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Early trauma and familial risk in the development of the extended psychosis phenotype in adolescence

Wigman JTW, van Winkel R, Ormel J, Verhulst FC, van Os J, Vollebergh WAM. Early trauma and familial risk in the development of the extended psychosis phenotype in adolescence.

Objective: Both genetic and environmental factors are thought to play a role in the development of psychotic outcomes; however, their respective contributions over time, including possible developmental interactions, remain largely unknown.

Method: The contribution of parental general and psychotic psychopathology as proxies of genetic risk to the development of subthreshold psychosis and its hypothesized interaction with childhood trauma were studied in a general population sample of 2230 adolescents, followed from age 10–16 years. Outcome measures were: i) level of psychotic experiences at age 16 years and ii) persistence of such experiences over the total follow-up period.

Results: General parental psychopathology was associated with CAPE score (OR = 1.08; $P < 0.043$ for highest quintile) and suggestively predicted psychosis persistence (OR, 1.16; $P < 0.072$). Psychotic parental psychopathology was suggestively associated with CAPE score (OR, 2.25; $P < 0.063$ for highest quintile), predicted membership of the Persistent group (OR, 3.72; $P < 0.039$) and suggestively predicted membership of the Decreasing group (OR 2.04; $P < 0.051$). Childhood trauma was associated with CAPE score and with all developmental trajectories of subclinical psychosis. No evidence was found for an interaction between trauma and parental psychopathology.

Conclusion: The development and persistence of subthreshold psychotic symptoms may be conditional on non-interacting proxy genetic and environmental influences.

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Key words: adolescence; psychosis; development; trauma; parental psychopathology

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Significant outcomes

- Developmental patterns of subthreshold psychosis in adolescents are influenced by a familial liability component, using parental psychopathology as a proxy for genetic liability, and by early trauma.
- No interaction was found between familial liability and trauma.
- Adolescents whose parents have experienced psychotic pathology have an almost four times higher risk of experiencing persistent subclinical psychotic experiences.

Limitations

- Some of the developmental trajectories of psychotic experiences represented only small numbers of individuals, thereby limiting statistical power.
- Developmental trajectories were identified with the Thought Problems subscale, which covers a broader range of psychopathology and does not specifically target psychotic symptoms. However, earlier work has shown that the trajectories can be assumed to represent subthreshold psychotic experiences.

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Introduction

Environmental factors may play a role in the development of psychosis outcomes (1). One of the most extensively studied environmental factors in this context is developmental trauma (2). Early trauma has been associated with a later diagnosis of schizophrenia (or other psychotic disorder) (3–8), with transition to clinical psychosis in individuals at ultra-high risk (UHR) of psychosis (9) as well as with psychotic symptoms and subthreshold psychotic experiences (10–14), in line with a dimensional view on psychosis (15, 16). Early trauma has also been associated with longitudinal course of subclinical psychotic experiences, particularly in terms of abnormal persistence (17–20).

Associations between traumatic experiences and psychosis have been found for emotional, physical and sexual abuse as well as for bullying, with more severe (e.g. sexual) trauma displaying the strongest associations (2, 3). Furthermore, associations were usually stronger with increasing frequency and severity of the trauma experienced (2, 10–12) and when there was an intention to harm (10). Recently, it was shown that exposure to early trauma may impact on later psychosis via increased sensitivity to later adversity (21). Analyses attempting to identify the most vulnerable developmental period for the risk-increasing effects of interpersonal traumatic experience remain inconclusive. For example, one study reported the strongest associations for exposure before the age of 12 years (6), others for exposure after age 12 years (3), and yet others did not find evidence for effect modification by age (10, 17).

The heritability of schizophrenia is currently estimated at around 60% (22). In line with this estimate are observations that the risk of developing psychosis for a non-affected monozygotic cotwin of a person with schizophrenia is 50% (23, 24) and that up to 85% of patients with schizophrenia do not have a first- or second-generation relative with psychotic disorder (25). Genes and environment are unlikely to act in isolation (1). Instead, the focus is on ‘the synergistic coparticipation where the effect of one is conditional on the other’ (26–28). Given that not all individuals who experience trauma develop psychosis, genetic liability may play a moderating role (26, 29). One study reported likely interaction between trauma and genetic liability (30), and early adversity was shown to moderate genetic risk of psychosis outcomes in two adoption studies (31, 32). Another recent study (10), however, found no evidence for interaction between genetic liability and specific measures of childhood trauma.

