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Psychotic-like experiences in adolescence occurring in combination or isolation: associations with schizophrenia risk factors

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ABSTRACT

Objectives: Individual adolescent psychotic-like experiences (PLEs) are associated with schizophrenia risk factors. As DSM-5 schizophrenia requires the co-occurrence of at least two psychotic symptoms, we investigated whether co-occurring adolescent PLEs have stronger associations with schizophrenia risk factors, lower quality of life and functioning, and have higher heritability, than individual PLEs.

Methods: Participants were 9,646 16-year-old twins from the longitudinal Twins Early Development Study. We investigated co-occurrence of high questionnaire scores for three PLE combinations: 1) paranoia and hallucinations; 2) paranoia or hallucinations, and cognitive disorganisation; and 3) paranoia or hallucinations, and negative symptoms, and their associations with 11 schizophrenia-relevant variables by regression analysis and structural equation twin modelling.

Results: Against expectation, none of the co-occurring PLEs had the nominally strongest associations significantly more often than individual PLEs. Co-occurring PLEs had the strongest associations with bullying victimization, cannabis use and lower life satisfaction, but individual PLEs had the strongest associations with cognitive function variables. Obstetric complications were most associated with negative symptoms. Secondary analysis revealed that co-occurrence of cognitive disorganisation and negative symptoms had the nominally strongest associations with most schizophrenia-relevant variables overall and relatively high heritability (67%).

Conclusions: Focusing on co-occurrence enhances some individual PLE associations but obscures others. The combination of subjective cognitive disorganisation plus observed negative symptoms showed a broad range of enhanced associations with schizophrenia-relevant variables. Future research could investigate associations with other risk factors, and the ability of this PLE combination to predict onset of schizophrenia.

INTRODUCTION

There is considerable interest in the relationships between psychotic-like experiences (PLEs) in the general population and schizophrenia (1, 2), particularly PLEs occurring during adolescence, just prior to the main period of onset of schizophrenia (3-5). As these PLEs are unaffected by the consequences of having a clinical disorder, such as the effects of antipsychotic medication, they may give new insights into the etiology and conceptualization of schizophrenia, and potentially inform intervention and prevention approaches.

The term psychotic-like experience (PLE) covers a wide range of phenomena occurring in the general population, from mild feelings of suspiciousness or unusual perceptions to positive psychotic symptoms such as delusions and hallucinations (3, 6). Broad definitions also include cognitive disorganisation and negative symptoms (3). PLEs are also known as psychotic experiences (PEs) or psychotic experiences and negative symptoms (PENS) (7), and have some similarities to the concept of schizotypy (8).

Individual PLEs are associated with a range of schizophrenia risk factors (9-14). DSM-5 schizophrenia requires the co-occurrence of at least two psychotic symptoms. Additionally, schizophrenia is associated with lower quality of life and functioning (15, 16), and has higher twin heritability (~80%) (17, 18) than individual general population PLEs (15-59%) (14) as well as higher SNP heritability (7, 19). This raises the question of whether co-occurring PLEs have stronger associations with schizophrenia-relevant variables than their individual component PLEs.

Previous studies have found that, compared to one form of PLE occurring alone, co-occurrence of delusional and hallucinatory PLEs is associated with poorer functioning (20) and greater risk of psychotic disorder (21, 22), family history of psychosis (23), anxiety symptoms, negative symptoms, childhood trauma, persistence of PLEs and clinical need

(24). Co-occurrence of positive PLEs and negative symptoms is associated with poorer functioning (25) and greater risk of schizophrenia (2).

We aimed to investigate, for the first time specifically in adolescents, and broadening the range of prospectively-assessed risk factors compared to previous studies, whether co-occurring PLEs have stronger associations with a) schizophrenia risk factors, b) lower quality of life and functioning, and c) have higher twin heritability than individual PLEs.

METHODS

Participants

Participants were members of the Longitudinal Experiences And Perceptions (LEAP) study (3), which is part of the Twins Early Development Study (TEDS), a general population sample of monozygotic (MZ) and dizygotic (DZ) twins born in England and Wales in 1994-1996 and assessed longitudinally across childhood and adolescence (26). TEDS and LEAP have full ethical approval and written informed consent was obtained after the procedures had been fully explained at each point of contact.

