Association between stressful life events and psychotic experiences in adolescence: evidence for gene-environment correlations

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ABSTRACT

Background: Stressful life events (SLEs) are associated with psychotic experiences (PEs). SLEs might act as an environmental risk factor, but may also share a genetic propensity with PEs.
Aims: Estimate the extent to which genetic and environmental factors influence the relationship between SLEs and PEs.
Method: Self and parent-reports from a community-based twin sample (4,830 16-year-old pairs) were analysed using structural equation model-fitting.
Results: SLEs correlated with positive PEs (r = .12-.14, all p<. 001). Modest heritability was shown for PEs (25-57%) and dependent SLEs (32%). Genetic influences explained the majority of the modest covariation between dependent SLEs and paranoia and cognitive disorganisation (bivariate heritabilities = 74-86%). The relationship between SLEs and hallucinations and grandiosity was explained by both genetic and common environmental effects.
Conclusion: Further to dependent SLEs being an environmental risk factor, individuals may have an underlying genetic propensity increasing their risk of dependent SLEs and positive PEs.

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Studies investigating the aetiology of adolescent PEs report modest heritability estimates ranging between 33%- 58%, with the remaining variances attributable to environmental influences[1,2,3]. Population based studies of children and adolescents have found that stress-provoking life experiences such as trauma and victimisation are predictive of PEs[4]. It is thus reasonable to hypothesise that the same may be true for other stressful life events (SLEs).

SLEs are defined as events that require individuals to readjust or experience a change in life[5]. Literature on SLEs has made a distinction between dependent life events which are typically reliant on an individual's behaviour (such as breaking up with a boy/girlfriend), and independent life events where an individual usually has no control on the occurrence of the event (such as death of a friend or relative)[6]. The relationship between SLEs and PEs has been explored within the adult population[7], with estimates of a four fold increased risk of PEs amongst adults who experienced 2 SLEs and a six fold increased risk of PEs amongst adults who reported 6 or more SLEs[8]. Less however is known about the relationship between SLEs and PEs in adolescents. In one study, researchers found that young adolescents who had more than 3 SLEs were more likely to experience PEs[9]. In another, researchers found that over a 3 year period, adolescents with a larger number of SLEs had the highest risk of persistent auditory hallucinations[10]. These observations support the notion that SLEs in general, as well as trauma and victimisation, also contribute towards their risk of PEs.

SLEs are often considered as an index of 'environmental risk', yet their heritability has been estimated on average as 28%[11], 31% for dependent' SLEs and 17% for independent' SLEs[11]. Since dependent SLEs are more influenced by an individual's behaviour than independent SLEs, they may share a genetic propensity with other heritable behaviours such as PEs. It is thus feasible to suggest that SLEs are *not* solely an environmental risk factor for PEs, but rather that SLEs and PEs co-occur due to a shared genetic propensity. This possibility needs investigation because the implications for clinical prevention and intervention strategies differ depending on the degree to which the association is driven by genes and the environment. For example if SLEs co-occur with PEs due to underlying shared genetic influences[11], this would indicate the need for future research prevention and intervention strategies to investigate other heritable correlates of PEs and SLEs such as underlying personality traits[12–14].

The heritability of 'environmental' factors such as SLEs is indicative of gene-environment correlation,

whereby genetic factors may in part influence an individual's exposure to specific environments which in turn results in the environmental factors themselves being partly heritable (a gene-environment correlation (rGE))[15]. Assuming an absence of rGE by investigating 'environmental' risk factors outside of the context of genetic influences may provide a biased estimation of the magnitude of effect an 'environmental' factor has on traits such as PEs. The investigation of rGE contributes to our understanding of 'environmental' risk factors by showing that experiences are in part due to genetic infleunces[16], thus targeting 'environmental' risk factors alone may not be beneficial. In addition to exploring environmental effects directly, this research area demonstrates that focusing attention on underlying pathways through which genetic propensities influence behaviours and traits will also be fruitful.

Although to our knowledge no other studies have investigated the genetic and environmental overlap between SLEs and PEs amongst adolescents, there is some evidence to suggest that there is a modest degree of genetic overlap between SLEs and depression[17]. The considerable comorbidity between PEs and depression[18] lends support to the hypothesis that some degree of genetic overlap will also be observed between SLEs and PEs. This is the first study to utilise data from an adolescent twin sample to investigate the genetic and environmental influences contributing to the associations between SLEs and PEs, as well as the first to assess SLEs in relation to dimensional scales of self-reported PEs. Our aims were twofold, firstly to examine if dependent and independent SLEs are associated with specific PEs in adolescence, and secondly, to estimate the extent to which genetic and environmental factors influence the association between dependent SLEs and PEs.

METHODS

Sample

The Longitudinal Experiences And Perceptions (LEAP) study[19] is part of the Twins Early Development Study (TEDS) which comprises a community sample of monozygotic (MZ) and dizygotic (DZ) twins born in England and Wales between 1994-1996[20].

10,874 families from TEDS were invited to take part in the LEAP study. Parent reports for 5,076 (46.7%) families and twin reports for 5,059 (46.5%) pairs were obtained. Adolescents who participated in the LEAP project had a mean age of 16.32 years. Individuals were excluded (N = 327 families) if they did not provide consent at first contact (when TEDS was started), if they had a severe medical disorder, had experienced severe perinatal complications or if their zygosity was unknown. Exclusions for medical disorders included individuals with cystic fibrosis, cerebral palsy, fragile X syndrome, autism spectrum disorder, and individuals with chromosomal abnormalities such as Downs syndrome.