To capture gene–environment interactions, a fruitful paradigm may be to also study psychotic experiences below the threshold of clinical disorder, as subthreshold phenomena may better capture the genetic vulnerability that is shared between the clinical and the non-clinical phenotypes (33, 34) and may be less biased by secondary factors related to the disorder or its treatment (15, 27).

Within the extended phenotype of subthreshold psychotic experiences, persistence of psychotic experiences over time may be of particular relevance, as this excludes more transient phenomena (35) and has been shown to be most predictive of later (psychotic) psychopathology (19, 36). A recent study (20) reported that in female young adult twins from the general population, persistence of psychotic experiences was associated with childhood trauma. Additionally, persistence was subject to substantial genetic influence. Replication of these findings is needed in adolescence, a period of substantial brain plasticity in which interactions between genetic and environmental factors may directly impact on brain development (37, 38), and psychosis proneness has been shown to be particularly dynamic (19, 39).

Aims of the study

To investigate the contribution of genetic liability for psychosis – using parental psychopathology as an indirect measure for liability for psychosis – and its interactive effects with trauma on developmental patterns of subthreshold psychotic experiences in a large sample of adolescents from the general population, prospectively followed from age 10 to 16 years.

Material and methods

Sample

Participants were enrolled in the TRacking Adolescents’ Individual Lives Survey (TRAILS), a prospective cohort study among adolescents in the Dutch general population. TRAILS investigates the development of mental and somatic health from pre-adolescence into adulthood (40, 41). Data of the first three data collection waves were used: T1 (2001–2002), T2 (2003–2004) and T3 (2005–2007). Detailed information on sample and selection procedures can be found elsewhere (40, 41). At T1, 2230 children participated (mean age, 11.1 years; SD = 0.6; 51% girls). At T2, 96% of these participants ($N = 2149$) were reassessed (mean age, 13.6 years; SD = 0.5; 51% girls). T3 was completed with 81% of the original

number of participants ($N = 1816$; mean age, 16.3 years; $SD = 0.7$; 52% girls). Mean number of months was 29.5 between T1 and T2 ($SD = 5.4$; range, 16.7–48.1) and 32.6 ($SD = 7.1$; range 11.0–53.0) between T2 and T3.

Measurements

Developmental courses of subthreshold psychotic experiences. Developmental courses in the present sample were identified in an earlier study using growth mixture modelling (19), revealing four distinct developmental trajectories of Thought Problems, representing different expression of subthreshold psychotic experiences over time, namely a Low ($N = 1804$), Decreasing ($N = 204$), Increasing ($N = 163$) and Persistent ($N = 41$) pattern. These trajectories were based on items of the optimized Thought Problem subscale of the Youth Self-Report (42, 43), assessed three times between age 12 and 16 years, and represent distinct psycho(patho)logical courses in adolescence. Three items of this subscale (on skin picking, storing up many things and sleeping less than other children) were excluded based on their low interitem correlations with the other items (19), leaving nine items in the optimized scale on taking one's mind off things, thinking about self-harm, hearing things that others do not, twitching/nervous behaviour, repeating certain behaviours, seeing things that others do not, displaying behaviour that others find strange, having ideas that others find strange and sleeping problems. The four distinct developmental patterns differed in a dose–response manner in levels of associated psychopathology (anxiety/depression, social and attentional problems, distress secondary to psychotic experiences) and level of parental report of *Thought Problems*, and were differentially associated with several risk factors associated with clinical psychotic disorder (ethnic minority status, cannabis use, developmental problems, stressful life events before age 11 years and trauma between ages 12 and 16 years) (19).

