbendam L, Bak M, Hanssen M, Vollebergh W, de Graaf R, van Os J (2004). Childhood abuse as a risk factor for psychotic experiences. *Acta Psychiatrica Scandinavica* **109**, 38–45.

Kapur S (2003). Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *American Journal of Psychiatry* **160**, 13–23.

Kelleher I, Harley M, Lynch F, Arseneault L, Fitzpatrick C, Cannon M (2008). Associations between childhood trauma, bullying and psychotic symptoms among a school-based adolescent sample. *British Journal of Psychiatry* **193**, 378–382.

Kendler KS, Karkowski-Shuman L (1997). Stressful life events and genetic liability to major depression: genetic control of exposure to the environment? *Psychological Medicine* **27**, 539–547.

Kendler KS, Kessler RC, Walters EE, MacLean C, Neale MC, Heath AC, Eaves LJ (1995). Stressful life events, genetic liability, and onset of an episode of major depression in women. *American Journal of Psychiatry* **152**, 833–842.

Kokkevi A, Fotiou A, Richardson C (2007). Drug use in the general population of Greece over the last 20 years: results from nationwide household surveys. *European Addiction Research* **13**, 167–176.

Kokkevi A, Nic Gabhainn S, Spyropoulou M (2006). Early initiation of cannabis use: a cross-national European perspective. *Journal of Adolescent Health* **39**, 712–719.

Konings M, Bak M, Hanssen M, van Os J, Krabbendam L (2006). Validity and reliability of the CAPE: a self-report instrument for the measurement of psychotic experiences in the general population. *Acta Psychiatrica Scandinavica* **114**, 55–61.

Konings M, Maharajh HD (2006). Cannabis use and mood disorders: patterns of clinical presentations among adolescents in a developing country. *International Journal of Adolescent Medicine and Health* **18**, 221–233.

Kuepper R, Morrison PD, van Os J, Murray RM, Kenis G, Henquet C (2010). Does dopamine mediate the psychosis-inducing effects of cannabis? A review and integration of findings across disciplines. *Schizophrenia Research* **121**, 107–117.

Laruelle M (2000). The role of endogenous sensitization in the pathophysiology of schizophrenia: implications from recent brain imaging studies. *Brain Research Reviews* **31**, 371–384.

Lataster T, van Os J, Drukker M, Henquet C, Feron F, Gunther N, Myin-Germeys I (2006). Childhood victimisation and developmental expression of non-clinical delusional ideation and hallucinatory experiences: victimisation and non-clinical psychotic experiences. *Social Psychiatry and Psychiatric Epidemiology* **41**, 423–428.

Mackie CJ, Castellanos-Ryan N, Conrod PJ (2010). Developmental trajectories of psychotic-like experiences across adolescence: impact of victimization and substance use. *Psychological Medicine* **29**, 1–12.

MacLean KI, Littleton JM (1977). Environmental stress as a factor in the response of rat brain catecholamine metabolism to delta8-tetrahydrocannabinol. *European Journal of Pharmacology* **41**, 171–182.

MacMillan HL, Boyle MH, Wong MY, Duku EK, Fleming JE, Walsh CA (1999). Slapping and spanking in childhood and its association with lifetime prevalence of psychiatric disorders in a general population sample. *Canadian Medical Association Journal* **161**, 805–809.

Marcelis M, van Os J, Sham P, Jones P, Gilvarry C, Cannon M, McKenzie K, Murray R (1998). Obstetric complications and familial morbid risk of psychiatric disorders. *American Journal of Medical Genetics* **81**, 29–36.

Menti E, Lekka NP, Assimakopoulos K, Varvarigou A, Beratis NG, Beratis S (2007). Smoking, psychosocial factors, psychopathologic behavior, and other related conditions in hospitalized youth suicide attempters. *Comprehensive Psychiatry* **48**, 522–528.

