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**A systematic review of genome-wide research on psychotic experiences  
and negative symptom traits: New revelations and implications for  
psychiatry**

Angelica Ronald, Department of Psychological Sciences, Birkbeck, University of  
London, London, WC1E 7HX, United Kingdom

Oliver Pain, Department of Psychological Sciences, Birkbeck, University of  
London, London, WC1E 7HX, United Kingdom

Corresponding author:

Professor Angelica Ronald,  
Centre for Brain and Cognitive Development  
Department of Psychological Sciences  
Birkbeck, University of London  
Malet Street, London WC1E 7HX, UK  
Email: [a.ronald@bbk.ac.uk](mailto:a.ronald@bbk.ac.uk)  
Telephone: 00 44 207 631 6342

## **Abstract**

We present a systematic review of genome-wide research on psychotic experience and negative symptom traits (PENS) in the community. We integrate these new findings, most of which have emerged over the last four years, with more established behaviour genetic and epidemiological research. The review includes the first genome-wide association studies of PENS, including a recent meta-analysis, and the first SNP heritability estimates. Sample sizes of <10,000 participants mean that no genome-wide significant variants have yet been replicated. Importantly, however, in the most recent and well-powered studies, polygenic risk score prediction and linkage disequilibrium (LD) score regression analyses show that all types of PENS share genetic influences with diagnosed schizophrenia and that negative symptom traits also share genetic influences with major depression. These genetic findings corroborate other evidence in supporting a link between PENS in the community and psychiatric conditions. Beyond the systematic review, we highlight recent work on gene-environment correlation, which appears to be a relevant process for psychotic experiences. Genes that influence risk factors such as tobacco use and stressful life events are likely to be harbouring 'hits' that also influence PENS. We argue for the acceptance of PENS within the mainstream, as heritable traits in the same vein as other subclinical psychopathology and personality styles such as neuroticism. While acknowledging some mixed findings, new evidence shows genetic overlap between PENS and psychiatric conditions. In sum, normal variations in adolescent and adult thinking styles, such as feeling paranoid, are heritable and show genetic associations with schizophrenia and major depression.

## Introduction

This review covers what is known about the genetic causes of psychotic experience and negative symptom traits (PENS) in the community. First PENS are introduced and the phenotypic association of PENS with psychiatric disorders is discussed. We then provide the first systematic review of research taking a genome-wide approach to PENS. Next we go beyond additive genetic effects to consider gene-environment correlation and gene-environment interaction underlying PENS. Finally we discuss this new genome-wide literature and consider how the field has arrived at a new position regarding the causes of PENS.

Here PENS include positive psychotic experiences (such as paranoia and hallucinations), cognitive psychotic experiences (such as cognitive disorganisation), and negative symptom traits (such as flattened affect and lack of motivation). These traits are grouped together because at the extreme, they reflect the symptoms of psychotic disorders such as schizophrenia. While some groups focus solely on positive psychotic experiences, several independent groups now include a range of positive psychotic experiences, cognitive psychotic experiences and negative symptom trait measures in their studies e.g., (1-4). As with all trait measures, this definition does not mean that PENS are equivalent to schizophrenia. Psychosis-proneness and psychotic-like experiences are also labels used in a similar way to PENS (2). Schizotypy is another conceptualization of subclinical psychosis which is included in our review: it has a long history (5) and the construct overlaps with PENS.

Research on psychopathological traits such as PENS is sometimes thought to clash with the motivations of psychiatry but the limitations and lack of confidence in psychiatric nosology is widely acknowledged (6-8). Common genetic variants act in a probabilistic manner to influence a liability for disorders such as schizophrenia (9, 10): as such, quantitative traits may make more sense than categorical diagnoses in psychiatric genetic research. Research on psychopathological traits such as PENS has an important role to play in terms of understanding the nature of individual differences in the full spectrum of cognition and experiences, and also in helping to understand how sometimes troubling traits are involved in the pathway leading up to a wide array of clinical diagnoses. In fact, in a recent review, Caspi and Moffitt hypothesise that PENS and other related abnormal thought processes will prove to be the most useful diagnostically under their transdiagnostic  $p$  model of psychopathology ( $p$  being a single dimension of general psychopathology) (8).

When assessed quantitatively, it is apparent that PENS are dimensional and have a normal to positively skewed quantitative distribution (11). When categorized as present or absent, prevalence of positive psychotic experiences has been estimated. For example, the lifetime prevalence estimate from the WHO World Mental Health Surveys of ever having positive psychotic experiences was 5.6% (12) see also (13-15). There are far fewer prevalence estimates of negative symptom traits and no consensus on how to categorise NS as present or absent. For example, a large community sample of young adults employed a mix of self report and interviewer items and reported that each individual domain of

negative symptoms occurred in 1.7-8.3% of participants, and 20% of the sample had at least one symptom (16). Another community sample reported that 12-13% were rated by interviewers as having negative symptoms (17). Prevalence rates in nonclinical samples tend to be higher for questionnaires compared to in-person interviews, especially if the latter capture more severe negative symptoms such as retardation of movement (18). In general, prevalence estimates of PENS are affected by measurement and where the cut-off is placed. An advantage of quantitative scales is the avoidance of potentially arbitrary choices about cut-offs and loss of power from removing quantitative information.

Twin studies show that approximately a third to a half of variation in PENS is explained by genetic influences in adolescent samples with the remaining variance explained largely by nonshared environment (19-24). Across gender, females tend to report more hallucinations, paranoia and cognitive disorganization, whereas males have higher scores on grandiosity and negative symptoms (11, 18, 25).

### **Psychotic experience and negative symptom traits (PENS) and their association with psychiatric conditions**

Epidemiological evidence from multiple studies shows that positive psychotic experiences increase risk of developing psychiatric disorders, including schizophrenia, major depression and post-traumatic stress disorder (significant odds ratios of 1.3-5.6) (26-30). Furthermore, odds ratios increase if positive psychotic experiences persist over time (31). PENS are known to be associated with similar environmental risk factors as schizophrenia (15). For several decades it has been known that relatives of individuals with schizophrenia show elevated rates of positive and negative schizotypal traits compared to controls (32, 33). Adoption designs provided an early and very powerful means of showing that wider schizophrenia "spectrum" disorders and schizotypal personality disorder were elevated in biological relatives of adoptees with schizophrenia, thus suggesting a genetic link with these disorders and schizophrenia (34, 35)

Research has attempted to explore empirically if a "cut off" is evident in the spectrum of positive psychotic experiences that might suggest a qualitative distinction between positive psychotic experiences in the community and extreme psychotic experiences in the clinic. For example, is subclinical paranoia that many people experience part of a continuum with severe paranoia that is considered a clinical symptom? (36) After all, individuals suffering from severe positive psychotic experiences such as delusions are known to lose insight into their own experiences, which might suggest a qualitative difference between subclinical and clinical PENS.

Several taxometric analyses support a fully dimensional model of positive psychotic experiences: that is, evidence does not suggest discontinuity between milder and more severe forms of positive psychotic experiences (37-39). A large adolescent twin study demonstrated that the heritability of PENS does not

change significantly across the severity spectrum (23). Another study rated families according to their 'level' of psychosis as a proxy for genetic risk, varying from nothing i.e. no psychotic experiences or subclinical psychotic experiences, to 'low' or 'high' impact psychotic symptoms, and clinical psychosis (40). Rates of mental illness in a selected "proband" within each family increased *linearly* across these severity levels (40). These forms of evidence largely support continuity across the PENS severity spectrum.

Yet there is evidence also to suggest discontinuity. Negative symptom traits show evidence of higher heritability in adolescence at the impaired extreme than in the normal range within the community (23) and the above family study also found some evidence of non-linearity across the psychosis spectrum in families with more than one individual with mental illness (40). Heritability estimates of schizophrenia are considerably higher than of PENS in the community (80% versus 30-50%, respectively) (23, 41) but it is not a like for like comparison because the schizophrenia estimate assumes an underlying liability. While the question of a qualitative cut off is not settled, as discussed below in our systematic review, genome-wide studies have considerably advanced our understanding of the link between psychiatric conditions and PENS through estimating shared genetic variance using measured DNA variants (1, 3, 4, 42-47).

## **Systematic review of genome-wide studies of psychotic experiences and negative symptoms traits (PENS)**

### **Inclusion/exclusion criteria**

In this systematic review, all genome-wide studies of PENS with any of the following aims were included:

- 1) To identify common genetic variation in a genome-wide association study of PENS assessed using questionnaire or interview, and categorical or dimensional scales.
- 2) To estimate variance in PENS attributable to common genetic variation using genome-wide genotypic data.
- 3) To evaluate at a genome-wide level the genetic association between PENS and other phenotypes.

### **Data sources and search terms**

To identify all papers, a series of search terms were used in PubMed to capture relevant studies published on PubMed before the 21st of February 2018 in terms of phenotype and type of analysis. The search was conducted using the following argument: (psychotic OR psychosis OR schizotypy OR schizotypal OR psychotic experiences OR psychotic-like-experiences OR prodromal OR psychosis proneness OR paranoia OR hallucinations OR anhedonia OR negative symptoms OR cognitive disorganisation OR cognitive disorganization OR grandiosity OR delusions) AND (gwas OR genome-wide OR polygenic OR gcta OR greml OR SNP heritability OR ldsc OR ld score regression).