CAPE. The Community Assessment of Psychic Experiences (CAPE) positive experiences subscale (20 self-reported items) was assessed only at T3 and was used to address psychotic experiences (44, 45). The CAPE is based on the Peters et al. Delusions Inventory (46) (PDI), modified to also include hallucinatory experiences. Each item in the CAPE rates two aspects of psychotic experiences: i) frequency and ii) associated distress, both rated on a four-point scale of never/not distressed (1), sometimes/a bit distressed (2), often/quite

distressed (3), and nearly always/very distressed (4). The frequency and distress items together showed good internal consistency (Cronbach's $\alpha = 0.93$). As the CAPE scores were not normally distributed, the scores were divided into quintiles and treated as a categorical outcome variable.

Trauma. Consistent with a previous report (19), occurrence of life events before the age of 11 years was calculated as the sum of the following experiences: moving, hospitalization (of self or family), sickness or death (of self, family or friends), parental divorce or being at least 3 months away from home by parent report (all yes/no), plus a rating of the number of negative events children experienced between i) 0–5 and ii) 6–11 years by self-report (scale, 0–10). Consistent with a previous report (19), trauma between 11 and 16 years was based on T2 and T3 assessments and calculated as the sum score of the following experiences: victim of violence, gossip, bullying or sexual harassment during the last 2 years by self-report (all yes/no) at T2 plus two ratings at T3: a rating of the number of negative events children experienced in the last 2 years by self-report (scale 0–10) and a rating of the stressfulness of the child's life by parent report (scale 0–10). A single trauma measure was constructed from these measures of trauma and life events, by dividing both scores by their quintiles (1–5) and calculating the sum of the two resulting five-point scores, resulting in a 10-point trauma scale.

Parental psychopathology. Parental psychopathology was measured during an interview with one of the parents at T1 with the Brief TRAILS Family History Interview (47). Several syndromes (depression, anxiety, substance use, antisocial behaviour and psychosis) were introduced by a vignette describing the main symptoms and followed by a series of questions to assess lifetime occurrence, professional treatment and medication use. Parental psychopathology was coded as (0) = (probably) not present, (1) = (probably) present, (2) = present with additional treatment/medication (substance use, depression, anxiety and psychosis) or having experienced police arrest (antisocial behaviour). These measures were recorded to two categories of (1) (probably or certainly) present and (0) not present. Two sum scores were calculated: i) general parental psychopathology, by adding the number of all disorders present for both father and mother, and ii) psychotic pathology, by adding the scores of psychotic pathology of both father and mother.

Analyses. First, main effects of both trauma and (general and psychotic) parental psychopathology

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predicting i) CAPE score (in quintiles) and ii) developmental course (class membership) were assessed. Multinomial logistic regression was used to predict i) CAPE score in quintiles with the lowest quintile as reference group and ii) developmental course class membership, taking the Low group as reference group. The possibility that parental psychopathology may serve as a confounding variable in the association between psychotic experiences and trauma was also addressed by i) examining the association between parental psychopathology and trauma and ii) rerunning the analyses with parental (general and psychotic) psychopathology added as a confounder.

Second, interaction effects between (general and psychotic) parental psychopathology and trauma predicting i) CAPE score and ii) class membership were addressed. Interaction effects were tested additively, using binomial regression with identity link function specified, as biological synergism (i.e. the degree of coparticipation of causes in producing some outcome) can be better estimated from the additive statistical interaction than the often used multiplicative statistical interaction (26, 48, 49). All analyses were controlled for sex.

Results

The number and characteristics of participants with available data are presented in Table 1.

Associations with trauma

Trauma significantly predicted CAPE score in the second (OR, 1.08; 95% CI 1.00–1.16; $P < 0.044$), third (OR, 1.21; 95% CI, 1.13, 1.31; $P < 0.001$), fourth (OR, 1.27; 95% CI, 1.17, 1.39; $P < 0.001$) and fifth (OR, 1.39; 95% CI, 1.28, 1.51; $P < 0.001$) quintiles at T3.

Trauma also significantly predicted class membership: it predicted belonging to the Decreasing (OR, 1.32; 95% CI, 1.21, 1.44; $P < 0.001$), Increasing (OR, 1.41; 95% CI, 1.28, 1.55; $P < 0.001$) and Persistent class (OR, 1.85; 95% CI, 1.48, 2.31; $P < 0.001$).