Mokler DJ, Robinson SE, Johnson JH, Hong JS, Rosecrans JA (1987). Neonatal administration of delta-9-tetrahydrocannabinol (THC) alters the neurochemical response to stress in the adult Fischer-344 rat. *Neurotoxicology and Teratology* **9**, 321–327.

Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, Lewis G (2007). Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* **370**, 319–328.

Morgan CJ, Schafer G, Freeman TP, Curran HV (2010). Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study: naturalistic study [corrected]. *British Journal of Psychiatry* **197**, 285–290.

Myin-Germeys I, Delespaul P, van Os J (2005). Behavioural sensitization to daily life stress in psychosis. *Psychological Medicine* **35**, 733–741.

Peters ER, Day S, Garety PA (1996). The Peters *et al*. Delusions Inventory (PDI): new forms for the 21-item version. *Schizophrenia Research* **18**, 118.

Polanczyk G, Moffitt TE, Arseneault L, Cannon M, Ambler A, Keefe RS, Houts R, Odgers CL, Caspi A (2010). Etiological and clinical features of childhood psychotic symptoms: results from a birth cohort. *Archives of General Psychiatry* **67**, 328–338.

Poulton R, Caspi A, Moffitt TE, Cannon M, Murray R, Harrington H (2000). Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. *Archives of General Psychiatry* **57**, 1053–1058.

Read J, Bentall RP, Fosse R (2009). Time to abandon the bio-bio-bio model of psychosis: exploring the epigenetic and psychological mechanisms by which adverse life events lead to psychotic symptoms. *Epidemiologia e Psichiatria Sociale* **18**, 299–310.

Read J, Perry BD, Moskowitz A, Connolly J (2001). The contribution of early traumatic events to schizophrenia in

some patients: a traumagenic neurodevelopmental model. *Psychiatry* **64**, 319–345.

Read JP, Stern AL, Wolfe J, Ouimette PC (1997). Use of a screening instrument in women's health care: detecting relationships among victimization history, psychological distress, and medical complaints. *Women and Health* **25**, 1–17.

Rodrigues AJ, Leao P, Carvalho M, Almeida OF, Sousa N (2011). Potential programming of dopaminergic circuits by early life stress. *Psychopharmacology* (*Berlin*) **214**, 107–120.

Schreier A, Wolke D, Thomas K, Horwood J, Hollis C, Gunnell D, Lewis G, Thompson A, Zammit S, Duffy L, Salvi G, Harrison G (2009). Prospective study of peer victimization in childhood and psychotic symptoms in a nonclinical population at age 12 years. *Archives of General Psychiatry* **66**, 527–536.

Scott J, Chant D, Andrews G, Martin G, McGrath J (2007). Association between trauma exposure and delusional experiences in a large community-based sample. *British Journal of Psychiatry* **190**, 339–343.

Semple DM, McIntosh AM, Lawrie SM (2005). Cannabis as a risk factor for psychosis: systematic review. *Journal of Psychopharmacology* **19**, 187–194.

Shevlin M, Dorahy MJ, Adamson G (2007). Trauma and psychosis: an analysis of the National Comorbidity Survey. *American Journal of Psychiatry* **164**, 166–169.

Shevlin M, Houston JE, Dorahy MJ, Adamson G (2008). Cumulative traumas and psychosis: an analysis of the National Comorbidity Survey and the British Psychiatric Morbidity Survey. *Schizophrenia Bulletin* **34**, 193–199.

Shevlin M, Murphy J, Houston JE, Adamson G (2009). Childhood sexual abuse, early cannabis use, and psychosis: testing the effects of different temporal orderings based on the National Comorbidity Survey. *Psychosis: Psychological, Social and Integrative Approaches* **1**, 19–28.

Smeets R (1993). *Composite International Diagnostic Interview* (*CIDI*), *version 1.1*. World Health Organization: Geneva.

Soliman A, O'Driscoll GA, Pruessner J, Holahan AL, Boileau I, Gagnon D, Dagher A (2008). Stress-induced dopamine release in humans at risk of psychosis: a [^{11}C]raclopride PET study. *Neuropsychopharmacology* **33**, 2033–2041.