The resulting publications were then selected for review based on the following criteria:

- 1) Studies using genome-wide array or sequence data. Studies using linkage analysis and candidate genes were not included in this review.
- 2) Studies focusing on at least one dimension of PENS in a general population sample. This does not include studies focusing on psychosis symptoms in a clinical sample, nor does it include studies regarding only psychosis endophenotypes, such as ERP, EEG, or brain metrics. If other phenotypes were analysed, only the results referring to PENS are discussed.
- 3) Studies reported in English.

In addition to the systematic database search using PubMed, bibliographies of original research and review papers were investigated by hand to identify additional studies meeting the above criteria.

### **Data collection**

From the initial search on PubMed, 1342 papers were returned. Based on the title and abstract, 1315 were excluded by one author (O.P.), leaving 29 papers for further consideration. After closer reading of the remaining 29 papers, 19 were excluded (reasons for exclusion of the 19 papers provided in Supplementary Information Table S1). Ten papers remained after these exclusions. The number of papers identified by looking through reference lists was 0. Three other studies were identified by the authors through reading unpublished manuscripts on Biorxiv or from being involved in the work or citing the studies (1, 48, 49), making a total of 13 studies. Results were summarised in a table form.

### **Results of systematic review**

Thirteen publications were identified as genome-wide studies of PENS using the above search terms on the 21<sup>st</sup> of February 2018 (Table 1).

Insert Table 1 here

*SNP heritability studies.* The review revealed that three studies to date have estimated the SNP heritability of PENS (1, 2, 50) (see Table 1). Figure 1 shows the twin and SNP heritability estimates for specific PENS from the largest respective studies (1, 23). SNP heritability estimates of PENS are modest with non-significant differences in estimates across types of PENS. As with many traits and disorders, SNP heritability estimates are lower than the twin heritability estimates (51, 52). Of the 3 studies, two are from individual samples, the UK Twins Early Development Study (TEDS) assessed at age 16 years (50, 51), and the Northern Finland Birth Cohort 1966 study assessed at age 31 years (2). The third and largest study is a meta-analysis of three samples including TEDS, as well as the Child and Adolescent Twin Study in Sweden (CATSS) and the Avon Longitudinal Study of Parents and Children (ALSPAC), who were all assessed in mid to late adolescence (1).

Insert Figure 1 here

In relation to these new SNP heritability results, it is noted that there are several different methodologies available; two of the most commonly used are linkage

disequilibrium (LD) score regression (53) and genomic-relatedness-matrix restricted maximum likelihood (GREML) (54). GREML is based on the relationship between phenotypic and genotypic similarity between individuals (thus requiring individual-level genotypic and phenotypic data). In contrast, LD score regression calculates SNP heritability from the relationship between each genetic variants' genome-wide association study (GWAS) derived effect size (chi-square) and LD-score (thus requiring only GWAS summary statistics). Two of the studies employed GREML (2, 50), whereas the meta-analysis had enough power to use both LD score regression and GREML (1). As shown in Figure 1, LD score estimates are higher than the GREML estimates with overlapping confidence intervals.

A second point about the SNP heritability estimates in Figure 1 is that they are based on normalised PENS scores due to positive skew (1). Normalisation to reduce skew is standard practice but it can introduce artificial variance (i.e. noise) and thereby reduce SNP heritability estimates. Normalisation will have a larger effect on more highly skewed variables, which could explain why in Figure 1 the more skewed PENS (paranoia and hallucinations combined scale and parent-rated negative symptoms) show a lower SNP heritability than less skewed PENS traits (cognitive disorganisation and anhedonia). Although GREML SNP heritability estimates were consistent when using untransformed PENS scores (51, 55), it has been reported that GREML underestimates the SNP heritability of skewed traits (56). Simulation studies are required to investigate the effect of skew on estimates of SNP heritability.

Finally, minor allele frequency (MAF)-stratified SNP heritability analyses have been reported on one of the SNP heritability studies. In the TEDS sample with approximately 2100 individuals, results suggested that the majority of the anhedonia SNP heritability was explained by variants with  $MAF < .05$  (50). Estimation of SNP heritability stratified by MAF is a means to understand the genetic architecture of a trait in terms of MAF. Further studies are needed in larger samples, given the demands on power of this approach due to the larger number of estimated parameters.

In sum, PENS appear to be influenced by additive genetic influences, with some modest differences in heritability estimates across specific types of PENS. Samples are still relatively small (largest sample is 8665 including related cotwins) and it is known that different programs produce slightly different estimates (57).

*Genome-wide association studies.* The search identified three GWAS to date aiming to identify new variants associated with PENS: two on individual samples and one mega-analysis combining three cohorts. The first study was on participants in the ALSPAC cohort, who were assessed at ages 12 and 18 on positive psychotic experiences using interview measures (43). Second, the Northern Finland Birth Cohort (NFBC) self-reported on a range of PENS domains at age 31 years (2) (see further study on same sample stratified by *DISC1* (58)). Finally a mega-analysis on the TEDS, ALSPAC and CATSS samples reported on results from mid-adolescence combining data on self-reported positive and

cognitive PENS and parent-rated negative PENS (1). The latter two GWAS studies each identified one genome-wide significant variant, but neither of these genome-wide significant variants has been replicated in an independent sample.

*Polygenic risk score studies.* As shown in Table 1, 10 studies to date have explored genetic overlap between genome-wide common variant genetic risk for other phenotypes and PENS. In all but one of these studies (59) the other phenotypes were psychiatric disorders, most commonly schizophrenia, using PRS derived from the PGC (<http://www.med.unc.edu/pgc>). The 10 studies can be broadly categorized into those that studied association between *selected* genome-wide significant SNPs and PENS (43, 45, 47), those testing the association between PRS derived from *PGC1* and PENS (42, 43), and those testing the association between PRS derived from *PGC2* and PENS using samples of <2500 (4, 45, 48) and >2500 individuals (1, 44, 46). Finally one study also reported on PRS associations using phenotypes outside of PGC with PENS (59). All the studies using the PGC2 SCZ PRS or PGC1 MDD PRS with samples >2500, and one smaller study (4), report significant genetic association between PENS and psychiatric disorders (schizophrenia or major depression) (1) (44, 46). The other studies using PGC2 with n<2500 samples or using selected SNPs or the PGC1 PRSs reported non-significant findings or negative associations.

As such there are four studies reporting a significant genetic link between schizophrenia and PENS in the community (1, 4, 44, 46) (Table 1 and Figure 2). Effect sizes in terms of percent variance explained in PENS by the schizophrenia PGC2 PRS ranged between .08%-.7%, with one study not reporting effect sizes (4). In terms of positive psychotic experiences, within these four studies, some consistencies and discrepancies emerge. Of the two studies using interview measures of positive psychotic experiences, one reported a significant association with schizophrenia PRS in adults (4) while the other did not find this in adolescents (44). Of the three studies using questionnaire measures of positive psychotic experiences, two of the studies were on adolescents and reported a significant positive association with schizophrenia PRS (1, 46). A third smaller study, on adults, did not find an association (4). Notably, the largest study found that this association only held in the non-zero scorers (see Figure 2) (1).

Insert Figure 2 here

Schizophrenia PGC2 PRS was shown to predict negative symptom traits in adolescence across three studies, as assessed by self, parent report and interview, respectively (1, 4, 44), although there was a significant association in the smaller study only for the interview data and not the self-rated questionnaires (4). Schizophrenia PRS also predicted self-rated cognitive disorganization and anhedonia in the only study to include these domains (1).

In terms of PRS for phenotypes other than schizophrenia, one study found the major depression PRS and this study found to share genetic influences with negative symptoms and anhedonia but not positive or cognitive PENS (1). In the two studies where bipolar disorder PRS was employed, it did not show a

significant positive association with PENS (1, 45). In the meta-analysis, a significant negative association between PRS for bipolar disorder and adolescent paranoia and hallucinations was identified ( $r^2 = 0.12\%$ )(Figure 1) (1). Finally, in a large multi-phenome analysis, no associations between PENS and PRS were significant after correcting for multiple testing but a small number were nominally significant (59) (see Table 1).

*GxE studies.* Gene-environment interaction (GxE) analyses on PENS using genome-wide data are reported in two studies in Table 1 (3, 47) as well as one unpublished thesis known to the authors (60). The only positive GxE finding at a genome-wide level is that high birth weight appears to interact with selected genome-wide SNPs from PGC2 schizophrenia in predicting more social anhedonia (47). Other work found that the stress of signing up as a conscript interacted with the PGC2 Schizophrenia PRS in predicting *less* schizotypy (although not all subscales were significant) (3). Finally, no interactions were reported between adolescent cannabis use, tobacco use or psychosis family history and the PGC2 schizophrenia PRS in predicting PENS in the TEDS sample in adolescence (60).

