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Recent quantitative genetic research on psychotic experiences: new approaches to old questions

Angelica Ronald



It is common, particularly in young people, to report psychotic experiences (PEs) such as feeling paranoid and having hallucinations. The questions of the role of genes and environment on PEs in the general population, and how PEs relate to schizophrenia, have not, until recently, been addressed empirically. New approaches demonstrate the heritability and role of the environment on the full range of PEs (including positive, cognitive and negative types) and show that extreme, severe forms are linked genetically to milder, less severe forms. New approaches have tested whether PEs are associated with the genome-wide significant genetic variants known to predict schizophrenia. Although at an early stage, this research will impact how we understand PEs in everyday life.

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Introduction

This review covers quantitative genetic literature on psychotic experiences (PEs) over the last four years (2011–2014). ‘PEs’ are used here to refer to normal traits in the general population, such as paranoia (see also schizotypal traits for more personality-based constructs), that at the extreme are characteristic of symptoms of psychotic disorders such as schizophrenia [1]. Quantitative genetic research aims to investigate the genetic and environmental influences on quantitative phenotypes [2].

PEs are common [3] and are associated with many negative consequences, including increased risk of suicide [4,5]. Furthermore, PEs are risk factors for schizophrenia, a potentially debilitating illness and one of the UK’s most resource-consuming brain disorders [6]. As such, research on PEs can not only help us understand PEs themselves, but may also shed light on the neurodevelopment that underlies psychotic illness.

Family studies

Family studies can reveal the degree to which PEs are influenced by familiarity, which includes both genetic and shared environmental effects, for example [7,8]. A disadvantage is that family studies cannot disentangle the roles of genes and shared environment. For this reason, and because of the brief format of this review, family studies of PEs are not reviewed in full; for a review of schizotypy in relatives of individuals with schizophrenia, see [9].

Twin studies

Table 1 reviews twin studies in the last four years on PEs in the general population. Across all studies, the range of heritability estimates suggests between a third and a half of variance in PEs/schizotypy scales is explained by additive genetic effects in the population (although note the relatively lower heritability for hallucinations in males in the most recent and largest study) [10^{••}]. The remaining half-to-two-thirds of the variance in PEs and schizotypy scales was accounted for by nonshared environmental effects (which refers to environmental effects that make children growing up in the same family different, and includes measurement error). Effects of shared environment (environmental effects that make children growing up in the same family similar) were nonsignificant in all studies, with the exception of modest effects on hallucinations and parent-rated negative symptoms in one study [10^{••}].

Heritability of individual PEs

A new approach has been to investigate the heritability of the full range of individual positive, cognitive, and negative PEs assessed quantitatively in the general population [10^{••}]. A recent study, reported in Table 1, demonstrated that hallucinations are the least heritable PE, particularly for males (males: 15%, females: 32%) (see also [11]), whereas negative symptoms and paranoia have comparably higher heritability (59% and 50%, respectively), and the other types of PEs show estimates in between these values [10^{••}].

Causes of longitudinal stability of PEs

Longitudinal data, available in one study reported in Table 1, have demonstrated that schizotypal traits are stable across adolescence and that this stability is explained by common genetic effects over time [12]. In a further study (not reported in Table 1 because it did not include twin model-fitting), female adults in the general population were assessed on PEs three times

Table 1

Twin studies of dimensional assessments of psychotic experiences and schizotypal traits in community samples published in 2011–2014 (presented reverse chronologically).