After exclusions, the sample reported on in this study comprised of 4,830 families (44.84% male, 35.94% MZ twin pairs). Comparing the participating and non-participating samples 94% versus 91% were white Caucasian, respectively, and 16% versus 12% had mothers with one or more A- levels (UK advanced educational qualification) as highest qualification, respectively.

Measures

Stressful life events

We assessed *stressful life events (SLEs)* using 20 items from the Coddington Life Events Record[5], Parents and adolescents were asked to report on SLEs which had occurred in the past year, by responding "*Yes*"(1) or "*No*"(0) to items such as "death of a close friend or relative". Parent and adolescent reports were combined to capture all occurrences of SLEs. This was done using an either/or approach, as simple combination rules work as well, if not better than, more complicated ones [21,22]. A SLE was scored as "*Yes*"(1) if either adolescent or parent had reported it. In line with the literature on SLEs [6,23,24], a distinction was made between *dependent* and *independent* life events. The *dependent stressful life events* scale was the sum of 10 items that assessed life events that occur or are potentially likely to arise as a consequence of one's behaviour (i.e. breaking up with a boy/girlfriend). The *independent stressful life events* scale was the sum of 10 items that assessed life events that occur or are likely to arise independent of one's behaviour (i.e. death of a friend or relative).

Psychotic Experiences

Psychotic experiences (PEs) were assessed using the Specific Psychotic Experiences Questionnaire *(SPEQ)* [19]. SPEQ assesses specific PEs as quantitative traits and includes five self-report subscales: Paranoia (15 items), Hallucinations (9 items), Cognitive Disorganisation (11 items), Grandiosity (8 items), Anhedonia (10 items) and one parent-rated subscale: parent-rated Negative Symptoms (10 items). SPEQ items were derived for the most part from existing scales that were adapted to be suitable for adolescents [19] . The subscales were derived from principal component analysis and show good-to-excellent internal consistency (r = 0.77 – 0.93) and test-retest reliability across a nine-month interval (r = 0.65 – 0.74) in this sample. In terms of validity, expert clinical opinion was obtained on the suitability of each item as a measure of adolescent psychotic experiences to ensure content validity [19]. Furthermore, levels of agreement between scores on SPEQ and the PLIKS (a known measure of psychosis-like symptoms) [25] showed that adolescents who reported "definitely" having any psychosis-like symptoms on the PLIKS had significantly more PEs on all the SPEQ subscales (with exception of Anhedonia) when compared to those who did not report any definite psychosis-like symptoms (all significant at p<.001). Positive and cognitive subscales of PEs showed significant positive correlations with the PLIKS quantitative score (Hallucinations r = .60, Paranoia r = .48, Cognitive Disorganization r

= .41, Grandiosity r = .27, all p<.001) [19,25]. Furthermore, for paranoia, cognitive disorganization, grandiosity and parent-rated negative symptoms SPEQ subscales, individuals who reported a family history of psychosis, as measured by having a first- or second-degree relative with schizophrenia or bipolar disorder, scored higher than individuals without a family history of psychosis (all $P < .05$)[3]. Further information on the measure can be found in Ronald et al., 2014 [19].

Statistical analyses

All analyses were performed using STATA 12 [26] and Open MX [27]. Open MX uses the method of maximum likelihood estimation and is widely used for analysing genetically sensitive data. In line with standard behavioural genetics procedure, the effects of gender and age were regressed out, and analyses were conducted using standardized residuals[28]. Scales of SLEs and PEs were transformed using square root transformation techniques to reduce skewness and kurtosis and to ensure that the assumption of having a normal distribution was met for genetic modelling.

The twin design

The twin design involves monozygotic (MZ) and dizygotic (DZ) twin pairs to determine the extent to which variation in a single phenotype, or covariation between phenotypes are attributable to genetic and environmental influences. Within pair similarities separately for MZ and DZ twin pairs were examined to establish the role of genetic and environmental influences based on the notion that: (1) MZ twin pairs share 100% of their segregating DNA code and DZ twin pairs share on average 50%; (2) MZ and DZ twin pairs share environmental factors common to both twins in the same family ('common environment'); and (3) Exposure to environmental factors which are experienced differently or are specific to the individual ('unique environment') contribute towards differences within twin pairs[16].

Twin analyses

Structural equation modelling techniques were employed to establish the relative importance of additive genetic (A), common environment (C) and unique environmental influences (E) contributing to a phenotype[16]. This technique further extends to bivariate analyses, by exploring the covariation between phenotypes. The relative contributions of genetic and environmental factors to the association between SLEs and PEs are referred to as bivariate heritability ($biva^2$), bivariate common environment ($bivc^2$) and bivariate unique environment ($bive^2$). Estimates of covariance between SLEs and PEs were also used to calculate genetic correlations (r_a), common environment correlations (r_c) and unique environment correlations (r_e), which indexed the extent to which the same set of genes or environments influence both phenotypes[29]. The relative fit of different models were compared to a saturated model (which provides a full description of the data) to establish the best fitting model for the data[30]. Parameter

estimates were then calculated with confidence intervals using the maximum-likelihood method. The best fitting models were selected based on the lowest Akaike's Information Criterion values (AIC). In instances where the AIC values were similar across models (i.e. ACE dropped r_a and ACE dropped r_c), resulting in the relative influences being difficult to distinguish, the full ACE model was chosen as being the most parsimonious.

Gene-environment correlation (rGE)

Further to distinguishing genetic and environmental influences contributing to phenotypic variances and co-variances, the twin design also allows for the investigation of gene-environment correlation (rGE). Univariate twin models were used to test if genetic factors influence an 'environmental' measure such as SLEs. A genetic influence on an 'environmental' measure would be indicative of rGE. Bivariate twin models were also used. Findings suggested rGE if genetic factors mediated the association between environmental measures (e.g. SLEs) and traits (e.g. PEs) [16].