### **Beyond additive genetic effects: Gene-environment correlation and PENS**

Here we move beyond the systematic review to discuss briefly research that is showing that environmental variables associated with PENS are in some cases tied in with genetic predisposition. We exemplify this point by describing a selection of recent findings from our group and others. We acknowledge parallel work in this area on schizophrenia e.g., (61) but, as with other sections of this review, we focus on PENS in the community.

It is well established that our environment is not independent of our genotype, with many “environments” being heritable (62, 63). Passive gene-environment correlation (passive rGE) exists due to the home environment being influenced by the parents’ genotype and biological children inheriting some of their genotype. Individuals’ active behaviour leads to an individual experiencing environments that link to their genotype (active rGE) and individuals evoke environmental responses from their genetically influenced behaviour (evocative rGE).

Using twin models to partition variation in genetic and environmental effects, a set of studies based on the TEDS community sample reported that in adolescence, cannabis use, bullying victimization and stressful life events were all partly heritable (64-66). In the case of bullying victimization and stressful life events, the genetic influences were partly overlapping with some PENS domains (65, 66). While such evidence does not rule out the possibility that some covariation between PENS and environmental risk factors is in fact environmental see e.g., (67), it suggests shared genetic pathways are in operation as well.

In terms of cannabis use, having ever used cannabis by age 16 was found to be 37% heritable in TEDS but covariation with psychotic experiences was explained fully by shared environmental factors (64). In an older sample of 19-36 year olds, and assessing cannabis use disorder rather than never/ever use, correlation with psychotic experiences (primarily positive psychotic experiences with two items relating to movement) was explained by both genetic and

environmental influences (68) suggesting some gene-environment correlation underlying the relationship with cannabis use disorder.

While the above rGE research might to some degree suggest a diminished role of environment on PENS, other new findings suggest that direct genetic effects may be inflated and actually harbour environmental processes from parenting. Parental genotypes that are not transmitted to offspring have recently been shown, when assessed as a polygenic score, to predict significantly the offspring's phenotype (69, 70). Concerns remain as to how assortative mating and genetic influences on other phenotypes are controlled for, but Kong et al (2018) conclude that GWAS direct effects may be inflated because part of the GWAS signal operates via "genetic nurture" -- the effects of the parents' nontransmitted alleles on the rearing environment of the child. Educational attainment was their example phenotype, but this process of genetic nurture may extend to other phenotypes, such as PENS.

In sum, while direct additive genetic effects and direct additive environmental effects are likely involved in PENS, approaches that can capture genetic effects within the context of environment, and environment within the context of genetics are likely to be fruitful for understanding the etiology of PENS in full. We predict that successful identification of causal genetic variants associated with PENS will be aided by research on "environmental risk factors", such as smoking, cannabis use, urbanicity, stressful life events, and bullying victimization.

## **Discussion**

To our knowledge this is the first systematic review of genetic research on PENS. For a review of research on phenotypes associated with genetic risk for schizophrenia please see (71). Based on recent genome-wide research, a new position has been reached in our understanding of psychotic experience and negative symptom traits (PENS) in the community. The new research stemming from four studies suggests that genetic risk for diagnosed schizophrenia overlaps significantly with the genetic causes of PENS in the community during adolescence and adulthood (1, 4, 44, 46). To some degree, normal variation in adolescent and adult thinking styles, such as feeling paranoid, is caused by the same common genes that influence risk for schizophrenia. At the same time, the magnitude of the genetic association from current evidence does not suggest that PENS and schizophrenia are equivalent or that PENS should be used instead of or as a proxy for schizophrenia in genetic research. In the same vein, genetic risk for major depression overlaps significantly with negative symptom traits in the community (1) yet the modest associations do not suggest that negative symptom traits and major depressive disorder are interchangeable or completely equivalent at a genetic level.

How does the effect size for the PENS-schizophrenia genetic overlap compare to other trait-psychiatric disorder pairings? The percent variance in PENS explained by schizophrenia genetic scores is between .08-.7% in the most recent well-powered studies (1, 44, 46) with one study reporting a positive association but not including effect sizes (4). One study reported that the major depression PRS predicted .08-.11% variance in negative symptom traits in the community (1). Similar percent variance was explained for other trait-

psychiatric disorder pairings in a recent study on the CATSS sample (46). Importantly, the degree to which a PRS predicts a different phenotype (for example, schizophrenia genetic risk predicting PENS) is capped at the amount of variance a PRS can explain of its own phenotype in an independent sample. The schizophrenia PGC2 PRS explained 7% variance in liability to schizophrenia in an independent sample (10). The largest effect size for the schizophrenia PRS explaining any individual PENS is .7%, thus it is about 10% of the size of how strongly it predicts liability to schizophrenia (.7/7%). The MDD PGC1 PRS explained 0.72% variance in MDD on a liability scale (based on the authors' calculations) (72). The effect size for the MDD PRS explaining negative symptom traits in the community in adolescence appears to be 15% of the size (.11/.72). As a comparison, the ASD PRS predicts 1.13% variance in ASD on a liability scale in an independent sample (Grove et al 2018) and .1% variance in ASD traits in the community (46), that is, (.1/1.13) 9% of the size. The MDD PRS predicts 0.72% variance in MDD on a liability scale in an independent sample (72) and .2% variance in MDD traits in the community (46), that is, (.2/.72) 28% of the size. Finally, the ADHD PRS predicts 1.03% variance in ADHD on a liability scale in an independent sample (73) and 0.8% variance in ADHD traits in the community (46), that is, (.8/1.03) 78% of the size. We note some caveats in these calculations because the 'target' sample used to derive PRS estimates differs for the clinical and community studies.

Nevertheless, these ballpark estimates suggest that the genetic link between PENS and schizophrenia, when the reliability of the PRS is taken into account, is similar to other psychopathological trait-disorder pairings such as ASD and weaker than major depression and ADHD which show stronger genetic links between trait and disorder. What would cause a disorder PRS such as schizophrenia to predict less variance in PENS than in schizophrenia itself? It is noted that most of the results for PENS comes from adolescent samples (1, 44, 46) (although not all e.g., (4)). This is relevant because PENS may not have emerged in all people by adolescence and as such adolescent PENS will reflect a developmentally specific form of PENS. In contrast the schizophrenia PRS is derived from adult samples. As such adolescent PENS may overlap to a lesser degree with the schizophrenia PRS than lifetime PENS; this can be tested in future work on older samples. In the meta-analysis report (1), and shown in Figure 2, paranoia and hallucinations was only significantly positively predicted by the schizophrenia PRS in the non-zero scorers. Teenagers who reported no paranoia and hallucinations during mid-adolescence existed anywhere on the schizophrenia genetic liability spectrum (1).

A second potential reason for weaker genetic links between PENS and schizophrenia than with schizophrenia itself is the diagnosis of schizophrenia. It requires individuals to show multiple symptoms that have parallels in PENS, but PENS are typically measured as individual traits (paranoia, hallucinations, cognitive disorganisation, anhedonia, and so forth). It is realistic to predict that the schizophrenia PRS would explain more variance if multiple PENS were included in an analysis together.

Not all the studies addressing the link between schizophrenia PRS and PENS found a significant association. In our systematic review we noticed a pattern which is that the studies using an older, less reliable PRS (the "PGC1" version), as well as smaller studies tended not to find significant associations,

whereas all the studies using the more reliable PGC2 PRS with samples over 2500 (as well as one smaller study (4)) reported some significant positive associations between schizophrenia and PENS. As noted elsewhere, long-term prospective cohorts such as ALSPAC may have attrition bias whereby individuals with high schizophrenia PRS selectively drop out and this will under-power analyses in those cohorts (74)

The negative association between bipolar disorder PRS and PENS may be due to a lack of reliability in the available bipolar disorder PRS; future research can test this further (1, 45).

Our review shows that recent genome-wide research corroborates twin research in showing modest additive genetic influences on PENS. SNP heritability estimates are now reported for PENS using a variety of methods (GREML, LD score, MAF-stratified) and for adolescents and young adults (1, 2, 50). While the SNP heritability estimates may seem low, particularly for the estimates from adolescent samples (1) the estimates are consistent with child and adolescent psychopathology in which modest SNP heritability estimates are being reported across a range of traits (51). Considerations such as which SNP heritability method is chosen (57), how linkage disequilibrium is handled (50), and how skew is handled (1), along with reliability of items and informant will affect estimates (51).

One possibility regarding apparent genetic links between PENS and schizophrenia is that individuals with the illness in a community sample assessed on PENS might be driving any apparent association between schizophrenia genetic risk and PENS. The findings by van Os and colleagues allay this concern however because they find a positive association between the schizophrenia PGC2 PRS and PENS in general community controls with no family history of schizophrenia, to a stronger degree than in relatives of individuals with psychotic disorders (4). Furthermore, another of the studies showed that the positive associations between schizophrenia PGC2 PRS and negative symptoms still held when individuals with a diagnosed psychotic disorder were removed from the sample and when individuals with a parent with a diagnosed psychotic disorder were removed from the sample (44).