Study	Measure (name; number of items; rater)	Sample (study; <i>N</i> for MZ and DZ individuals; age; gender)	Phenotypes (principal component analysis, subscale divisions)	Quantitative genetic findings
Zavos <i>et al.</i> (2014) [10**]	Specific Psychotic Experiences Questionnaire (SPEQ) [3]; 63 items; six subscales; self-/parent-rated	Twins Early Development Study; 3395 MZ, 6087 DZ; age 16; 45% male	Six subscales derived from principal component analysis [3]: paranoia, hallucinations, cognitive disorganisation, grandiosity, anhedonia (all self-rated), negative symptoms (parent-rated)	<i>Univariate.</i> Heritabilities: paranoia (50%), hallucinations (males 15%, females 32%), cognitive disorganisation (43%), grandiosity (44%), anhedonia (47%), parent-rated negative symptoms (59%). C was modest for hallucinations and negative symptoms (17–24%) and nonsignificant for other scales. E was considerable for all scales (49–64%) but lower for parent-rated negative symptoms (17%) <i>Sex differences.</i> No qualitative sex differences found; only hallucinations showed quantitative sex differences (see above) <i>Multivariate.</i> High genetic correlations (0.61–0.63) and modest nonshared environment correlations (.24–.33) observed between paranoia and hallucinations, paranoia and cognitive disorganisation, and hallucinations and cognitive disorganisation. Moderate genetic correlation (.27) and low nonshared environment correlation (.10) between cognitive disorganisation and negative symptoms. Majority of covariance explained by genetic influences (54–71%) <i>Extremes analysis.</i> See Figure 1
Hur <i>et al.</i> (2012) [11]	Launay–Slade Hallucination Scale-Revised (LSHS-R) [46]; 12 items; self-rated	South Korean Twin Registry; 802 MZ, 394 DZ; age 12–19 years; 45% male	One Hallucinations scale	Hallucinations heritability 33%, remaining variance explained by E (67%). No quantitative sex differences
Ericson <i>et al.</i> (2011) [12]	Schizotypal Personality Questionnaire child version (SPQ-C); 22 items; self-rated	Southern California Twin Project; wave 2: 182 MZ, 173 DZ, wave 3: 377 MZ, 584 DZ; age 11–13 (wave 2) and 14–16 (wave 3); 47–48% male	Three subscales derived from principal component analysis: cognitive-perceptual, interpersonal-affective, disorganisation	<i>Univariate.</i> Heritabilities at waves 2 and 3: cognitive-perceptual (53% and 53%, respectively), interpersonal-affective (46% and 38%, respectively), disorganisation (42% and 57%, respectively); remaining variance explained by E. No significant or consistent changes from wave 2 to wave 3. Three subscales loaded onto a separate common factor at each age, and the two common factors were stable ($r = .58$) and this stability was mainly explained by genetic effects (81%)

Table 1 (Continued)

Study	Measure (name; number of items; rater)	Sample (study; N for MZ and DZ individuals; age; gender)	Phenotypes (principal component analysis, subscale divisions)	Quantitative genetic findings
Kendler <i>et al.</i> (2011) [14]	Structured interview for DSM-IV personality (SIDP-IV); semi-structured diagnostic interview by trained interviewer (over 92% face-to-face; 8% by telephone)	Norwegian Institute for Public Health Twin Panel; 1338 MZ and 754 DZ pairs; mean age 28.2 years (SD 3.9); 36.5% male	Ordinal counts of number of positively endorsed criteria for paranoid personality disorder, schizoid personality disorder and schizotypal personality disorder	<i>Univariate.</i> Heritabilities of ordinal counts of endorsed criteria for paranoid personality disorder (29%), schizoid personality disorder (34%) and schizotypal personality disorder (38%). Remaining variance explained by E <i>Multivariate.</i> All three scales loaded onto genetic factor labelled 'Axis-II Internalising'

Note: MZ, monozygotic twins; DZ, dizygotic twins. C, shared environmental effects; E, nonshared environmental effects. Only twin studies that reported structural equation twin model-fitting included.

across two years. Concordance in identical (or monozygotic, MZ) twins for being in a persistent group (derived from latent class analysis) was higher than the fraternal (dizygotic, DZ) twin concordance, suggesting genetic effects on persistence of PEs over time in adults [13]. As such, available evidence suggests considerable phenotypic and genetic stability in PEs.

Heritability of questionnaire versus interview measures

While most twin studies in Table 1 relied on questionnaire data, one study employed trained interviewers to conduct structured interviews [14]. Heritability of the symptom counts derived from interviews was similar to the heritability estimates from the self-report questionnaire data in other studies. Self-report of PEs has been validated against in-depth clinical interviews but is known to give higher mean scores than interviews [15]. As such, it is helpful to observe similarities in heritability estimates across different methods of assessment.

Genetic and environmental overlap between PEs

Multivariate analyses have explored the degree to which different PEs share genetic and environmental influences. Whether for individual PEs [10^{••}], individual schizotypal domains [12], or symptom counts from different types of personality disorder [14], all studies reported considerable overlap in genetic effects across different PEs. For example, in a recent study of adolescents, paranoia and hallucinations correlated $r = .47$, and 64% of this covariation was explained by genetic influences, and the genetic correlation was high (0.61). Together, the multivariate results suggest considerable pleiotropic genetic effects across the different individual types of PE, together with some genetic effects being specific to individual PEs. Twin studies can also explore the degree to which causal influences on PEs are shared with other forms of psychopathology, cognition, and personality (for recent findings see [14,16–19]).