RESULTS

Phenotypic analyses

Analyses of variance illustrated significant mean effects of sex on PEs (Table 1). Females reported higher levels of paranoia, hallucinations and cognitive disorganisation, in contrast to males who reported higher levels of grandiosity, anhedonia and had more parent-rated negative symptoms. Females also reported more dependent SLEs than males. No main effect for gender was present for independent SLEs. A main effect for zygosity was observed for paranoia, hallucinations, cognitive disorganisation, and parent-rated negative symptoms, whereby DZs reported higher levels in comparison to MZs. However, the combined effect of gender and zygosity on the means was small (R^2 = 0.00 - 0.06).

Phenotypic correlations between SLEs and PEs are presented in *Table 2*. Dependent and independent SLEs in adolescence were modestly associated with increased levels of positive PEs: paranoia, hallucinations, cognitive disorganisation, and grandiosity (r = .12-.14, all p<. 001). Correlations with negative PEs were low for dependent SLEs (anhedonia r = -.04, p<. 05, parent-rated negative symptoms r = .04, p<. 05) and independent SLEs (anhedonia r = -.03, p<. 10).

The mean scores on specific PEs scales for individuals with each type of SLE are reported in supplementary tables 2-8. For example, the largest effect sizes for paranoia (Cohen's d=0.48) and anhedonia (Cohen's d=0.34) were observed amongst adolescents who experienced the SLE 'becoming involved in drugs'. Those who reported 'being responsible for a road accident' had the largest effect size for cognitive disorganisation (Cohen's d=0.50). Adolescents who experienced 'suspension from

school/college' had the largest effect size for hallucinations (Cohen's d=0.48), grandiosity (Cohen's d=0.28), and parent-rated negative symptoms (Cohen's d=0.48).

We did not perform behaviour genetic twin analyses on the independent SLEs measure because these events were family-wide and experienced by both twins within a twin pair. It was therefore not possible to partition variance into genetic and environmental influences. Behaviour genetic analysis of anhedonia and parent-rated negative symptoms with dependent SLEs were not assessed, as phenotypic correlations were considered to be too small (r = -0.04 and r = 0.04, respectively) to be decomposed into genetic and environmental influences.

Behaviour genetic analyses

For both PEs and SLEs, univariate twin correlations (*Table 2*) were indicative of genetic influences (A), because MZ correlations were consistently larger than DZ correlations. As the DZ correlations were greater than half of MZ correlations, this suggested some common environmental (C) influence. Furthermore, as MZ correlations were less than unity, this implied a moderate unique environmental effect (E).

Univariate model fitting analyses confirmed initial observations from the twin correlations by showing that genetic (A= 0.25 – 0.57) and unique environmental (E= 0.17- 0.57) factors contributed the most to variances observed in PEs and dependent SLEs (*Table 3*). All univariate ACE models did not provide a significantly worse fit compared to the saturated models. C could be dropped from the models for paranoia, cognitive disorganisation and anhedonia, and explained small amounts of the variance (0.11-0.26) for the remaining scales.

Bivariate cross-twin cross-trait (CTCT) correlations (*Table 2*) provided an insight into the extent to which the covariance between dependent SLEs and PEs was explained by genetic and environmental influences. Collectively, MZ CTCT correlations were larger than DZ CTCT correlations, which is indicative of a genetic influence on the phenotypic associations between SLEs and PE. DZ CTCT correlations were somewhat greater than half of MZ CTCT correlations thus implying a modest common environmental effect. Where MZ CTCT correlations were less than the phenotypic correlations between SLEs and PEs, correlations were suggestive of a unique environmental influence on the covariation.

Results from the bivariate correlated factors solution *(Table 4)* showed that for the association between dependent SLEs and paranoia and cognitive disorganisation scales, the ACE correlated factors solution

with dropped r_c fitted the data best based on the AIC fit index. Analyses demonstrated that the relationship between dependent SLEs and paranoia was almost completely explained by genetic influences (biva^2= 0.86), with the remaining covariance explained by unique environment. Genetic correlation indicated that a moderate degree of genetic influences overlapped between the two phenotypes (r_a =0.33). Furthermore, a small proportion of unique environmental overlap between dependent SLEs and paranoia was also found (r_e=0.04). Analyses investigating the association between dependent SLEs and cognitive disorganisation showed a similar pattern whereby high bivariate heritability was found (biva^2= 0.74). The remaining covariance was explained by unique environment (bive^2 = 0.26). Genetic and unique environment correlations showed that there was modest genetic (r_a =0.21) and unique environmental (r_e =0.05) overlap between dependent SLEs and cognitive disorganisation.

Bivariate analyses further showed that for the association between dependent SLEs and hallucinations and SLEs and grandiosity, the ACE correlated factors solution fitted the data best (*Table 4*). Both genetic and common environmental influences appeared to explain part of the covariance between dependent SLEs and hallucinations, and SLEs and grandiosity (as indicated by the biva^2 and bivc^2 values), and both genetic and common environmental influences had some overlapping influences across SLEs and these PEs (as indicated by the r_a and r_c values) but notably the confidence intervals all overlapped with zero. This meant it was not possible to differentiate the relative role of genetic and common environmental influences on the covariance, suggesting they may both play a role. The association between dependent SLEs and grandiosity was also influenced by a modest degree of unique environmental effects (bive^2 = 0.23).