These initial findings raise interesting questions for future research. Would a measure of stable PENS across time show a stronger genetic link with schizophrenia than PENS assessed cross-sectionally? Is it essential, as some suggest, to control for confounds such as anxiety or other PENS when assessing the link between a specific PENS domains and another phenotype (4, 44)? This is a more stringent approach that does not allow for natural covariation between PENS domains; we know that PENS domains correlate positively and show some genetic overlap between them e.g., (2, 23).

We acknowledge some limitations to the scope of our review. The type of genetic research we reviewed focuses on common additive genetic variation. We limited our review to measures of PENS in the community. It is not yet known to what degree PENS are genetically related to other types of psychiatric disorders. In depth considerations of measurement of PENS were beyond the scope of this review but, as with all complex traits, are a critical issue (75)(11).

PENS in the community and psychiatric disorders, particularly schizophrenia, have for a long time appeared to be associated with one another. The new genome-wide genetic research reviewed here acts both to establish

concretely that PENS and schizophrenia are genetically linked, but also to show that the genetic link is present but mild. Genetic correlation or genetic covariance estimates only take causal models so far (76). To find out what underlies the purported genetic overlap indicated by a significant genetic correlation between two phenotypes, further evidence is needed. Examples include finding out the correlation of variant effect sizes across the two phenotypes, or through learning about the molecular action of a genetic variant in relation to two phenotypes.

The practical utility of new knowledge about the genetic basis of PENS deserves discussion. For example, with increasing knowledge from epidemiology and psychiatric genetics regarding the link between PENS and psychiatric disorders, informed decisions can be made about the place PENS can have in aiding prevention and intervention of mental health conditions. Second, their role in contributing to new models of psychopathology has recently been proposed (8).

Whether PENS form part of a “psychosis continuum” with clinical schizophrenia -- in the sense that PENS are a milder manifestation of the same phenotype as schizophrenia -- has been questioned for many years, and as discussed earlier, taxometric, twin and family studies have attempted to test this continuum hypothesis empirically (23, 32, 37-40). The new finding of a degree of genetic overlap between PENS and schizophrenia supports an at least partial aetiological continuum. A more far-reaching question is how useful PENS can be as a transdiagnostic predictor of the  $p$  (psychopathology) factor (8). The biologically-driven information derived from this new genome-wide research takes PENS research to a new position, in terms of new forms of evidence and models. Genome-wide research allows the mechanisms of the cognitions, behaviours and perceptual experiences that underlie PENS in the community to begin to be understood at a molecular level.

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## References

- 1 Pain, O., Dudbridge, F., Cardno, A.G., Freeman, D., Lu, Y., Lundstrom, S., Lichtenstein, P. and Ronald, A. (2018) Genome-wide analysis of adolescent psychotic-like experiences shows genetic overlap with psychiatric disorders. *Am J Med Genet B Neuropsychiatr Genet*, in press.
- 2 Ortega-Alonso, A., Ekelund, J., Sarin, A.P., Miettunen, J., Veijola, J., Jarvelin, M.R. and Hennah, W. (2017) Genome-Wide Association Study of Psychosis Proneness in the Finnish Population. *Schizophr Bull*, **43**, 1304-1314.

- 3 Hatzimanolis, A., Avramopoulos, D., Arking, D.E., Moes, A., Bhatnagar, P., Lencz, T., Malhotra, A.K., Giakoumaki, S.G., Roussos, P., Smyrnis, N. *et al.* (2018) Stress-Dependent Association Between Polygenic Risk for Schizophrenia and Schizotypal Traits in Young Army Recruits. *Schizophr Bull*, **44**, 338-347.
- 4 van Os, J., van der Steen, Y., Islam, M.A., Guloksuz, S., Rutten, B.P., Simons, C.J. and Investigators, G. (2017) Evidence that polygenic risk for psychotic disorder is expressed in the domain of neurodevelopment, emotion regulation and attribution of salience. *Psychol Med*, **47**, 2421-2437.
- 5 Meehl, P.E. (1962) Schizotaxia, schizotypy, schizophrenia. *American Psychologist*, **17**, 827-838.
- 6 Lawrie, S.M., Hall, J., McIntosh, A.M., Owens, D.G. and Johnstone, E.C. (2010) The 'continuum of psychosis': scientifically unproven and clinically impractical. *Br J Psychiatry*, **197**, 423-425.
- 7 Frances, A. (2013) *Saving normal*. Harper Collins, New York.
- 8 Caspi, A. and Moffitt, T.E. (2018) All for One and One for All: Mental Disorders in One Dimension. *Am J Psychiatry*, in press., appiajp201817121383.
- 9 Gottesman, II and Shields, J. (1967) A polygenic theory of schizophrenia. *Proc Natl Acad Sci U S A*, **58**, 199-205.
- 10 Schizophrenia Working Group of the Psychiatric Genomics, C. (2014) Biological insights from 108 schizophrenia-associated genetic loci. *Nature*, **511**, 421-427.
- 11 Ronald, A., Sieradzka, D., Cardno, A.G., Haworth, C.M., McGuire, P. and Freeman, D. (2014) Characterization of psychotic experiences in adolescence using the specific psychotic experiences questionnaire: findings from a study of 5000 16-year-old twins. *Schizophrenia bulletin*, **40**, 868-877.
- 12 McGrath, J.J., Saha, S., Al-Hamzawi, A.O., Alonso, J., Andrade, L., Borges, G., Bromet, E.J., Oakley Browne, M., Bruffaerts, R., Caldas de Almeida, J.M. *et al.* (2016) Age of Onset and Lifetime Projected Risk of Psychotic Experiences: Cross-National Data From the World Mental Health Survey. *Schizophrenia bulletin*, **42**, 933-941.
- 13 Davis, K.A.S., Coleman, J.R.I., Adams, M., Allen, N., Breen, G., Cullen, B., Dickens, C., Fox, E., Graham, N. and Holliday, J. (2018) Mental health in UK Biobank: development, implementation and results from an online questionnaire completed by 157 366 participants. *BJPsych Open*, **4**, 83-90.
- 14 Kelleher, I., Connor, D., Clarke, M.C., Devlin, N., Harley, M. and Cannon, M. (2012) Prevalence of psychotic symptoms in childhood and adolescence: a systematic review and meta-analysis of population-based studies. *Psychological medicine*, **42**, 1857-1863.
- 15 Linscott, R.J. and van Os, J. (2013) An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychol Med*, **43**, 1133-1149.
- 16 Werbeloff, N., Dohrenwend, B.P., Yoffe, R., van Os, J., Davidson, M. and Weiser, M. (2015) The association between negative symptoms, psychotic experiences and later schizophrenia: A population-based longitudinal study. *PLoS one*, **10**, e0119852.
- 17 Wigman, J.T., van Nierop, M., Vollebergh, W.A., Lieb, R., Beesdo-Baum, K., Wittchen, H.U. and van Os, J. (2012) Evidence that psychotic symptoms are

prevalent in disorders of anxiety and depression, impacting on illness onset, risk, and severity--implications for diagnosis and ultra-high risk research.

*Schizophrenia bulletin*, **38**, 247-257.

18 Maric, N., Krabbendam, L., Vollebergh, W., de Graaf, R. and van Os, J.

(2003) Sex differences in symptoms of psychosis in a non-selected, general population sample. *Schizophr Res*, **63**, 89-95.

19 Linney, Y.M., Murray, R.M., Peters, E.R., MacDonald, A.M., Rijdsdijk, F. and Sham, P.C. (2003) A quantitative genetic analysis of schizotypal personality traits. *Psychol Med*, **33**, 803-816.

20 Polanczyk, G., Moffitt, T.E., Arseneault, L., Cannon, M., Ambler, A., Keefe, R.S., Houts, R., Odgers, C.L. and Caspi, A. (2010) Etiological and clinical features of childhood psychotic symptoms: results from a birth cohort. *Arch Gen Psychiatry*, **67**, 328-338.

21 Hur, Y.M., Cherny, S.S. and Sham, P.C. (2012) Heritability of hallucinations in adolescent twins. *Psychiatry Res*, **199**, 98-101.

22 Wigman, J.T., van Winkel, R., Jacobs, N., Wichers, M., Derom, C., Thiery, E., Vollebergh, W.A. and van Os, J. (2011) A twin study of genetic and environmental determinants of abnormal persistence of psychotic experiences in young adulthood. *Am J Med Genet B Neuropsychiatr Genet*, **156B**, 546-552.

23 Zavos, H.M., Freeman, D., Haworth, C.M., McGuire, P., Plomin, R., Cardno, A.G. and Ronald, A. (2014) Consistent etiology of severe, frequent psychotic experiences and milder, less frequent manifestations: a twin study of specific psychotic experiences in adolescence. *JAMA psychiatry*, **71**, 1049-1057.

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

25 Wigman, J.T., Vollebergh, W.A., Raaijmakers, Q.A., Iedema, J., van Dorsselaer, S., Ormel, J., Verhulst, F.C. and van Os, J. (2011) The structure of the extended psychosis phenotype in early adolescence--a cross-sample replication. *Schizophr Bull*, **37**, 850-860.