Molecular genetic studies

PEs and genes associated with schizophrenia liability

Table 2 outlines the two molecular genetic publications on PEs in general population samples on genome-wide identified variants. Overall, both studies, which employed adolescent samples, found some tentative evidence that genome-wide significant variants associated with schizophrenia also influence variance in PEs in the community, as well as several negative results.

One genome-wide significant schizophrenia-associated risk allele (rs17512836, in TCF4) was significantly associated with higher quantitative scores on a paranoia scale in the general population at age 16 [20^{••}]. TCF4 (transcription factor 4 gene) encodes a basic Helix-Loop-Helix (bHLH) transcription factor and is highly expressed in the brain, where it plays a role in neurodevelopment [21]. On the other hand, a second study, which used a categorical score of presence of at least one definite PE at age 12 or 18, found no individual schizophrenia-associated variants to be significantly associated with their measure of PEs [22^{••}].

Polygenic risk scores (the weighted sum of the number of risk alleles carried by an individual [23^{••}]) were also employed in both studies in Table 2. Schizophrenia and bipolar disorder polygenic risk scores did not significantly predict any of six quantitative PE subscales at age 16 [20^{••}] (scores were derived from the Psychiatric Genomics Consortium (PGC) stage-1 mega-analysis). The same schizophrenia polygenic risk score was investigated in the second study and did not predict the presence of at least one definite PE at either age 12 or 18 [22^{••}]. Notably, individuals who had at least one definite PE had on average higher schizophrenia polygenic risk scores than those who had not had at least one PE [22^{••}].

In sum, both studies provide some evidence for a genetic link between PEs in adolescence and diagnosed schizophrenia, but both studies also report negative findings. To

Table 2

Molecular genetic research on psychotic experiences in community or general population samples published in 2011–2014 on genome-wide identified variants (see text for candidate gene studies) (presented reverse chronologically).

Study	Phenotype measure (name; number of items; rater)	Sample (study; <i>N</i> individuals; age; gender)	Analyses	Findings
Sieradzka <i>et al.</i> (2014) [20**]	Specific Psychotic Experiences Questionnaire (SPEQ) [3]; 63 items; six quantitative subscales (paranoia, hallucinations, cognitive disorganisation, grandiosity, anhedonia, negative symptoms): self-/parent-rated	Twins Early Development Study; <i>N</i> = 2152; age 16; 43% male	<p><i>Individual SNP association.</i> 28 genome-wide significant schizophrenia-associated SNPs with six quantitative PEs</p> <p><i>Unweighted SNP composite association.</i> Association of unweighted SNP score of 28 SNPs (as above) with six quantitative PEs</p> <p><i>PRS prediction.</i> Schizophrenia and bipolar disorder PRS from the PGC used to predict six quantitative PEs</p>	<p><i>Individual SNP association.</i> One SNP, rs17512836, in TCF4 significantly associated (both allelic and genotypic), after correction for multiple testing, with Paranoia PE subscale. No significant associations for other individual SNPs or with other five PE subscales</p> <p><i>Unweighted SNP composite association.</i> SNP composite not significantly associated with any PEs</p> <p><i>PRS prediction.</i> Schizophrenia and bipolar disorder PRS did not significantly predict higher PE scores</p>
Zammit <i>et al.</i> (2013) [22**]	Psychotic-like Symptoms interview (PLIKSI), 11 questions on positive and cognitive PEs, trained interviewers. 'Narrow' categorical phenotype: one or more definite PE at either age. 'Broader' phenotype: any suspected or definite PEs	Avon Longitudinal Study of Parents and Children; <i>N</i> = 3483; age 12 and 18, % male unknown	<p><i>Individual SNP association.</i> 17 genome-wide significant schizophrenia-associated SNPs with one or more definite PE</p> <p><i>SNP composite association.</i> Association of SNP score of same 17 SNPs (as above) with one or more definite PE</p> <p><i>PRS prediction.</i> Schizophrenia PRS from PGC used to predict presence of one or more definite PE</p> <p><i>GWAS.</i> Genome-wide association study to identify SNPs associated with presence of one or more definite PE</p>	<p><i>Individual SNP association.</i> No significant associations between individual schizophrenia-associated SNP risk alleles and presence of one or more definite PE after correction for multiple testing</p> <p><i>SNP composite association.</i> SNP composite was not associated with increased risk of one or more definite PE</p> <p><i>PRS prediction.</i> PRS did not significantly predict presence of one or more definite PE, although on average participants with at least one definite PE had higher PRS than those without</p> <p><i>GWAS.</i> None of ~2.5 million SNPs were genome-wide significant ($p < 5 \times 10^{-8}$). SNPs with probable signals ($p < 5 \times 10^{-5}$) not enriched with variants associated with schizophrenia from PGC. Same conclusions reached with 'broader' PE phenotype</p>