DISCUSSION

Using a community sample of 16-year-old twins, this study showed that SLEs were correlated with positive PEs (paranoia, hallucinations, cognitive disorganisation, grandiosity) and weakly correlated with negative PEs. Shared genetic influences explained a substantial proportion of the covariation between paranoia, cognitive disorganisation and dependent SLEs. For hallucinations, and grandiosity, both genes and environment explained some of the covariation with SLEs.

Are stressful life events associated with psychotic experiences in adolescence?

In our sample of adolescents, females reported more positive psychotic experiences (with exception of grandiosity) and males reported more grandiosity, anhedonia, and had more parent-rated negative symptoms. These findings are similar to those from other cohort based studies[31], and suggest that there may be continuity in gender differences in PEs amongst the general population and those with

schizophrenia, where males report severer negative symptoms than females[32]

In keeping with previous studies[9,10] having an increased number of dependent and independent SLEs was associated with higher levels of PEs. This association was stronger for positive (paranoia, hallucinations, cognitive disorganisation, grandiosity) than negative PEs. Among SLEs, 'becoming involved in drugs', 'suspension from school/college' and 'being responsible for a road accident' were associated with the highest levels of positive PEs. This specificity of life events is of interest as it is consistent with the association between substance use and PEs amongst adolescents[33]. It also highlights that other correlates such as 'suspension from school' may also be of relevance for understanding positive PEs in adolescence. Collectively, the modest associations reported in this study show that not all adolescents who experience SLEs have PEs, and vice-versa. Experiencing a number of SLEs or specific SLEs such as 'becoming involved in drugs' may therefore be a trigger for having elevated levels of positive PEs.

The association between SLEs and PEs is consistent with cognitive psychological theories of the development of PEs [34], which suggests that exposure to 'triggering events' are particularly damaging in individuals predisposed to disruptions in their cognitive processes. This disruption in cognitive processes in turn may contribute to the risk for PEs. For example, experiencing an increased number of SLEs may lead individuals to develop cognitive biases which result in viewing their environment to be hostile and threatening. This feeling that 'the world is out to get me' may trigger PEs such as paranoia. Our results inform these models by showing that part of the explanation for individuals having SLEs that co-occur with PEs is an underlying genetic propensity for both SLEs and PEs. As we could not examine the temporal relationship between SLEs and PEs in the present study, it is also possible that adolescents with PEs may be more likely to have SLEs. For example, experiencing paranoia may lead to being suspicious of others and result in SLEs such as breaking up with a boyfriend or girlfriend. However, evidence from a number of studies has shown life stress (i.e. SLEs) to be a risk factor for PEs and psychosis amongst adults and adolescents[8,10,35,36], thus supporting the role of SLEs as a catalyst for PEs such as paranoia.

To what extent do genetic and environmental factors influence the associations between stressful life events and psychotic experiences?

In line with previous research amongst adolescents within the general population, dependent SLEs and PEs were in part heritable[37,1,2,11], with the remaining variance largely attributable to unique environmental factors. Our findings extend those of previous studies by showing that the relationship between dependent SLEs and PEs (paranoia and cognitive disorganisation) was almost completely

explained by genetic influences. Our findings also provide support for the concept of gene–environment correlation. This can be in one of three ways: active, evocative or passive[11]. Gene-environment correlations could be 'active', whereby the genetic propensity which leads individuals' to seek out situations resulting in dependent SLEs, is the same genetic influence that increases the risk for PEs (paranoia and cognitive disorganisation). Alternatively, it could be 'evocative', whereby dependent SLEs, which are partly genetically influenced, result in environments or incite behaviours from others, which result in elevated levels of paranoia and cognitive disorganisation. Lastly, gene-environment correlations may be 'passive', whereby genetic factors that increase the likelihood of dependent SLEs on the part of the parent are shared with adolescents through the environments parents raise them in, and in turn are associated with PEs. Focusing on 'environmental' factors in isolation may not therefore be an optimal research strategy. Examining factors through which a genetic vulnerability for having dependent SLEs and PEs are translating into behaviours (e.g., home environment or parenting), may help in identifying underlying mechanisms contributing towards PEs and SLEs amongst adolescents. For the relationship between dependent SLEs and hallucinations, and grandiosity, both genetic and common environmental influences appeared to play a role but their relative role was not clear.

Limitations and strengths

The study's cross-sectional design did not make it possible to test for temporal priority. Therefore, although interpretations were in the direction of SLEs leading to PEs, it is possible that PEs may have altered individuals' behaviours resulting in the SLEs being reported here. Furthermore as participants were asked to report on their PEs from the past month and SLEs from the past 12 months, there may be recall bias, whereby SLEs were more difficult to remember given that the reporting period was more distal. Secondly, we used self-reports of paranoia, hallucinations, cognitive disorganisation, grandiosity and anhedonia. This work could be replicated using in-depth interviews and reports from other informants. Thirdly, we observed modest correlations between SLEs and PEs. Estimates of bivariate heritability and environmental influences reported in this study are therefore explaining small proportion of variance within PEs.

This study also has a number of strengths. It is the first to investigate PEs and SLE amongst a large community sample of adolescents, an age just prior to the modal age of onset of psychotic disorders such as schizophrenia. Furthermore the genetically informative study design allowed the relationships to be decomposed into genetic and environmental influences. In contrast to other studies that have focused on a specific type of psychotic experience (i.e. hallucinations[38]), this study included multiple informant reports of specific PEs, which were measured as dimensions and included both positive and negative

PEs. Adolescents reported on paranoia, hallucinations, cognitive disorganisation, grandiosity, and anhedonia and parents reported on negative symptoms.