26 McGrath, J.J., Saha, S., Al-Hamzawi, A., Andrade, L., Benjet, C., Bromet, E.J., Browne, M.O., Caldas de Almeida, J.M., Chiu, W.T., Demyttenaere, K. *et al.* (2016) The Bidirectional Associations Between Psychotic Experiences and DSM-IV Mental Disorders. *Am J Psychiatry*, in press., e-pub ahead of print.

27 Kelleher, I., Keeley, H., Corcoran, P., Lynch, F., Fitzpatrick, C., Devlin, N., Molloy, C., Roddy, S., Clarke, M.C., Harley, M. *et al.* (2012) Clinicopathological significance of psychotic experiences in non-psychotic young people: evidence from four population-based studies. *The British journal of psychiatry : the journal of mental science*, **201**, 26-32.

28 Werbeloff, N., Drukker, M., Dohrenwend, B.P., Levav, I., Yoffe, R., van Os, J., Davidson, M. and Weiser, M. (2012) Self-reported attenuated psychotic symptoms as forerunners of severe mental disorders later in life. *Archives of general psychiatry*, **69**, 467-475.

29 Fisher, H.L., Caspi, A., Poulton, R., Meier, M.H., Houts, R., Harrington, H., Arseneault, L. and Moffitt, T.E. (2013) Specificity of childhood psychotic symptoms for predicting schizophrenia by 38 years of age: a birth cohort study. *Psychol Med*, **43**, 2077-2086.

30 Zammit, S., Kounali, D., Cannon, M., David, A.S., Gunnell, D., Heron, J., Jones, P.B., Lewis, S., Sullivan, S., Wolke, D. *et al.* (2013) Psychotic experiences and

psychotic disorders at age 18 in relation to psychotic experiences at age 12 in a longitudinal population-based cohort study. *The American journal of psychiatry*, **170**, 742-750.

31 Dominguez, M.D., Wichers, M., Lieb, R., Wittchen, H.U. and van Os, J. (2011) Evidence that onset of clinical psychosis is an outcome of progressively more persistent subclinical psychotic experiences: an 8-year cohort study. *Schizophrenia bulletin*, **37**, 84-93.

32 Kendler, K.S., McGuire, M., Gruenberg, A.M. and Walsh, D. (1995) Schizotypal symptoms and signs in the Roscommon Family Study. Their factor structure and familial relationship with psychotic and affective disorders. *Arch Gen Psychiatry*, **52**, 296-303.

33 Fanous, A., Gardner, C., Walsh, D. and Kendler, K.S. (2001) Relationship between positive and negative symptoms of schizophrenia and schizotypal symptoms in nonpsychotic relatives. *Arch Gen Psychiatry*, **58**, 669-673.

34 Kety, S.S., Rosenthal, D., Wender, P.H., Schulsinger, F. and Jacobsen, B. (1976) Mental illness in the biological and adoptive families of adopted individuals who have become schizophrenic. *Behav Genet*, **6**, 219-225.

35 Kendler, K.S., Gruenberg, A.M. and Strauss, J.S. (1981) An independent analysis of the Copenhagen sample of the Danish adoption study of schizophrenia. II. The relationship between schizotypal personality disorder and schizophrenia. *Arch Gen Psychiatry*, **38**, 982-984.

36 Bebbington, P.E., McBride, O., Steel, C., Kuipers, E., Radovanovic, M., Brugha, T., Jenkins, R., Meltzer, H.I. and Freeman, D. (2013) The structure of paranoia in the general population. *Br J Psychiatry*, **202**, 419-427.

37 Daneluzzo, E., Stratta, P., Di Tommaso, S., Pacifico, R., Riccardi, I. and Rossi, A. (2009) Dimensional, non-taxonic latent structure of psychotic symptoms in a student sample. *Soc Psychiatry Psychiatr Epidemiol*, **44**, 911-916.

38 Ahmed, A.O., Buckley, P.F. and Mabe, P.A. (2012) Latent structure of psychotic experiences in the general population. *Acta Psychiatr Scand*, **125**, 54-65.

39 Taylor, M.J., Freeman, D. and Ronald, A. (2016) Dimensional psychotic experiences in adolescence: Evidence from a taxometric study of a community-based sample. *Psychiatry research*, **241**, 35-42.

40 Binbay, T., Drukker, M., Elbi, H., Tanik, F.A., Ozkinay, F., Onay, H., Zagli, N., van Os, J. and Alptekin, K. (2012) Testing the psychosis continuum: differential impact of genetic and nongenetic risk factors and comorbid psychopathology across the entire spectrum of psychosis. *Schizophr Bull*, **38**, 992-1002.

41 Sullivan, P.F., Kendler, K.S. and Neale, M.C. (2003) Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Arch Gen Psychiatry*, **60**, 1187-1192.

42 Derks, E.M., Vorstman, J.A., Ripke, S., Kahn, R.S., Schizophrenia Psychiatric Genomic, C. and Ophoff, R.A. (2012) Investigation of the genetic association between quantitative measures of psychosis and schizophrenia: a polygenic risk score analysis. *PLoS One*, **7**, e37852.

43 Zammit, S., Hamshere, M., Dwyer, S., Georgiva, L., Timpson, N., Moskvina, V., Richards, A., Evans, D.M., Lewis, G., Jones, P. *et al.* (2014) A population-based study of genetic variation and psychotic experiences in adolescents. *Schizophrenia bulletin*, **40**, 1254-1262.

- 44 Jones, H.J., Stergiakouli, E., Tansey, K.E., Hubbard, L., Heron, J., Cannon, M., Holmans, P., Lewis, G., Linden, D.E., Jones, P.B. *et al.* (2016) Phenotypic Manifestation of Genetic Risk for Schizophrenia During Adolescence in the General Population. *JAMA Psychiatry*, **73**, 221-228.
- 45 Sieradzka, D., Power, R.A., Freeman, D., Cardno, A.G., McGuire, P., Plomin, R., Meaburn, E.L., Dudbridge, F. and Ronald, A. (2014) Are genetic risk factors for psychosis also associated with dimension-specific psychotic experiences in adolescence? *PloS one*, **9**, e94398.
- 46 Taylor, M.J., Martin, J., Lu, Y., Brikell, I., Lundstrom, S., Larsson, H. and Lichtenstein, P. (2017) Genetic evidence for shared risks across psychiatric disorders and related traits in a Swedish population twin sample. *BioRxiv*, in press.
- 47 Liuhanen, J., Suvisaari, J., Kajantie, E., Miettunen, J., Sarin, A.P., Jarvelin, M.R., Lonnqvist, J., Veijola, J. and Paunio, T. (2018) Interaction between compound genetic risk for schizophrenia and high birth weight contributes to social anhedonia and schizophrenia in women. *Psychiatry research*, **259**, 148-153.
- 48 Krapohl, E., Euesden, J., Zabaneh, D., Pingault, J.B., Rimfeld, K., Von Stumm, S., Dale, P.S., Breen, G., O'reilly, P.F. and Plomin, R. (2016) Phenome-wide analysis of genome-wide polygenic scores. *Molecular psychiatry*, **21**, 1188-1193.
- 49 Taylor, M.J., Martin, J., Lu, Y., Brikell, I., Lundstrom, S., Larsson, H. and Lichtenstein, P. (2018) Genetic evidence for shared risks across psychiatric disorders and related traits in a Swedish population twin sample. *BioRxiv*, in press.
- 50 Sieradzka, D., Power, R.A., Freeman, D., Cardno, A.G., Dudbridge, F. and Ronald, A. (2015) Heritability of Individual Psychotic Experiences Captured by Common Genetic Variants in a Community Sample of Adolescents. *Behavior genetics*, **45**, 493-502.
- 51 Cheesman, R., Selzam, S., Ronald, A., Dale, P.S., McAdams, T.A., Eley, T.C. and Plomin, R. (2017) Childhood behaviour problems show the greatest gap between DNA-based and twin heritability. *Translational psychiatry*, **7**, 1284.
- 52 Yang, J., Zeng, J., Goddard, M.E., Wray, N.R. and Visscher, P.M. (2017) Concepts, estimation and interpretation of SNP-based heritability. *Nature genetics*, **49**, 1304-1310.
- 53 Bulik-Sullivan, B.K., Loh, P.-R., Finucane, H.K., Ripke, S., Yang, J., Patterson, N., Daly, M.J., Price, A.L., Neale, B.M. and Schizophrenia Working Group of the Psychiatric Genomics, C. (2015) LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nature genetics*, **47**, 291.
- 54 Yang, J., Benyamin, B., McEvoy, B.P., Gordon, S., Henders, A.K., Nyholt, D.R., Madden, P.A., Heath, A.C., Martin, N.G. and Montgomery, G.W. (2010) Common SNPs explain a large proportion of the heritability for human height. *Nature genetics*, **42**, 565-569.
- 55 Pain, O. (2018), In *Psychological Sciences*. Birkbeck, University of London, Vol. PhD.
- 56 Nivard, M.G., Middeldorp, C.M., Lubke, G., Hottenga, J.-J., Abdellaoui, A., Boomsma, D.I. and Dolan, C.V. (2016) Detection of gene–environment interaction in pedigree data using genome-wide genotypes. *European Journal of Human Genetics*, **24**, 1803-1809.