Associations with parental psychopathology

General parental psychopathology significantly predicted the highest quintile of CAPE score at T3 (OR, 1.08; 95% CI, 1.00, 1.17; $P < 0.043$) but not the second (OR, 0.96; 95% CI, 0.88, 1.04; $P < 0.292$), the third (OR, 1.03; 95% CI, 0.95, 1.11; $P < 0.499$) or the fourth quintile (OR, 1.07; 95% CI, 0.98, 1.17; $P < 0.148$). General parental

Table 1. Descriptions of number of participants with available data

General	<i>N</i>	Mean age (SD)	Sex (% girls)
T1	2230	11.1 (0.6)	51
T2	2149	13.6 (0.5)	51
T3	1816	16.3 (0.7)	52
Developmental trajectories of			
Thought problems (T1–T3)	2212		
Low	1804		49
Decreasing	204		51
Increasing	163		66
Persistent	41		68
Instruments			
	<i>N</i>	Mean score (SD)/Percentage	Range
CAPE (T3)	1637	25.56 (4.4)	20–57
Parental general psychopathology (T1)	2165		0–13
No		55%	
Yes (more than one disorder possible)		45%	
Parental psychotic psychopathology (T1)	2163		0–2
No		96%	
Yes		4%	
Trauma (T1–T3)	2118	5.43 (2.1)	2–10

NB developmental trajectories were based on the T1–T3 reports of the Thought Problems subscale of the Youth Self Report.

psychopathology did not predict class membership (OR, 1.05; 95% CI, 0.97–1.14; $P < 0.267$ for the Increasing group; OR, 1.05; 95% CI, 0.96–1.16; $P < 0.232$ for the Decreasing group) although a trend was seen for the Persistent group (OR, 1.16; 95% CI, 0.99–1.35; $P < 0.072$).

Psychotic psychopathology in the parents showed suggestive association with the highest quintile of CAPE score (OR, 2.25; 95% CI, 0.96, 5.27; $P < 0.063$) and significantly predicted membership of the Persistent class (OR, 3.72; 95% CI, 1.07–12.98; $P < 0.039$), suggestively predicted membership of the Decreasing group (OR, 2.04; 95% CI, 0.99–4.17; $P < 0.051$) and did not predict membership of the Increasing class (OR, 0.53; 95% CI, 0.13–2.23; $P < 0.387$).

Trauma was significantly correlated with parental general psychopathology (Spearman's $\rho = 0.25$, $P < 0.001$), and more trauma was reported in those with parental psychotic pathology than in those without ($F_{(1,2060)} = 45.92$, $P < 0.001$); thus, parental psychopathology could be a potential confounder in the association between trauma and psychotic experiences. However, when rerunning the above-described analyses with parental psychopathology (both general and psychotic) added as confounding variable, the association remained significant and patterns similar, for example, the strongest associations for the Persistent class, although the effect sizes were somewhat reduced.

When controlling for general parental psychopathology, trauma significantly predicted CAPE score in the second (OR, 1.09; 95% CI, 1.01, 1.18; $P < 0.001$), third (OR, 1.22; 95% CI, 1.12, 1.32; $P < 0.001$), fourth (OR, 1.28; 95% CI, 1.17, 1.40; $P < 0.001$) and fifth (OR, 1.41; 95% CI, 1.29, 1.53; $P < 0.001$) quintiles at T3. It also still predicted belonging to the Decreasing (OR, 1.32; 95% CI, 1.21, 1.44; $P < 0.001$), the Increasing (OR, 1.41; 95% CI, 1.27, 1.56; $P < 0.001$) and the Persistent (OR, 1.94; 95% CI, 1.27, 2.45; $P < 0.001$) class. When controlling for psychotic parental psychopathology, trauma significantly predicted CAPE score in the second (OR, 1.07; 95% CI, 0.99, 1.15; $P < 0.078$), third (OR, 1.21; 95% CI, 1.12, 1.31; $P < 0.001$), fourth (OR, 1.28; 95% CI, 1.17, 1.40; $P < 0.001$) and fifth (OR, 1.41; 95% CI, 1.30, 1.53; $P < 0.001$) quintiles at T3. It also still predicted belonging to the Decreasing (OR, 1.31; 95% CI, 1.20, 1.42; $P < 0.001$), the Increasing (OR, 1.41; 95% CI, 1.28, 1.56; $P < 0.001$) and the Persistent (OR, 1.93; 95% CI, 1.52, 2.45; $P < 0.001$) class.