Implications

Our work underlines the importance of viewing certain 'environmental' risk factors within the context of genetics. It highlights the importance of not always categorising risk factors as either 'environmental' or 'genetic as they may be a combination of the two.

Our finding of a shared genetic propensity between SLEs and paranoia and cognitive disorganisation, could help research and interventions focus on other types of (heritable) behaviours shown developmentally earlier (i.e. impulsivity), which may jointly increase the risk of PEs and dependent SLEs. Moreover, as DNA does not change throughout the life course, a shared genetic propensity between SLEs and PEs would imply that clinical intervention should take into account the continued vulnerability of individuals with PEs to have dependent SLEs. Further research is needed, but the results are suggestive that focusing on, and dampening the effects of common environmental risks that contribute towards SLEs might decrease the risk of PEs such as hallucinations in vulnerable individuals.

Conclusions

SLEs are associated with positive PEs in adolescence. This is via a shared genetic propensity in addition to the more recognised mechanism of shared environment risk. An accurate understanding of the mechanisms by which risk factors increase the risk for PEs is imperative for improving intervention and prevention strategies in adolescence.

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REFERENCES

1 Hur YM, Cherny SS, Sham PC. Heritability of hallucinations in adolescent twins. *Psychiatry Res* 2012; **199**: 98–101.

2 Ericson M, Tuvblad C, Raine A, Young-Wolff K, Baker L. Heritability and longitudinal stability of schizotypal traits during adolescence. *Behav Genet* 2011; **41**: 499–511.

3 Zavos HMS, Freeman D, Haworth CMA, McGuire P, Plomin R, Cardno AG, *et al.* Consistent etiology of severe, frequent psychotic experiences and milder, less frequent manifestations: a twin study of specific psychotic experiences in adolescence. *JAMA Psychiatry* 2014; **71**: 1049–57.

4 Arseneault L, Cannon M, Fisher HL, Caspi A. Childhood trauma and children's emerging psychotic symptoms: a genetically sensitive longitudinal cohort study. *Am J Psychiatry* 2011; **168**: 65–72.

5 Coddington RD. The significance of life events as etiological factors in the diseases of children: II: a study of a normal population. *J Psychosom Res* 1972; **16**: 205–13.

6 Brown GW, Harris TO. *Social Origins of Depression: A Study of Psychiatric Disorder in Women.* London: Tavistock, 1978.

7 Johns LC, Cannon M, Singleton N, Murray RM, Farrell M, Brugha T, *et al.* Prevalence and correlates of self-reported psychotic symptoms in the British population. *Br J Psychiatry* 2004; **185**: 298–305.

8 Wiles NJ, Zammit S, Bebbington P, Singleton N, Meltzer H, Lewis G. Self-reported psychotic symptoms in the general population: results from the longitudinal study of the British National Psychiatric Morbidity Survey. *Br J Psychiatry* 2006; **188**: 519–26.

9 Bartels-Velthuis AA, van de Willige G, Jenner JA, Wiersma D, van Os J. Auditory hallucinations in childhood: associations with adversity and delusional ideation. *Psychol Med* 2012; **42**: 583–93.

10 Escher S, Romme M, Buiks A, Delespaul P, Van Os J. Independent course of childhood auditory hallucinations: a sequential 3-year follow-up study. *Br J Psychiatry* 2002; **181**: 10–8.

11 Kendler KS, Baker JH. Genetic influences on measures of the environment: a systematic review. *Psychol Med* 2007; **37**: 615–26.

12 Loehlin JC. The differential heritability of personality item clusters. *Behav Genet* 2012; **42**: 500–7.

13 Boyette L, Korver-Nieberg N, Verweij K, Meijer C, Dingemans P, Cahn W, *et al.* Associations between the Five-Factor Model personality traits and psychotic experiences in patients with psychotic disorders, their siblings and controls. *Psychiatry Res* 2013; **210**: 491–7.

14 Kardum I, Krapic N. Personality traits, stressful life events, and coping styles in early adolescence. *Pers Individ Dif* 2001; **30**: 503–15.

15 Jaffee SR, Price TS. Gene-environment correlations: a review of the evidence and implications for prevention of mental illness. *Mol Psychiatry* 2007; **12**: 432–42.

16 Plomin R, Defries J, Knopik VS, Neiderhiser JM. *Behavioral genetics*. (6th edn) Worth Publishers; Basingstoke: W.H. Freeman, 2013.

17 Boardman J, Alexander K, Stallings M. Stressful life events and depression among adolescent twin pairs. *Biodemography Soc Biol* 2011; **57**: 53–66.

18 Varghese D, Scott J, Welham J, Bor W, Najman J, O'Callaghan M, *et al.* Psychotic-like experiences in major depression and anxiety disorders: a population-based survey in young adults. *Schizophr Bull* 2011; **37**: 389–93.

19 Ronald A, Sieradzka D, Cardno A, Haworth C, McGuire P, Freeman D. Characterization of psychotic experiences in adolescence using the Specific Psychotic Experiences Questionnaire (SPEQ): findings from a study of 5000 16-year-olds. *Schizophr Bull* 2014.

20 Haworth CMA, Davis OSP, Plomin R. Twins Early Development Study (TEDS): a genetically sensitive investigation of cognitive and behavioral development from childhood to young adulthood. *Twin Res Hum Genet* 2013; **16**: 117–25.

21 Bird HR, Gould MS, Staghezza B. Aggregating data from multiple informants in child pychiatry epidemiological research. *J Am Acad Child Adolesc Psychol* 1992; **31**: 78–85.