- 57 Speed, D., Cai, N., Consortium, U., Johnson, M.R., Nejentsev, S. and Balding, D.J. (2017) Reevaluation of SNP heritability in complex human traits. *Nature genetics*, **49**, 986-992.
- 58 Tomppo, L., Ekelund, J., Lichtermann, D., Veijola, J., Jarvelin, M.R. and Hennah, W. (2012) DISC1 conditioned GWAS for psychosis proneness in a large Finnish birth cohort. *PLoS One*, **7**, e30643.
- 59 Krapohl, E., Hannigan, L.J., Pingault, J.B., Patel, H., Kadeva, N., Curtis, C., Breen, G., Newhouse, S.J., Eley, T.C., O'Reilly, P.F. *et al.* (2017) Widespread covariation of early environmental exposures and trait-associated polygenic variation. *Proc Natl Acad Sci U S A*, **114**, 11727-11732.
- 60 Sieradzka, D. (2015), In *Psychological Sciences*. Birkbeck, University of London, Vol. PhD.
- 61 Sariaslan, A., Fazel, S., D'Onofrio, B.M., Langstrom, N., Larsson, H., Bergen, S.E., Kuja-Halkola, R. and Lichtenstein, P. (2016) Schizophrenia and subsequent neighborhood deprivation: revisiting the social drift hypothesis using population, twin and molecular genetic data. *Translational psychiatry*, **6**, e796.
- 62 Plomin, R. and Bergeman, C.S. (1991) The nature of nurture: Genetic influence on "environmental" measures. *Behavioral & Brain Sciences*, **14**, 373-427.
- 63 Thapar, A. and McGuffin, P. (1996) Genetic influences on life events in childhood. *Psychol Med*, **26**, 813-820.
- 64 Shakoor, S., Zavos, H.M., McGuire, P., Cardno, A.G., Freeman, D. and Ronald, A. (2015) Psychotic experiences are linked to cannabis use in adolescents in the community because of common underlying environmental risk factors. *Psychiatry research*, **227**, 144-151.
- 65 Shakoor, S., McGuire, P., Cardno, A.G., Freeman, D., Plomin, R. and Ronald, A. (2015) A shared genetic propensity underlies experiences of bullying victimization in late childhood and self-rated paranoid thinking in adolescence. *Schizophr Bull*, **41**, 754-763.
- 66 Shakoor, S., Zavos, H.M., Haworth, C.M., McGuire, P., Cardno, A.G., Freeman, D. and Ronald, A. (2016) Association between stressful life events and psychotic experiences in adolescence: evidence for gene-environment correlations. *The British journal of psychiatry : the journal of mental science*, **208**, 532-538.
- 67 Singham, T., Viding, E., Schoeler, T., Arseneault, L., Ronald, A., Cecil, C.M., McCrory, E., Rijdsdijk, F. and Pingault, J.B. (2017) Concurrent and Longitudinal Contribution of Exposure to Bullying in Childhood to Mental Health: The Role of Vulnerability and Resilience. *JAMA Psychiatry*, **74**, 1112-1119.
- 68 Nesvag, R., Reichborn-Kjennerud, T., Gillespie, N.A., Knudsen, G.P., Bramness, J.G., Kendler, K.S. and Ystrom, E. (2017) Genetic and Environmental Contributions to the Association Between Cannabis Use and Psychotic-Like Experiences in Young Adult Twins. *Schizophr Bull*, **43**, 644-653.
- 69 Kong, A., Thorleifsson, G., Frigge, M.L., Vilhjalmsdottir, B.J., Young, A.I., Thorgeirsson, T.E., Benonisdottir, S., Oddsson, A., Halldorsson, B.V., Masson, G. *et al.* (2018) The nature of nurture: Effects of parental genotypes. *Science*, **359**, 424-428.
- 70 Bates, T.C., Maher, B.S., Medland, S.E., McAloney, K., Wright, M.J., Hansell, N.K., Kendler, K.S., Martin, N.G. and Gillespie, N.A. (2018) The Nature of Nurture:

Using a Virtual-Parent Design to Test Parenting Effects on Children's Educational Attainment in Genotyped Families. *Twin Res Hum Genet*, **21**, 73-83.

71 Mistry, S., Harrison, J.R., Smith, D.J., Escott-Price, V. and Zammit, S. (2017) The use of polygenic risk scores to identify phenotypes associated with genetic risk of schizophrenia: Systematic review. *Schizophr Res*, in press.

72 Ripke, S., Wray, N.R., Lewis, C.M., Hamilton, S.P., Weissman, M.M., Breen, G., Byrne, E.M., Blackwood, D.H., Boomsma, D.I., Cichon, S. *et al.* (2013) A mega-analysis of genome-wide association studies for major depressive disorder. *Mol Psychiatry*, **18**, 497-511.

73 Demontis, D., Walters, R.K., Martin, J., Mattheisen, M., Als, T.D., Agerbo, E., Belliveau, R., Bybjerg-Grauholm, J., Bækved-Hansen, M. and Cerrato, F. (2017) Discovery of the first genome-wide significant risk loci for ADHD. *bioRxiv*, in press., 145581.

74 Martin, J., Tilling, K., Hubbard, L., Stergiakouli, E., Thapar, A., Davey Smith, G., O'Donovan, M.C. and Zammit, S. (2016) Association of Genetic Risk for Schizophrenia With Nonparticipation Over Time in a Population-Based Cohort Study. *Am J Epidemiol*, **183**, 1149-1158.

75 Kelleher, I., Harley, M., Murtagh, A. and Cannon, M. (2011) Are screening instruments valid for psychotic-like experiences? A validation study of screening questions for psychotic-like experiences using in-depth clinical interview. *Schizophr Bull*, **37**, 362-369.

76 Pickrell, J.K., Berisa, T., Liu, J.Z., Segurel, L., Tung, J.Y. and Hinds, D.A. (2016) Detection and interpretation of shared genetic influences on 42 human traits. *Nature genetics*, **48**, 709-717.

77 Tomppo, L., Hennah, W., Miettunen, J., Järvelin, M.-R., Veijola, J., Ripatti, S., Lahermo, P., Lichtermann, D., Peltonen, L. and Ekelund, J. (2009) Association of variants in DISC1 with psychosis-related traits in a large population cohort. *Archives of general psychiatry*, **66**, 134-141.

78 Chapman, L.J., Chapman, J.P. and Raulin, M.L. (1976) Scales for physical and social anhedonia. *Journal of abnormal psychology*, **85**, 374.

79 Andreasen, N.C., Flaum, M. and Arndt, S. (1992) The Comprehensive Assessment of Symptoms and History (CASH): an instrument for assessing diagnosis and psychopathology. *Archives of general psychiatry*, **49**, 615-623.

80 Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium. (2011) Genome-wide association study identifies five new schizophrenia loci. *Nature genetics*, **43**, 969-976.

81 Boyd, A., Golding, J., Macleod, J., Lawlor, D.A., Fraser, A., Henderson, J., Molloy, L., Ness, A., Ring, S. and Smith, G.D. (2012) Cohort profile: the 'children of the 90s'—the index offspring of the Avon Longitudinal Study of Parents and Children. *International journal of epidemiology*, in press., dys064.

82 Haworth, C.M.A., Davis, O.S.P. and Plomin, R. (2013) Twins Early Development Study (TEDS): a genetically sensitive investigation of cognitive and behavioral development from childhood to young adulthood. *Twin Research and Human Genetics*, **16**, 117-125.

83 Zammit, S., Owen, M.J., Evans, J., Heron, J. and Lewis, G. (2011) Cannabis, COMT and psychotic experiences. *The British Journal of Psychiatry*, **199**, 380-385.

84 Yang, J., Lee, S.H., Goddard, M.E. and Visscher, P.M. (2011) GCTA: a tool for genome-wide complex trait analysis. *The American Journal of Human Genetics*, **88**, 76-82.