In total 10,874 families from TEDS were invited to take part in LEAP. Parent reports for 5,076 (46.7%) families and twin reports for 5,059 (46.5%) pairs were obtained (3). Adolescents involved in the LEAP project had a mean age of 16.3 years (SD 0.68) (3). Individuals were excluded if they did not provide consent at first contact (when TEDS was started) or for this study, had severe perinatal complications, or a severe medical disorder. After exclusions, the sample comprised 9,646 individual twins with data on multiple PLEs.

Psychotic-like Experiences

PLEs were assessed using the Specific Psychotic Experiences Questionnaire (SPEQ) at age 16 years (3). SPEQ includes self-report subscales for paranoia, hallucinations and cognitive disorganisation, and a parent-rated subscale for negative symptoms. Each

subscale includes multiple items relating to the relevant concept (see supplementary methods for further information).

The primary analysis focused on the following PLE combinations: 1) paranoia and hallucinations; 2) paranoia or hallucinations, and cognitive disorganisation; and 3) paranoia or hallucinations, and negative symptoms.

We defined PLEs as binary variables, being counted as present if their score was over the threshold closest to the top 15%, and co-occurring phenotypes as over this threshold for multiple PLEs, e.g. for both paranoia and hallucinations. This gave at least 500 individual twins in each PLE group, and in previous analysis of this sample the heritabilities at this threshold were not significantly different from those at more extreme thresholds (14).

Schizophrenia Risk Factors

Schizophrenia risk factors were as follows: family history (27) measured as presence/absence of schizophrenia in a first or second degree relative (14) and validated with the schizophrenia polygenic risk score; older paternal age (28); ethnic minority status (29); obstetric complications (30); slower developmental milestones (31) measured with total vocabulary at age 2 years; lower premorbid IQ (32) measured as general cognitive ability (g) at age 12 years; bullying victimization (33) at age 12 years (12); and cannabis use (34) by age 16 years (13). Further information is presented in Table 1 and supplementary methods.

Quality of Life and Functioning Variables

Quality of life and functioning variables were life satisfaction measured at age 16 years and General Certificate of Secondary Education (GCSE) attainment at age 16 years, respectively. (See Table 1 and supplementary methods.)

Analysis

For schizophrenia risk factors, we used logistic regression analysis with the PLE groups as dependent variables. For example, for analysis of paranoia (P) and hallucinations (H) there were four exclusive groups: twins who scored high on neither P nor H (baseline group); those who scored high on P only; those who scored high on H only; and those who scored high on both P and H (P+H). The neither P nor H baseline group was compared with the P only group, the H only group, and the P+H group. The risk factor was the independent variable (with adjustment for birth order, age and sex). We also adjusted for socioeconomic status at first contact whenever there were significant associations. We included all twins and adjusted for clustering within twin pairs using a generalized estimating equations (GEE) approach.

We hypothesised that the co-occurring PLE group (e.g. P+H) would have the at-least nominally highest odds ratio (OR) for each risk factor. Where this was the case, we conducted a post hoc logistic regression analysis between the co-occurring group (e.g. P+H) and the group with the next highest odds ratio (e.g. P only) to determine if the association for the co-occurring group was significantly greater than for the group with the next strongest association.

For analyses of life satisfaction and reduced functioning, we used linear regression analysis with the life satisfaction or GCSE score as the dependent variable, and the PLE groups as the independent variable.

For initial description of the results, statistical significance was taken as $p<0.05$, two-tailed, with thresholds of $p<0.01$ and $p<0.001$ also reported.

Heritability Estimates

These were based on monozygotic (MZ) and same-sex dizygotic (SS DZ) twin pairs, following the approach used previously in TEDS (14), and most twin studies of schizophrenia (17, 18). Zygosity of twins was determined either using parental questionnaires (accuracy >95%) or DNA (26).

The twin design involves comparing within-pair similarities of monozygotic (MZ) and dizygotic (DZ) twin pairs to determine the extent to which variation in a phenotype is attributable to genetic and environmental influences. For a detailed explanation of the twin model please see (35). We calculated probandwise concordances and tetrachoric correlations for each PLE group, e.g. P only, H only, and P+H, in MZ and SS DZ pairs, to obtain an initial impression of the MZ and DZ similarities. We then carried out univariate model-fitting of the PLE groups based on a liability-threshold ACE model to establish the relative contribution of additive genetic (A), common environmental (C) and individual-specific environmental influences (E) (14). We treated heritability (h^2) estimates as statistically significant at $p<0.05$ if their 95% confidence intervals (95% CI) did not include zero, and two h^2 estimates as significantly different if their 95% CIs did not overlap.