22 Piacentini JC, Cohen P, Cohen J. Combining discrepant diagnostic information from multiple sources: are complex algorithms better than simple ones? *J Abnorm Child Psychol* 1992; **20**: 51–63.

23 Silberg J, Rutter M, Neale M, Eaves L. Genetic moderation of environmental risk for depression and anxiety in adolescent girls. *Br J Psychiatry* 2001; **179**: 116–21.

24 Zavos H, Wong CC, Barclay NL, Keers R, Mill J, Rijsdijk F., *et al.* Anxiety sensitivity in adolescence and young adulthood: The role of stressful life events, 5HTTLPR. *Depress Anxiety* 2012; **29**: 400–8.

25 Zammit S, Owen MJ, Evans J, Heron J, Lewis G. Cannabis, COMT and psychotic experiences. *Br J Psychiatry* 2011; **199**: 380–5.

26 StataCorp. Stata Statistical Software: Release 12. 2011.

27 Boker S, Neale M, Maes H, Wilde M, Spiegel M, Brick T, *et al.* OpenMx: an open source extended structural equation modeling frame- work. *Psychometrika* 2011; **76**: 306–17.

28 Eaves L, Eysenck HJ, Martin NG. *Genes, culture, and personality: an empirical approach*. London: Academic Press., 1989.

29 Neale MC, Cardon LR. *Methodology for Genetic Studies of Twins and Families*. Springer Netherlands, 1992.

30 Rijsdijk F V., Sham PC. Analytic approaches to twin data using structural equation models. *Brief Bioinform* 2002; **3**: 119–33.

31 Wigman JTW, Vollebergh WAM, Raaijmakers QAW, Iedema J, van Dorsselaer S, Ormel J, *et al.* The structure of the extended psychosis phenotype in early adolescence: a cross-sample replication. *Schizophr Bull* 2011; **37**: 850–60.

32 Verdoux H, van Os J. Psychotic symptoms in non-clinical populations and the continuum of psychosis. *Schizophr Res* 2002; **54**: 59–65.

33 Hides L, Lubman DI, Buckby J, Yuen HP, Cosgrave E, Baker K, *et al.* The association between early cannabis use and psychotic-like experiences in a community adolescent sample. *Schizophr Res* 2009; **112**: 130–5.

34 Garety PA, Kuipers E, Fowler D, Freeman D, Bebbington PE. A cognitive model of the positive symptoms of psychosis. *Psychol Med* 2001; **31**: 189–95.

35 Tessner KD, Mittal V, Walker EF. Longitudinal study of stressful life events and daily stressors among adolescents at high risk for psychotic disorders. *Schizophr Bull* 2011; **37**: 432–41.

36 Van Winkel R, Stefanis NC, Myin-Germeys I. Psychosocial stress and psychosis. A review of the neurobiological mechanisms and the evidence for gene-stress interaction. *Schizophr Bull* 2008; **34**: 1095–105.

37 Polanczyk G, Moffitt TE, Arseneault L, Cannon M, Ambler A, Keefe RSE, *et al.* Etiological and clinical features of childhood psychotic symptoms. *Arch Gen Psychiatry* 2010; **67**: 328–38.

38 Shevlin M, Dorahy M, Adamson G. Childhood traumas and hallucinations: an analysis of the National Comorbidity Survey. *J Psychiatr Res* 2007; **41**: 222–8.

Table 1: Means, standard deviations and analysis of variance by sex and zygosity for psychotic experiences and stressful life events

	Total	Male	Female	MZ	DZ	Score	Cronbach	ANOVA				
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	Range	α	Sex	Zyg	Sex*Zyg	R^2	N
Psychotic experiences												
Paranoia	12.17 (10.62)	11.75 (10.42)	12.50 (10.77)	11.79 (10.46)	12.38 (10.70)	0-71	0.93	<0.01	0.01	0.45	0.00	4,777
Hallucinations	4.65 (6.00)	4.30 (5.77)	4.94 (6.16)	4.47 (5.91)	4.76 (6.05)	0-45	0.87	<0.01	0.01	0.53	0.01	4,785
Cognitive disorganisation	3.96 (2.85)	3.40 (2.72)	4.41 (2.87)	3.86 (2.82)	4.01 (2.86)	0-11	0.73	<0.01	0.01	0.66	0.03	4,778
Grandiosity	5.32 (4.42)	5.82 (4.56)	4.91 (4.27)	5.26 (4.35)	5.35 (4.46)	0-24	0.85	<0.01	0.56	0.96	0.01	4.781
Anhedonia	17.33 (7.93)	19.50 (7.98)	15.58 (7.44)	17.07 (7.96)	17.48 (7.91)	0-50	0.78	<0.01	0.44	0.85	0.06	4.781
Parent-rated negative symptoms	2.81 (3.89)	3.17 (4.10)	2.52 (3.69)	2.64 (3.57)	2.91 (4.06)	0-30	0.85	<0.01	0.03	0.02	0.01	4,792
Dependent SLEs	1.68(1.22)	1.66 (1.29)	1.70 (1.16)	1.63 (1.18)	1.71 (1.25)	0-10	0.41	0.01	0.06	0.16	0.00	4,782
Independent SLEs	1.58 (1.40)	1.58 (1.42)	1.57 (1.38)	1.53 (1.35)	1.61 (1.43)	0-10	0.42	0.58	0.06	0.02	0.00	4,784

Note: SLEs= stressful life events. Means and standard deviation reported prior to transformation. MZ=monozygotic, DZ=dizygotic twins. Analyses of variances were performed using one random member of each twin pair. Sex= p-value associated with the effect of sex on the means; Zyg. = p-value associated with the effect of zygosity on the means; Sex*Zyg = p-value associated with the effects of the interaction between sex and zygosity on the means; R^2 = proportion of the total variance explained by sex and zygosity; N= number of 1 randomly selected individual from each twin pair.