Note: GWAS, genome-wide association study; PE, psychotic experience; PGC, Psychiatric Genomics Consortium; SNP, single nucleotide polymorphism; PRS, polygenic risk score.

take these findings forward, research needs to continue with larger samples and with more reliable polygenic risk scores, as well as to find ways to tackle the phenotypic heterogeneity inherent in the schizophrenia risk score. Schizophrenia has no universal symptom, and therefore when considering the link between a specific PE, such as hallucinations, and clinical schizophrenia, not all individuals with clinical

schizophrenia will have the specific experience. Schizophrenia is also often characterised by social dysfunction, which is not captured by many existing measures of PEs.

Genome-wide association studies

In terms of systematic gene-discovery work, so far there is one genome-wide association study of PEs. With

$N = 3483$ and a categorical assessment of PEs, this study yielded no genome-wide significant loci [22**]. On the basis of the known effect sizes of common variants associated with other complex traits, it is likely that a GWAS of PEs requires a sample size of over 10,000 individuals to identify genome-wide significant loci [24].

Candidate gene studies

Candidate genes, most notably those related to activity of the dopamine neurotransmitter, such as catechol-O-methyltransferase (COMT), have been investigated in relation to PEs with mixed results (e.g. [22**,25]). A systematic review of gene–environment interaction studies on candidate genes is available elsewhere [26]. Importantly, large-scale projects underway will address some of the methodological challenges in this type of research [27].

Environmental risk factors

Twin studies reviewed in Table 1 demonstrate that nonshared, rather than shared, environment is important in explaining variance in PEs. It is clear from estimates of nonshared environment and the known measurement error (estimated from test–retest reliability and internal consistency values), that there is significant nonshared environmental influence on PEs above and beyond variance explained by measurement error, for example [10**]. In terms of the types of environments involved, examples include cannabis use and stressful life events, which have both been associated with PEs in young

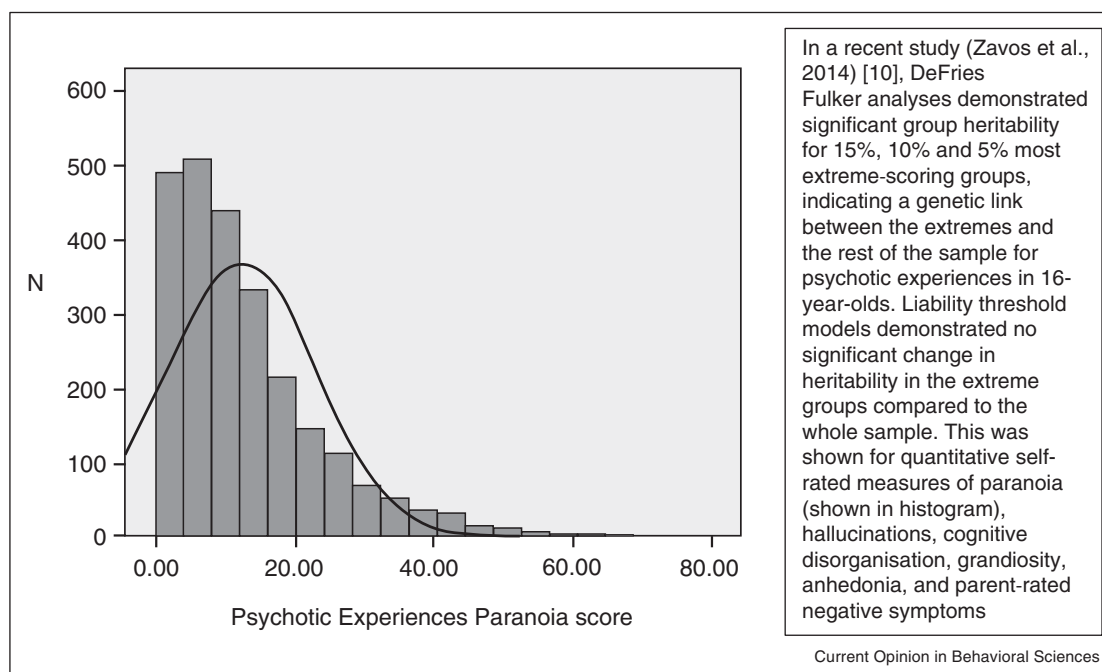
people, for example [28,29]. Largely similar environmental risk factors are found for PEs as for psychotic disorders [30].