Overall Test of Associations with Schizophrenia-Relevant Variables

The primary study outcome was whether the co-occurring PLE group (e.g. P+H) had the at-least nominally strongest association with significantly more of the 11 schizophrenia-relevant variables analysed than its individual component PLEs (e.g. P only, or H only), where at least one PLE group was significantly associated. A one-sample binomial test was used compared with a null proportion of 1 in 3 (0.33) (e.g. in a comparison of P+H, P only and H only, the P+H group would be expected to have the strongest association 1 in 3 times by chance).

The threshold for statistical significance was p<0.017, two-tailed, for these overall tests (p<0.05 with Bonferroni adjustment for three sets of analyses 1) paranoia and hallucinations; 2) paranoia or hallucinations, and cognitive disorganisation; and 3) paranoia or hallucinations, and negative symptoms).

Analysis Software

We used SPSS version 24 (https://www.ibm.com/products/spss-statistics) for the analysis of risk factors, quality of life and functioning variables, and calculation of probandwise concordances. We used OpenMx (https://openmx.ssri.psu.edu/) for calculating tetrachoric correlations and twin modelling analyses.

RESULTS

Descriptive statistics are shown in Table 2. Paranoia, hallucinations and cognitive disorganisation were more common in females, while negative symptoms without paranoia or hallucinations was more common in males, consistent with previous reports (3). Family socioeconomic status at first contact was lower in individuals with negative symptoms, and to a lesser extent also in individuals with cognitive disorganisation, and hallucinations. (All p-values<0.001: Table 2.)

Primary Analysis

Results are summarised in Table 3 and detailed in supplementary Tables S1.01-S3.29. In none of the three primary analyses did the co-occurring PLE group have the strongest association with significantly more variables than its individual component PLEs overall (last row of Table 3: p-values 0.16-0.39).

Three variables had broad associations (bullying victimization, cannabis use, and lower life satisfaction), being significantly associated with almost every co-occurring and individual PLE group in all three analyses (the one exception was no significant association between

cannabis use and negative symptoms only). For victimization, and life satisfaction, the co-occurring PLE group had the significantly strongest association in all three analyses, and for cannabis use, the co-occurring PLE group had the significantly strongest association in two out of the three analyses. Effect sizes were greatest for cannabis use, with ORs of 2.61 to 3.15 for co-occurring PLE groups.

Family history of schizophrenia had its nominally strongest association with the co-occurring PLE group in all three analyses. The association was significant for cognitive disorganisation plus paranoia or hallucinations, and for negative symptoms plus paranoia or hallucinations. The family history variable was validated by showing significant association with the schizophrenia polygenic risk score (PRS) (n=3951, OR=1.73 (95% CI 1.16 to 2.57), p=0.007). We also performed a supplementary analysis of associations between PLE groups and schizophrenia PRS, but there were no statistically significant associations (supplementary Tables S4.01-S4.03). This was probably due to insufficient sample size, as PLEs have shown significant associations in larger analyses that included the current sample (7, 11).

The three variables relating to cognitive function (vocabulary, general cognitive ability, and GCSE score) had their nominally strongest association with an individual PLE (hallucinations, cognitive disorganisation, and negative symptoms). Effect sizes were greatest for GCSE score, where the maximal β-coefficient was 10.45 for negative symptoms occurring in the absence of paranoia or hallucinations.

Obstetric complications had significant associations with PLE groups that included negative symptoms and had its nominally strongest association with negative symptoms co-occurring with paranoia or hallucinations.

Results for ethnic minority status were inconsistent, being significantly associated with paranoia or hallucinations in the absence of cognitive disorganisation, and with negative symptoms in the absence of paranoia or hallucinations.

Paternal age was not significantly associated with any PLE group. As some studies have found the association with schizophrenia to be only with the oldest paternal age-group (28), we also looked at this variable by 10-year age bands (supplementary Tables S1.05, S2.06, S3.06). Each co-occurring PLE group showed a slight trend towards association with having the oldest fathers (aged 55 years+) but numbers were too small to allow formal analysis.