Interaction of parental psychopathology and trauma

There were no interactions between general parental psychopathology and trauma in their effect on CAPE score at T3 in the first ($\chi^2(1) = 1.05$; $P = 0.306$), second ($\chi^2(1) = 0.90$; $P = 0.342$), third ($\chi^2(1) = 0.02$; $P = 0.893$), fourth ($\chi^2(1) = 0.15$; $P = 0.703$) or fifth ($\chi^2(1) = 0.15$; $P = 0.697$) quintile, nor were there any interaction effects in predicting belonging to the Low ($\chi^2(1) = 0.03$; $P = 0.864$), Decreasing ($\chi^2(1) = 0.34$; $P = 0.560$), Increasing ($\chi^2(1) = 0.00$; $P = 0.988$) or Persistent group ($\chi^2(1) = 0.30$; $P = 0.586$).

In addition, no interaction effects were found for psychotic parental psychopathology on the one hand and trauma on the other, in their effect on CAPE score at T3 in the first ($\chi^2(1) = 0.05$; $P = 0.822$), second ($\chi^2(1) = 0.51$; $P = 0.476$), third ($\chi^2(1) = 0.48$; $P = 0.491$), fourth ($\chi^2(1) = 1.71$; $P = 0.191$) or fifth ($\chi^2(1) = 1.93$; $P = 0.164$) quintile, nor were there any interaction effects in predicting belonging to the Low ($\chi^2(1) = 0.98$; $P = 0.322$), Decreasing ($\chi^2(1) = 1.46$; $P = 0.227$), Increasing ($\chi^2(1) = 0.60$; $P = 0.439$) or Persistent group ($\chi^2(1) = 0.01$; $P = 0.937$).

Discussion

The present study investigated the familial liability component, as well as its interaction with trauma, to developmental patterns of subthreshold psychosis using parental psychopathology as a proxy for

genetic liability in a large sample of adolescents from the general population, followed up from age 10 to 16 years. Trauma significantly predicted both level of subthreshold psychotic experiences (CAPE score at T3) and different developmental courses of these experiences over time. General parental psychopathology predicted the (highest) level of subthreshold psychotic experiences at age 15–16 years, whereas psychotic parental pathology predicted the persistence of such experiences from age 10 to 16 years. Several trends were seen: general parental psychopathology suggestively predicted persistence of psychotic experiences; psychotic parental psychopathology was suggestively associated with the (highest) level of subthreshold psychotic experiences at age 15–16 years and with decreasing levels of subclinical psychotic experiences over time. No evidence for an interaction between childhood trauma and parental psychopathology as an indicator for liability to psychosis was found.

The finding that trauma is associated with both cross-sectional (2) and longitudinal (19) levels of subthreshold psychotic experiences is in line with a large body of existing literature. The risk-increasing effect of experience of early trauma may operate through cognitive or biological ‘sensitization’, although this remains speculative (28, 50). In the cognitive domain, experience of trauma may lead to negative appraisals and beliefs about the self, resulting in increased vulnerability for negative experiences. Biologically, trauma may lead to changes in the hypothalamic-pituitary-adrenal (HPA) axis and subsequently in the transmission of dopamine, possibly resulting in long-lasting neurodevelopmental alterations (1).