- 85 Ripke, S., Wray, N.R., Lewis, C.M., Hamilton, S.P., Weissman, M.M., Breen, G., Byrne, E.M., Blackwood, D.H.R., Boomsma, D.I. and Cichon, S. (2013) A mega-analysis of genome-wide association studies for major depressive disorder. *Molecular psychiatry*, **18**, 497-511.
- 86 PGC Bipolar Disorder Working Group. (2011) Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nature genetics*, **43**, 977-983.
- 87 Cross-Disorder Group of the Psychiatric Genomics Consortium. (2013) Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *The Lancet*, **381**, 1371-1379.
- 88 Davies, G., Armstrong, N., Bis, J.C., Bressler, J., Chouraki, V., Giddaluru, S., Hofer, E., Ibrahim-Verbaas, C.A., Kirin, M. and Lahti, J. (2015) Genetic contributions to variation in general cognitive function: a meta-analysis of genome-wide association studies in the CHARGE consortium (N= 53 949). *Molecular psychiatry*, **20**, 183.
- 89 Benyamin, B., Pourcain, B., Davis, O.S., Davies, G., Hansell, N.K., Brion, M.-J., Kirkpatrick, R.M., Cents, R.A.M., Franić, S. and Miller, M.B. (2014) Childhood intelligence is heritable, highly polygenic and associated with FNBP1L. *Molecular psychiatry*, **19**, 253.
- 90 Hibar, D.P., Stein, J.L., Renteria, M.E., Arias-Vasquez, A., Desrivières, S., Jahanshad, N., Toro, R., Wittfeld, K., Abramovic, L. and Andersson, M. (2015) Common genetic variants influence human subcortical brain structures. *Nature*, **520**, 224.
- 91 Furberg, H., Kim, Y., Dackor, J., Boerwinkle, E., Franceschini, N., Ardissino, D., Bernardinelli, L., Mannucci, P.M., Mauri, F. and Merlini, P.A. (2010) Genome-wide meta-analyses identify multiple loci associated with smoking behavior. *Nature genetics*, **42**, 441.
- 92 Rietveld, C.A., Medland, S.E., Derringer, J., Yang, J., Esko, T., Martin, N.W., Westra, H.-J., Shakhbazov, K., Abdellaoui, A. and Agrawal, A. (2013) GWAS of 126,559 individuals identifies genetic variants associated with educational attainment. *science*, in press., 1235488.
- 93 Lambert, J.C., Ibrahim-Verbaas, C.A., Harold, D., Naj, A.C., Sims, R., Bellenguez, C., DeStafano, A.L., Bis, J.C., Beecham, G.W. and Grenier-Boley, B. (2013) European Alzheimer's Disease Initiative (EADI); Genetic and Environmental Risk in Alzheimer's Disease; Alzheimer's Disease Genetic Consortium; Cohorts for Heart and Aging Research in Genomic Epidemiology. Meta-analysis of 74,046 individuals identifies 11 *Nature genetics*, **45**, 1452-1458.
- 94 Locke, A.E., Kahali, B., Berndt, S.I., Justice, A.E., Pers, T.H., Day, F.R., Powell, C., Vedantam, S., Buchkovich, M.L. and Yang, J. (2015) Genetic studies of body mass index yield new insights for obesity biology. *Nature*, **518**, 197-206.
- 95 Wood, A.R., Esko, T., Yang, J., Vedantam, S., Pers, T.H., Gustafsson, S., Chu, A.Y., Estrada, K., Luan, J.a. and Kutalik, Z. (2014) Defining the role of common variation in the genomic and biological architecture of adult human height. *Nature genetics*, **46**, 1173.
- 96 Stefanis, N.C., Hanssen, M., Smirnis, N.K., Avramopoulos, D.A., Evdokimidis, I.K., Stefanis, C.N., Verdoux, H. and Van Os, J. (2002) Evidence that three dimensions of psychosis have a distribution in the general population. *Psychological medicine*, **32**, 347-358.

- 97 Goodman, A., Heiervang, E., Collishaw, S. and Goodman, R. (2011) The 'DAWBA bands' as an ordered-categorical measure of child mental health: description and validation in British and Norwegian samples. *Social psychiatry and psychiatric epidemiology*, **46**, 521-532.
- 98 Goodman, R., Ford, T., Richards, H., Gatward, R. and Meltzer, H. (2000) The Development and Well-Being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. *The Journal of Child Psychology and Psychiatry and Allied Disciplines*, **41**, 645-655.
- 99 Steinberg, S., de Jong, S., Andreassen, O.A., Werge, T., Børglum, A.D., Mors, O., Mortensen, P.B., Gustafsson, O., Costas, J. and Pietiläinen, O.P.H. (2011) Common variants at VRK2 and TCF4 conferring risk of schizophrenia. *Human molecular genetics*, **20**, 4076-4081.
- 100 Kendler, K.S., Lieberman, J.A. and Walsh, D. (1989) The Structured Interview for Schizotypy (SIS): a preliminary report. *Schizophrenia bulletin*, **15**, 559.
- 101 Vollema, M.G. and Ormel, J. (2000) The reliability of the Structured Interview for Schizotypy-Revised. *Schizophrenia bulletin*, **26**, 619.
- 102 Chapman, L.J., Chapman, J.P. and Raulin, M.L. (1978) Body-image aberration in Schizophrenia. *Journal of abnormal psychology*, **87**, 399.
- 103 Eckblad, M. and Chapman, L.J. (1986) Development and validation of a scale for hypomanic personality. *Journal of abnormal psychology*, **95**, 214.
- 104 Golden, R.R. and Meehl, P.E. (1979) Detection of the schizoid taxon with MMPI indicators. *Journal of Abnormal Psychology*, **88**, 217.
- 105 Stefanis, N.C., Vitoratou, S., Ntzoufras, I., Smyrnis, N., Evdokimidis, I. and Stefanis, C.N. (2006) Psychometric properties of the Greek version of the Schizotypal Personality Questionnaire (SPQ) in young male obligatory conscripts: a two years test-retest study. *Personality and Individual Differences*, **41**, 1275-1286.
- 106 Roussos, P., Giakoumaki, S.G., Georgakopoulos, A., Robakis, N.K. and Bitsios, P. (2011) The CACNA1C and ANK3 risk alleles impact on affective personality traits and startle reactivity but not on cognition or gating in healthy males. *Bipolar disorders*, **13**, 250-259.
- 107 Raine, A. (1991) The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophrenia bulletin*, **17**, 555.
- 108 Claridge, G. and Broks, P. (1984) Schizotypy and hemisphere function—I: Theoretical considerations and the measurement of schizotypy. *Personality and Individual Differences*, **5**, 633-648.
- 109 Rantakallio, P. (1969) Groups at risk in low birth weight infants and perinatal mortality. *Acta Paediatrica Scandinavica*, **193**, Suppl-193.
- 110 Anckarsäter, H., Lundström, S., Kollberg, L., Kerekes, N., Palm, C., Carlström, E., Långström, N., Magnusson, P.K.E., Halldner, L. and Bölte, S. (2011) The child and adolescent twin study in Sweden (CATSS). *Twin Research and Human Genetics*, **14**, 495-508.
- 111 Kelleher, I., Harley, M., Murtagh, A. and Cannon, M. (2011) Are screening instruments valid for psychotic-like experiences? A validation study of screening questions for psychotic-like experiences using in-depth clinical interview. *Schizophrenia bulletin*, **37**, 362-369.
- 112 Palla, L. and Dudbridge, F. (2015) A fast method that uses polygenic scores to estimate the variance explained by genome-wide marker panels and

the proportion of variants affecting a trait. *The American Journal of Human Genetics*, **97**, 250-259.

113 Bulik-sullivan, B., Finucane, H.K., Anttila, V., Day, F.R., Consortium, R., Consortium, P.G., Price, A.L. and Neale, B.M. (2015) An Atlas of Genetic Correlations across Human Diseases and Traits. in press.

## Figure legends

Figure 1. SNP heritability estimates and twin heritability estimates for psychotic experiences and negative symptom traits (PENS) in the community. SNP and twin heritability estimates come from the largest respective studies (1, 23) and are shown with standard errors and 95% confidence intervals, respectively. For SNP heritability estimates, \*  $p < 0.05$ ; \*\* $p < 0.01$ .

Figure 2. Polygenic risk scores for schizophrenia, bipolar disorder and major depression and their prediction of adolescent psychotic experiences and negative symptom traits (PENS) in the community from a recent meta-analysis (1). Published by John Wiley & Sons Ltd. © The Authors. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics Published by Wiley Periodicals, Inc.

**Table 1. Genome-wide studies of psychotic experiences and negative symptom traits (PENS) in the community.**

Study	Type	Sample/s	Relevant Measure/s	Key Methods	Key Results
Tomppo et al., 2012 (58)	GWAS	Northern Finland Birth Cohort 1966 (NFBC66) (77): $N = 4,561$ unrelated individuals assessed at age 31 years. Individuals were stratified based on <i>DISC1</i> genotypes.	Self-report Revised Social Anhedonia Scale (SAS) and Revised Physical Anhedonia Scale (PHAS) (78).	GWAS: Univariate GWASs for each scale were performed within <i>DISC1</i> genotype-based subgroups of the sample. Three groups derived called 'risk', 'protective', and 'neutral', containing 3054, 962 and 545 individuals respectively. Univariate GWAS also performed using the whole sample with <i>DISC1</i> genotype as covariate. In total, 8 GWAS performed. Pathway analysis used to characterise relationship between implicated genes and the <i>DISC1</i> pathway, and functional enrichment analysis for implicated micro RNAs.	GWAS: No genome-wide significant markers across all GWASs. 18 loci suggestively associated based on three or more variants within a 300kb window with $p < 1 \times 10^{-3}$ . Ingenuity Pathway Analysis demonstrated 7 of 24 genes implicated by suggestive loci ( $p < 1 \times 10^{-3}$ ) were involved in the <i>DISC1</i> pathway. Two microRNAs were within suggestive loci.
Derks et al., 2012 (42)	PRS	Sample of schizophrenia cases and controls from The Netherlands. Analyses on controls discussed as per this review's inclusion criteria. Controls had no family history of psychiatric disorder. $N = 148$ control individuals assessed for psychotic symptom dimensions.	Structured interview by clinician using the Comprehensive Assessment of Symptoms and History (CASH) (79). Psychotic symptom dimensions, derived from factor analysis were Disorganisation, Positive, Negative, Mania, and Depression.	PRS analysis: Tested for Pearson correlation between genetic risk for schizophrenia (PGC1) (80) and psychotic symptom dimension scores in control individuals. Sensitivity analyses were performed to assess the variance explained by ancestry components.	No significant association identified between schizophrenia genetic risk and psychotic symptom dimensions in the control individuals.