Table 2: Phenotypic and twin correlations

Phenotypic correlations				
	Stressful life events			
	Dependent SLE		Independent SLE	
Psychotic experiences	r (CI)	N	r (CI)	N
Paranoia	0.14 (0.11, 0.17)	4,732	0.09 (0.06, 0.12)	4,734
Hallucinations	0.14 (0.11, 0.16)	4,740	0.12(0.09, 0.15)	4,742
Cognitive disorganisation	0.14 (0.11, 0.16)	4,733	0.10 (0.07, 0.13)	4,735
Grandiosity	0.12 (0.10, 0.15)	4,736	0.06 (0.04, 0.09)	4,738
Anhedonia	-0.04 (-0.06, -0.01)	4,736	-0.03 (-0.06, 0.00)	4,738
Parent-rated negative symptoms	0.04 (0.01, 0.06)	4,773	0.08 (0.05, 0.11)	4,775

Twin correlations		
	MZ	DZ
	ICC (CI)	ICC (CI)
Univariate twin correlations		
Psychotic experiences		
Paranoia	0.52 (0.49, 0.56)	0.29 (0.24, 0.34)
Hallucinations	0.43 (0.39, 0.47)	0.31 (0.26, 0.35)
Cognitive disorganisation	0.45 (0.41, 0.48)	0.23 (0.18, 0.28)
Grandiosity	0.48 (0.44, 0.52)	0.28 (0.23, 0.32)
Dependent SLEs	0.52 (0.48, 0.55)	0.34 (0.30, 0.39)
Cross-trait cross-twin correlation		
Psychotic experiences and dependent SLEs		
Paranoia	0.13 (0.08, 0.17)	0.08(0.03, 0.13)
Hallucinations	0.06 (0.02, 0.11)	0.08 (0.03, 0.13)
Cognitive disorganisation	0.07 (0.03, 0.12)	0.04 (-0.02, 0.09)
Grandiosity	0.13 (0.06, 0.15)	0.09 (0.04, 0.14)

Note: Correlations were performed using one random member of each twin pair. Intraclass correlations using transformed standardised age and sex regressed scales. r = Pearson's correlation, ICC= Intraclass correlations, CI= confidence intervals, SLEs = stressful life events

Table 3: Fit statistics and parameter estimates for best fitting univariate models

	Model Fit								
	Compared to saturated model							Parameter estimates: proportion of variance explained by genetic and environmental factors	
	Model	-2LL	df	LRT	Δdf	AIC	p	A (CI)	C (CI)	E (CI)
Paranoia	Sat	23525.91	6527	-	-	-	-	-	-	-
	ACE	23529.68	6533	3.77	6	-8.23	.71	.45 (.34, .54)	.07 (.00, .16)	.48 (.45, .52)
	CE	23598.74	6534	72.83	7	58.83	< 0.1	-	-	-
	*AE	23531.56	6534	5.64	7	-8.36	0.58	.52 (.49, .55)	-	.48 (.45, .51)
Hallucinations	Sat	22198.45	6537	-	-	-	-	-		
	*ACE	22199.49	6543	1.04	6	-10.96	.98	.25 (.14, .37)	.18 (.08, .27)	.57 (.53, .61)
	CE	22219.57	6544	21.12	7	7.12	<0.1	-	-	-
	AE	22211.86	6544	13.41	7	-0.59	0.06	-	-	-
Cognitive disorganisation	Sat	31571.04	6528	-	-	-	-	-	-	-
	ACE	31580.54	6534	9.50	6	-2.50	.15	.44 (.32, .48)	.01 (.00, .11)	.55 (.52, .59)
	CE	31637.18	6535	66.14	7	52.14	<. 01	-	-	-
	*AE	31580.58	6535	9.54	7	-4.46	.22	.45 (.42, .48)	-	.55 (.52, .58)
Grandiosity	Sat	18442.47	6531	-	-	-	-	-	-	-
	*ACE	18447.28	6537	4.81	6	-7.19	.57	.36 (.25, .47)	.11 (.01, .20)	.53 (.50, .57)
	CE	18488.48	6538	41.20	7	27.20	<. 01	-	-	-
	AE	18451.65	6538	4.37	7	-9.63	0.04	-	-	-
Anhedonia	Sat	44554.62	6531	-	-	-	-	-	-	-
	ACE	44560.00	6537	5.39	6	-6.61	.49	.47 (.36, .51)	.01 (.00, .10)	.52 (.49, .56)
	CE	44628.46	6538	73.84	7	59.84	<. 01	-	-	-
	*AE	44560.04	6538	0.04	7	-13.96	0.61	.48 (.45, .51)	-	.52 (.48, .55)
Parent-rated negative symptoms	Sat	17410.51	6512	-	-	-	-	-		
	*ACE	17416.10	6518	5.59	6	-6.41	.47	.57 (.50, .64)	.26 (.19, .32)	.17 (.16, .18)
	CE	17810.00	6519	399.50	7	385.50	<. 01	-	-	-
	AE	17465.87	6519	55.37	7	41.37	<. 01	-	-	-
Dependent SLEs	Sat	10380.92	6500	-	-	-	-	-	-	-
	*ACE	10387.40	6506	6.48	6	-5.52	.37	.32 (.22, .43)	.19 (.10, .28)	.49 (.46, .52)
	CE	10424.84	6507	43.92	7	29.92	<. 01	-	-	-
	AE	10403.11	6507	22.19	7	8.19	<. 01	-	-	-

Note: Sat = saturated model; ACE = full model testing genetic, common and unique environmental influences; AE = model testing genetic and unique environment influences; CE = model testing common and unique environmental influences; 2LL = negative 2 log likelihood; df = degrees of freedom; LRT = likelihood ratio X^2 test comparing the -2LL fit of each model to the -2LL fit of the saturated model; Δdf = difference in degrees of freedom comparing each model to the saturated model; AIC = Akaike's Information Criterion (lower values reflect a better fit); p = *p*-value. *Best fitting model.