Patterns of heritability showed variation across the three primary analyses. In the paranoia and hallucinations analysis, only paranoia without hallucinations had significant heritability. In the cognitive disorganisation analysis, heritability was nominally highest for cognitive disorganisation co-occurring with paranoia or hallucinations, while cognitive disorganisation without paranoia or hallucinations had zero heritability due to unexpectedly higher DZ than MZ concordance. This is more likely to be a chance finding than to be scientifically meaningful because plausible mechanisms for the DZ>MZ pattern are hard to envisage. In the negative symptoms analysis, all three PLE groups had significant heritability, and negative symptoms without paranoia or hallucinations was nominally highest.

Secondary Analysis

As cognitive disorganisation and negative symptoms groups were both associated with all three of the cognitive function variables, we speculated that co-occurrence of these two PLEs might have stronger associations with cognitive variables than either occurring alone. We therefore conducted a secondary analysis of cognitive disorganisation and negative symptoms occurring together or individually.

The summary results are given in supplementary Table S5.01 and detailed in Tables S5.02-S5.33. Co-occurring cognitive disorganisation and negative symptoms had the nominally strongest association with two of the cognitive variables (general cognitive ability, and GCSE score – significantly strongest for GCSE score), while cognitive disorganisation without negative symptoms was nominally strongest for vocabulary. Overall, the co-occurring cognitive disorganisation and negative symptoms group had the nominally strongest association with 7 of the 10 variables where at least one PLE group was significantly associated (Table S5.01: proportion 0.70, p=0.014).

The co-occurring cognitive disorganisation and negative symptoms group had the nominally highest heritability from all of the PLE analyses (0.67 or 67%), although CIs overlapped with the cognitive disorganisation only and negative symptoms only groups. The heritability estimate remained similar when based on residualized PLEs after regressing out the effects of sex (0.65, 95%CI 0.23 to 0.77), in male (0.64, 95%CI 0.36 to 0.83) and female (0.67, 95%CI 0.18 to 0.79) twin pairs, and when including opposite-sex DZ twin pairs (0.65, 95%CI 0.41 to 0.76).

In order to investigate the effects of applying a higher PLE threshold, we conducted the following analyses using a 10% cut-off. For all PLE combinations, we investigated associations with two prospectively-assessed risk factors which showed contrasting patterns of association, general cognitive ability and victimization. Additionally, for paranoia or hallucinations, and negative symptoms we investigated associations with obstetric complications, and for cognitive disorganisation and negative symptoms we investigated twin heritability. The results remained very similar (supplementary Tables S6.01-S6.15). The same associations were statistically significant at 15% and 10% cut-offs. Among these, the only change in order of nominal effect sizes was that at the 10% cut-off negative symptoms without paranoia or hallucinations had a marginally stronger association with obstetric complications than negative symptoms plus paranoia or hallucinations (OR 3.04, 95%CI

1.76 to 5.26 versus 2.87, 95%CI 1.30 to 6.33), reinforcing the previous impression that obstetric complications were most associated with negative symptoms. Also, for most associations at the 10% cut-off the largest effect size was marginally greater than at the 15% cut-off.

DISCUSSION

Three variables -- bullying victimization, cannabis use, and lower life satisfaction -- had broad associations with most PLE groups and their strongest associations with co-occurring PLEs, as predicted. These variables might be particularly related to clinical service use, through reduced quality of life or as proximal precipitants of clinical episodes. They may thus contribute to effects seen in adult samples where, relative to individual PLEs, co-occurring PLEs are associated with increased risk of clinical need (24), schizophrenia (2) and psychotic disorder (21, 22), and other clinically relevant variables, including poorer functioning (20, 25), anxiety symptoms (24) and persistence of PLEs (24). Also, consistent with the current study, co-occurring PLEs have previously been associated with childhood trauma (24): in that study any lifetime trauma when interviewed at 14-24 years, and in this study with bullying victimization assessed at age 12 years.

Co-occurring PLEs have previously been associated with more frequent family history of psychosis (23). In the current study, family history of schizophrenia in a first or second degree relative had its nominally strongest association with the co-occurring PLE group in all three primary comparisons.

The three variables relating to cognitive function had their strongest association with an individual PLE in all three primary analyses. This may have been due to paranoia not being associated with reduced cognitive function (and having a trend in the opposite direction in some analyses) leading to associations for co-occurring PLE groups that included paranoia being attenuated. To our knowledge, previous studies of co-occurring PLEs have not

investigated cognitive functioning prospectively. However, consistent with our findings, the Avon Longitudinal Study of Parents and Children (ALSPAC) study found only weak evidence for cognitive deficits in adolescence for a psychotic experiences group defined by the presence of hallucination- or delusion-like experiences (36).