Spauwen J, Krabbendam L, Lieb R, Wittchen HU, van Os J (2006). Impact of psychological trauma on the development of psychotic symptoms: relationship with psychosis proneness. *British Journal of Psychiatry* **188**, 527–533.

Stefanis NC, Delespaul P, Henquet C, Bakoula C, Stefanis CN, van Os J (2004). Early adolescent cannabis exposure and positive and negative dimensions of psychosis. *Addiction* **99**, 1333–1341.

Stokes PR, Egerton A, Watson B, Reid A, Breen G, Lingford-Hughes A, Nutt DJ, Mehta MA (2010). Significant decreases in frontal and temporal [11C]-raclopride binding after THC challenge. *NeuroImage* **52**, 1521–1527.

Stokes PR, Mehta MA, Curran HV, Breen G, Grasby PM (2009). Can recreational doses of THC produce significant dopamine release in the human striatum? *NeuroImage* **48**, 186–190.

Tanda G, Pontieri FE, Di Chiara G (1997). Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common mu1 opioid receptor mechanism. *Science* **276**, 2048–2050.

Tidey JW, Miczek KA (1996). Social defeat stress selectively alters mesocorticolimbic dopamine release: an in vivo microdialysis study. *Brain Research* **721**, 140–149.

Tzoumaka-Bakoula C (1987). The Greek National Perinatal Survey. I: Design, methodology, case ascertainment. *Paediatric and Perinatal Epidemiology* **1**, 43–55.

van Os J, Bak M, Hanssen M, Bijl RV, de Graaf R, Verdoux H (2002). Cannabis use and psychosis: a longitudinal population-based study. *American Journal of Epidemiology* **156**, 319–327.

van Os J, Kapur S (2009). Schizophrenia. *Lancet* **374**, 635–645.

van Os J, Pedersen CB, Mortensen PB (2004). Confirmation of synergy between urbanicity and familial liability in the causation of psychosis. *American Journal of Psychiatry* **161**, 2312–2314.

van Os J, Sham P (2003). Gene-environment interactions. In *The Epidemiology of Schizophrenia* (ed. R. M. Murray, P. B. Jones, E. Susser, J. van Os and M. Cannon), pp. 235–254. Cambridge University Press: Cambridge.

Verdoux H, Gindre C, Sorbara F, Tournier M, Swendsen JD (2003*a*). Effects of cannabis and psychosis vulnerability in daily life: an experience sampling test study. *Psychological Medicine* **33**, 23–32.

Verdoux H, Sorbara F, Gindre C, Swendsen JD, van Os J (2003*b*). Cannabis use and dimensions of psychosis in a nonclinical population of female subjects. *Schizophrenia Research* **59**, 77–84.

Voruganti LN, Slomka P, Zabel P, Mattar A, Awad AG (2001). Cannabis induced dopamine release: an in-vivo SPECT study. *Psychiatry Research* **107**, 173–177.

Whitfield CL, Dube SR, Felitti VJ, Anda RF (2005). Adverse childhood experiences and hallucinations. *Child Abuse and Neglect* **29**, 797–810.

Wicks S, Hjern A, Gunnell D, Lewis G, Dalman C (2005). Social adversity in childhood and the risk of developing psychosis: a national cohort study. *American Journal of Psychiatry* **162**, 1652–1657.

Wone I, Dia AT, Ndiaye P, Fall IS, Sarr YF (2004). Prevalence of cannabis use among students in Dakar [in French]. *Santé* **14**, 49–53.

Wurr CJ, Partridge IM (1996). The prevalence of a history of childhood sexual abuse in an acute adult inpatient population. *Child Abuse and Neglect* **20**, 867–872.

Zammit S, Spurlock G, Williams H, Norton N, Williams N, O'Donovan MC, Owen MJ (2007). Genotype effects of CHRNA7, CNR1 and COMT in schizophrenia: interactions with tobacco and cannabis use. *British Journal of Psychiatry* **191**, 402–407.