Table 4: Fit statistics and parameter estimates for best fitting bivariate models

	Model Fit						
	Compared to saturated model						
	Model	-2LL	df	LRT	Δdf	AIC	P
Paranoia	Saturated	35150.03	13019	-	-	-	-
	ACE	35177.92	13036	27.89	17	-6.11	0.05
	CE	35286.12	13039	136.10	20	96.10	<0.01
	AE	35194.87	13039	44.84	20	4.84	<0.01
	E	36556.99	13042	1406.97	23	1360.97	<0.01
	ACE dropped r_a	35184.18	13037	34.15	18	-3.85	0.01
	*ACE dropped r_c	35178.73	13037	28.70	18	-7.30	0.05
	ACE dropped r_a & r_c	35249.87	13038	99.84	19	61.84	<0.01
Hallucinations	Saturated	35413.78	13029	-	-	-	-
	*ACE	35432.21	13046	18.43	17	-15.57	0.36
	CE	35490.70	13049	76.92	20	36.92	<0.01
	AE	35459.80	13049	46.02	20	6.02	<0.01
	E	36644.26	13052	1230.48	23	1184.48	<0.01
	ACE dropped r_a	35433.93	13047	20.16	18	-15.84	0.32
	ACE dropped r_c	35434.07	13047	20.29	18	-15.71	0.32
	ACE dropped r_a & r_c	35476.56	13048	62.78	19	24.78	<0.01
Cognitive disorganisation	Saturated	35248.56	13020	-	-	-	-
	ACE	35269.67	13037	21.11	17	-12.89	0.22
	CE	35364.09	13040	115.52	20	75.52	<0.01
	AE	35285.26	13040	36.70	20	16.70	0.01
	E	36450.41	13043	1201.85	20	1161.85	<0.01
	ACE dropped r_a	35271.57	13038	23.00	18	-13.00	0.19
	*ACE dropped r_c	35270.06	13038	21.50	18	-14.50	0.25
	ACE dropped r_a & r_c	35295.90	13039	47.34	19	9.34	<0.01
Grandiosity	Saturated	35213.41	13023	-	-	-	-
	*ACE	35232.93	13040	19.52	17	-14.48	0.30
	CE	35311.78	13043	98.36	20	58.36	<0.01
	AE	35252.84	13043	39.42	20	-0.58	<0.01
	E	36501.75	13046	1288.34	20	1248.34	<0.01
	ACE dropped r_a	35235.63	13041	22.21	18	-13.79	0.22
	ACE dropped r_c	35235.38	13041	21.96	18	-14.04	0.23
	ACE dropped r_a & r_c	35298.95	13042	85.54	19	47.54	<0.01

Parameter estimates for best fitting models: proportion of variance explained by genetic and environmental factors

	Dependent Stressful Life Events					
	Biva^2	Bivc^2	Bive^2	r_a	r_c	r_e
Paranoia	0.86 (0.72, 1.00)	-	0.14 (-0.01, 0.30)	0.33 (0.24, 0.45)	-	0.04 (0.01, 0.09)
Hallucinations	0.44 (-0.22, 1.00)	0.39 (-0.18, 0.96)	0.17 (-0.04, 0.37)	0.18 (-0.09, 0.46)	0.25 (-0.12, 0.67)	0.04 (-0.01, 0.08)
Cognitive disorganisation	0.74 (0.52, 0.94)	-	0.26 (0.06, 0.48)	0.21 (0.13, 0.31)	-	0.05 (0.01, 0.10)
Grandiosity	0.42 (-0.09, 0.94)	0.35 (-0.09, 0.79)	0.23 (0.08, 0.38)	0.19 (-0.04, 0.42)	0.38 (-0.12, 1.00)	0.07 (0.02, 0.11)

Note: Sat= saturated model, ACE= full model testing genetic, common and unique environmental influences; AE= model testing genetic and unique environmental influences; CE= model testing common and unique environmental influences; ACE dropped ra= full model testing genetic, common and unique environmental influences with genetic correlation fixed to 0; ACE dropped rc= full model testing genetic, common and unique environmental influences with common environmental correlation fixed to 0; ACE dropped ra and rc= full model testing genetic, common and unique environmental influences with genetic and common environmental correlations fixed to 0; 2LL = negative 2 log likelihood; df = degrees of freedom; LRT = likelihood ratio X^2 test comparing the -2LL fit of each model to the -2LL fit of the saturated model; Δdf = difference in degrees of freedom comparing each model to the saturated model; AIC = Akaike's Information Criterion (lower values reflect a better fit); p = *p*-value. *Best fitting model. Bivariate genetic (Biva^2), common environment (Bivc^2) and unique environment (Bive^2) estimated indicate the proportion of phenotypic correlations explained by genetics, common and unique environment, respectively. Bivariate genetic (^{r}a), common environment (^{r}c) and unique environment (^{r}e) correlations indicate the genetic and environmental overlap between psychotic symptoms and life events. 95% confidence intervals in parentheses.