Obstetric complications have previously been studied in relation to positive PLEs with mixed results (37, 38), while we found them to be most associated with negative symptoms. Ethnic minority status has been associated with positive PLEs (39). Unfortunately our findings for PLE combinations were inconsistent, and further research is needed in samples that are more ethnically diverse. We found that paternal age was not significantly associated with any PLE group. The ALSPAC study found a non-significant trend towards an association between positive PLEs at age 12 years and older paternal age (40). As some studies of schizophrenia have found the association only with the oldest fathers (28), and there was a trend consistent with this in the current study, albeit with too small numbers for formal analysis, it is possible that an association with PLEs might be evident in larger samples.

In the secondary analysis of cognitive disorganisation and negative symptoms, the group where these two PLEs co-occurred had the strongest association with schizophrenia-relevant variables most frequently compared with their individual component PLEs, i.e. cognitive disorganisation alone and negative symptoms alone. It was also notable that this PLE combination had the highest heritability out of all the PLE groups analysed (67%). To our knowledge this PLE combination has not been investigated in previous co-occurrence studies. A negative/disorganised PLE group has been investigated in a past study, but it was predominantly composed of negative symptoms and the component PLEs were not disaggregated (25).

Are there potential implications of these PLE results for clinical diagnoses which are based on the co-occurrence of symptoms? Where processes underlying PLEs and symptoms are

similar, a diagnostic approach might enhance associations with risk factors where most individual symptoms are associated, but could attenuate associations with risk factors where only one type of symptom, e.g. negative symptoms, is associated. However, this depends on factors including the relationships between PLEs and symptoms and the processes that underlie the co-occurrence (22-24). Further insights may be gained from ongoing research, including longitudinal studies of PLEs and subsequent clinical disorders and their symptom profiles, where relevant risk factors are assessed.

Limitations

The variables used covered a broader range of prospectively-measured relevant variables than previously investigated, but it is possible that the results could have differed if other schizophrenia-relevant variables were used that were not available in this sample, e.g. measures of motor development, other forms of childhood trauma, or other aspects of impairment in life roles. Also results could have differed if alternative questionnaires or interview measures were employed, although the SPEQ is based on well-established measures that provide reliable and valid PLE subscales.

We defined PLEs in terms of dichotomised scores, which may have reduced power compared to quantitative variables, but gave relative clarity for defining PLE groups and flexibility in allowing both ‘and’ and ‘or’ combinations of PLEs.

Correlations between PLEs and schizophrenia-relevant variables could be elevated when they had the same rater, and lowered when there were different raters, and the power to detect associations may vary between risk factors because of differences in their prevalence, but the analysis focused on comparing associations for different PLE combinations with each risk factor individually, and then conducting an overall test based on how frequently the co-occurring PLE group had the strongest association.

We were able to investigate more schizophrenia risk factors than measures of quality of life and functioning. Future research in older participants could extend this to include assessment of, e.g. further education, employment, and social relationships.

As part of the development of the PLE measures, twin and singleton comparisons were made and showed no notable differences (3) - twin-related effects are unlikely but cannot be excluded.

These findings require independent replication, especially as many are reported here for the first time.

Conclusions

First, we found the patterns of association between PLE combinations and schizophrenia-relevant variables to vary considerably. Focusing on co-occurrence enhances some individual PLE associations but obscures others. Second, in terms of which variables are most associated with co-occurring PLEs, bullying victimization, cannabis use, and lower life satisfaction had the strongest associations with co-occurring PLEs compared with PLEs in isolation. These variables may be particularly relevant to the association between co-occurring PLEs and increased risk of clinical disorder and service use. Third, obstetric complications were most associated with negative symptoms, a finding that suggests opportunities for future research into the underlying neurodevelopmental pathways to psychosis vulnerability. Fourth, we found that co-occurring subjective cognitive disorganisation and observed negative symptoms had the at-least nominally strongest associations across a broad range of schizophrenia-relevant variables and relatively high heritability. Future research could investigate associations between this PLE combination and other schizophrenia risk factors, and also cumulative exposure to risk factors, and assess how well it predicts onset of schizophrenia.

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