Many apparent ‘environments’ are themselves partly heritable, a process termed gene–environment correlation [31]. For example, bullying victimisation, cannabis use and stressful life events are all themselves partly heritable [32–35]. To disentangle the role of nonshared environment from the impact of inherited genetic variation, the strongest design is the discordant MZ twin design [36,37**]. If the twins with more PEs have had on average more exposure to ‘environmental’ risk factors than their genetically identical cotwins, this demonstrates an association driven by nonshared environment. In addition, gene–environment correlation analyses can be conducted using twin data, where the heritability of ‘environmental’ variables such as cannabis use can be partitioned out, and thus the role of the environment can be assessed independent of heritability [2].

PEs and psychotic disorders: part of the same severity continuum?

Do PEs and psychotic disorders such as schizophrenia lie on the same severity continuum? There has been long standing interest in the relationship between PEs and clinical psychosis [38,39], see also [40]. This section focuses on two new empirical findings that have tackled this question using quantitative genetic designs.

Figure 1



Histogram showing quantitative distribution of paranoia assessed in 16-year-olds.

Recently it was shown that rates of mental illness in one family member increased linearly across five groupings in a general population sample of adults [41**]. These five groupings were based on 'level' of psychosis, varying from no PEs and subclinical PEs, to 'low' or 'high' impact psychotic symptoms and clinical psychotic disorder. Prevalence of mental illness in *multiple* family members increased extra-linearly across the five groups, suggesting there was more than a linear increase in apparent genetic risk (from the family information) with increasing PEs across the spectrum of severity. This study covered the full range of manifestations from no and few PEs all the way to diagnosed psychotic disorders within the same sample. It was limited by the fact that family history is not a direct measure of genetic risk: family members also provide environmental effects.

In a similar vein, new findings suggest that both mild and infrequent PEs and severe and frequent PEs in the general population in adolescence are part of the same aetiological continuum [10**] (see Figure 1). This study demonstrates that heritability does not differ significantly for high levels of PEs as for low or modest levels of PEs, and that there appears to be a genetic link between high and low levels of PEs [10**]. This was shown using a classic twin design, which is able to disentangle variance into genetic and environmental influences and estimate the net relative contributions of each. Because the sample were in mid-adolescence however, it was not possible to assess the genetic link between normal variation in PEs and diagnosed psychotic disorders, since the sample was too young to ascertain who would receive a diagnosis: the most severe group were defined as the highest-scoring 5% of the sample. These studies bring new approaches to the old question of how PEs relate to diagnosed psychotic disorders such as schizophrenia [38].

Conclusion

This brief review focuses on new quantitative genetic investigations of PEs over the last four years. It has shown how new approaches have tackled old questions regarding the relative role of genes and environment on PEs and how PEs relate to diagnosed psychotic disorders such as schizophrenia.

New findings on adolescence [10**,20**,22**] are advantageous because adolescence is before the typical age of onset of most cases of psychotic disorder, and PEs are common in this age group. Quantitative genetic research on PEs in adolescence may be particularly informative for identifying the causes underlying the precursors of psychotic illness and showing what leads PEs to be transitory or persistent.

Caution is needed in this field not to mislabel normal variation in PEs in the general population as psychiatric illness [42]. Evidence for or against psychotic illness

being on a continuum with PEs does not change the practical need for categorical definitions of psychiatric illness [43]. Vice versa, because there is clinical need for categorical definitions, this should not prevent researchers exploring the causes of PEs dimensionally, given that they exist dimensionally in the population (see Figure 1).

Another improvement has been research on specific individual PEs, which brings greater clarity to what causes individual experiences such as paranoia, hallucinations, and negative symptoms individually, rather than assuming that PEs form part of a single construct, which is in opposition to empirical psychometric evidence [3,12,44,45]. Going forward, it is unrealistic to expect a one-to-one mapping between PEs and schizophrenia, or to find large effect sizes between PEs and schizophrenia, in light of the heterogeneity inherent in the latter. There is much anticipation to understand the origins of PEs as normal aspects of life, particularly in young people, and as predictors of clinically relevant psychopathology.

Conflict of interest statement

Nothing declared.

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