The associations between general parental psychopathology and levels of subthreshold psychotic experiences at age 15–16 years and between psychotic parental pathology and persistence of such experiences are of interest. Inconsistent results have been reported regarding the question whether the predictive value of parental psychopathology for psychopathology in the offspring is disorder-specific (51, 52), (internalizing/externalizing) spectrum-specific (53) or more diffuse (54, 55). The present results suggest that general parental psychopathology is associated with a broader spectrum of mild psychotic symptomatology, as represented by the measurement of (cross-sectional) experiences at age 15–16 years, capturing both transitory and persistent phenomena. These results are in line with recent findings that a substantial proportion of schizophrenia incidence, at the population level, is attributable to non-psychotic disorders in first-degree relatives (56). In addition, psychotic parental psychopathology

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was associated with persistence of subthreshold psychotic experiences, which is more predictive of the development of clinical psychotic states (36); however, it also showed suggestive associations with cross-sectional assessment of psychotic experiences and with decreasing levels of experiences over time. Again, it suggests that parental psychopathology is associated with a broader spectrum of mild psychotic symptomatology. The finding of a familial liability component to subthreshold psychosis is in line with earlier work that found a genetic component to the endorsement of subthreshold psychotic experiences in twins from the general population (34) and the persistence of such experiences in these twin participants (20). Of course, familial liability can be both cultural and genetic. Twin, adoption and extended family studies, however, suggest that the largest part of familial recurrence risks is caused by genetic rather than environmental factors (57).

No interactions were found between childhood trauma and genetic liability, in contrast to a recent study that did report on a significant gene–trauma interaction (58). However, this study used a candidate-gene approach in contrast to the present familial liability approach; furthermore, statistical power was relatively low in the present study and more work is needed in this area. Nevertheless, absence of interaction was also reported by Arseneault *et al.* (2011) who found that the effect of trauma on later experience of psychotic symptoms was independent of genetic liability to psychosis. It is therefore possible that potentially causal effects of childhood trauma act independently of pre-existing genetic liability to increase risk of psychosis and that type, frequency and severity of the trauma are the crucial factors determining risk. Alternatively, methodological issues may have operated to obscure interactions between childhood trauma and genetic liability for psychosis; for example, trauma is usually assessed retrospectively, and although research has shown such reports to be reliable (59, 60), it may nevertheless not always be precise and contribute to low statistical power by increasing random error. Experimental designs using social stress as a proxy measure of sensitisation to ‘intention-to-harm’ experiences may be instrumental to study interactions between traumatic experiences and pre-existing genetic liability, as are prospective studies, although the latter are difficult to conduct (3).

The results of this study should be interpreted in the light of its strengths and limitations. A major strength is that it followed a large adolescent sample from the general population and that it followed the suggestion by Kelleher *et al.* (33) to

include subthreshold psychotic experiences in the study of genetic components to psychosis. Furthermore, the study used both cross-sectional and longitudinal measures of subthreshold psychotic experiences. However, some of the developmental trajectories of psychotic experiences represented only small numbers of individuals, limiting statistical power. Additionally, the *Thought Problems* subscale on which the trajectories are based covers a broader range of psychopathology and does not specifically target psychotic symptoms. However, as earlier work showed (19), the trajectories can be assumed to represent subthreshold psychotic experiences, as suggested by associations with the CAPE frequency scores, a validated instrument for the assessment of psychotic experiences (44), and their associations with several risk factors that are associated with psychosis such as secondary distress, cannabis use and trauma. Measures of familial liability for (psychotic) psychopathology were crude, serving as proxies for genetic liability; further replication using more extensive measures is needed. Furthermore, most data on both trauma and psychotic experiences were collected through self-report in the adolescents. Future research should aim to replicate the findings in larger samples with more statistical power, using multiple informants and assessments that reduce shared method variance between exposures and outcomes, and should especially focus on the possible interaction between trauma and liability to psychosis.

Declaration of interest

J. van Os is/has been an unrestricted research grant holder with, or has received financial compensation as an independent symposium speaker from, Eli Lilly, BMS, Lundbeck, Organon, Janssen-Cilag, GSK, AstraZeneca, Pfizer and Servier, companies that have an interest in the treatment of psychosis. F. C. Verhulst is director at the Department of Child and Adolescent Psychiatry, Erasmus University Medical Center, Sophia Children’s Hospital, which publishes the Dutch translations of the Achenbach System of Empirically Based Assessment and from which he receives remuneration. Dr. R. van Winkel is/has been an unrestricted research grant holder with Eli Lilly and Astra Zeneca. All other authors have nothing to declare.

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