Study	Type	Sample/s	Relevant Measure/s	Key Methods	Key Results
Zammit et al., 2014 (43)	GWAS; PRS	<p>Avon Longitudinal Study of Parents and Children (ALSPAC) (81): <math>N = 3,483</math> unrelated individuals assessed at 12 and 18 years. Definite and none psychotic experience groups (<math>N = 424</math> and <math>3,059</math>, respectively) defined by at least one definite psychotic experience at either 12 or 18.</p> <p>Secondary analysis was performed where definite/none psychotic experience groups were defined by at least one definite or suspected psychotic experience at either age (<math>N = 912</math> and <math>2,588</math>, respectively).</p>	<p>Semi-structured interview using the Psychosis-like Symptoms interview (PLIKSi) (30): based on the Schedule for Clinical Assessment in Psychiatry (SCAN). Included 11 questions assessing hallucinations, delusions, and thought interference.</p>	<p>Candidate variation analysis based on previously associated genetic variation for schizophrenia.</p> <p>GWAS: Logistic regression to identify genetic variants associated with definite/none psychotic experience groups.</p> <p>PRS analysis: Logistic regression to test for association between schizophrenia genetic risk (PGC1) (80) and definite/none psychotic experience groups.</p>	<p>Candidate variation analysis: No variant achieved significance after correcting multiple testing.</p> <p>GWAS: No variant achieved genome-wide significance (<math>p &lt; 5 \times 10^{-8}</math>). 121 variants achieved <math>p &lt; 5 \times 10^{-5}</math> representing 31 independent signals.</p> <p>PRS: No significant association between schizophrenia PRS and definite/none psychotic experience groups. Secondary analyses with broader phenotype were the same as primary analysis.</p>

Study	Type	Sample/s	Relevant Measure/s	Key Methods	Key Results
Sieradzka et al., 2014 (45)	PRS	Discovery sample: Twins Early Development Study (TEDS) (82): $N = 2,152$ unrelated individuals assessed at 16 years.  Replication sample: ALSPAC (81): $N = 3,427$ unrelated individuals assessed at age 16 years.	Discovery sample: Specific Psychotic Experiences Questionnaire (SPEQ) (11): Contains six subscales assessing PENS domains including self-reported Paranoia, Hallucinations, Grandiosity, Cognitive Disorganisation, Anhedonia and parent-report Negative Symptoms.  Replication sample: Self-reported Psychosis-like Symptoms Questionnaire (PLIKS-Q)(83). Assesses positive symptoms including paranoia, hallucinations and delusions.	Candidate variation analysis: Variants selected based on previously associated genetic variation for schizophrenia. First in TEDS, with any significant SNPs replicated in ALSPAC.  PRS analysis: Linear regression to test for association between schizophrenia genetic risk (PGC2) (10), bipolar disorder, and specific PENS within TEDS. A one-tailed hypothesis that there would be a positive association was used.  Genome-wide significant variation risk scoring: Tested for association between PENS and risk scores based on SNPs previously associated with schizophrenia at genome-wide significance.	Candidate variation analysis: After accounting for multiple testing, no candidate variation achieved significance. The strongest evidence for association was within Transcription Factor 4 ( <i>TCF4</i> ). The association between candidate SNPs within <i>TCF4</i> were not significant in the replication sample.  PRS: No significant positive association between PENS and schizophrenia PRS. Although a one tailed hypothesis was employed, there were nominally significant negative associations between schizophrenia genetic risk, Anhedonia and Negative Symptoms, and bipolar disorder genetic risk and Anhedonia.  Genome-wide significant variation risk scoring: The schizophrenia composite score based on selected genome-wide significant genetic variation did not significantly predict any adolescent PENS.
Sieradzka et al., 2015 (50)	SNP $h^2$	TEDS (82): $N = 2,152$ unrelated individuals assessed at 16.	Specific Psychotic Experiences Questionnaire (SPEQ) (11): see above.	Estimating SNP heritability: This was performed using GREML in GCTA (84).	Estimating SNP heritability: SNP heritability estimates for Paranoia (14%), Cognitive Disorganisation (19%), Grandiosity (17%) and Anhedonia (20%) suggest their variation is in part attributable to common genetic variation. Large standard errors due to sample size. Hallucinations and Negative Symptoms showed no evidence of non-zero SNP heritability.

<b>Study</b>	<b>Type</b>	<b>Sample/s</b>	<b>Relevant Measure/s</b>	<b>Key Methods</b>	<b>Key Results</b>
Krapohl et al., 2016 (48)	PRS	TEDS (82): <i>N</i> = 2,152 unrelated individuals assessed for PENS at 16 years. Same sample as Sieradzka et al 2014 (45) above.	As part of a phenome-wide cohort study on many adolescent outcomes, PENS captured using SPEQ (11) (described above).	PRS analysis: Tested for association between adolescent paranoia, grandiosity, cognitive disorganisation and negative symptoms (and other adolescent behaviours) and PRSs for schizophrenia (PGC2) (10), major depressive disorder (85), bipolar disorder (86), ADHD (87), autism (87), adult IQ (88), child IQ (89), intracranial volume (90), ever smoked (91), educational attainment (92), Alzheimer's (93), body mass index (94) and height (95).	Results showed no significant associations after multiple testing was accounted for. Nominally significant negative associations were found between Negative Symptoms and educational attainment, Grandiosity and ever smoked, and Cognitive Disorganisation and height. A nominally significant positive association was identified between Grandiosity and body mass index.

Study	Type	Sample/s	Relevant Measure/s	Key Methods	Key Results
Jones et al., 2016 (44)	PRS	<p>ALSPAC (81): Sample included unrelated individuals only.</p> <p><math>N = 5,444</math> individuals assessed for positive symptoms at 12 or 18 years. Definite and none positive symptom groups (<math>N=419</math> and <math>5,025</math> respectively) defined by at least one definite psychotic experience at either 12 or 18.</p> <p><math>N = 3,673</math> individuals assessed for negative symptoms at 16.5 years. High/low negative symptom groups: <math>N = 337</math> and <math>3,336</math> respectively.</p> <p><math>N = 4,106</math> individuals assessed for depression outcome likelihood at 15.5 years. High/low groups: <math>N= 373</math> and <math>3,733</math> respectively.</p> <p><math>N = 4,107</math> individuals assessed for anxiety outcome likelihood at 15.5 years. High/low groups: <math>N = 444</math> and <math>3,663</math> respectively.</p>	<p>Positive symptoms were assessed using the PLIKSi (30) (described above).</p> <p>Negative psychosis-like symptoms were assessed using a subset of 10 items from the Community Assessment of Psychotic Experiences (CAPE) self-report questionnaire (96). This measure assessed features such as apathy, anergia and asociality.</p> <p>Depressive and anxiety disorder outcomes were derived from the semi-structured Development and Well-Being Assessment (DAWBA) semi-structured interview (97, 98).</p>	<p>PRS analysis: Tested for association between genetic risk for schizophrenia (PGC2) (10) and positive symptoms, negative symptoms, anxiety and depression disorders using logistic regression.</p> <p>Sensitivity analyses performed to determine whether effects varied when using different thresholds to distinguish groups, varying measurement cut-offs or tools, the effect of including individuals with a psychotic disorder diagnosis at age 18, and the effect of including individuals with a parent with a diagnosis of a psychotic disorder.</p>	<p>PRS analysis: A significant positive association between schizophrenia PRS and negative symptoms (<math>OR = 1.21</math>; <math>r^2 = 0.7\%</math>) and anxiety disorder (<math>OR = 1.17</math>; <math>r^2 = 0.5\%</math>) was reported. Positive symptoms showed a near significant positive association when using more relaxed <math>p</math>-value thresholds for the PRS but a near significant negative association when using a stringent <math>p</math>-value threshold for the PRS.</p> <p>Sensitivity analyses demonstrated that the results were consistent when using different thresholds to determine the phenotypic groups. Results were also consistent when combining interview and questionnaire data of positive psychotic experiences, when excluding individuals with a psychotic disorder diagnosis at age 18, or when excluding individuals with a parent with a diagnosis of a psychotic disorder. Associations with negative symptoms and anxiety disorder persisted when including the other measures in a multivariate model</p>

<b>Study</b>	<b>Type</b>	<b>Sample/s</b>	<b>Relevant Measure/s</b>	<b>Key Methods</b>	<b>Key Results</b>
Van Os et al., 2017 (4)	PRS	Genetic Risk and Outcome of Psychosis (GROUP) study (99): <i>N</i> = 871 siblings and 812 parents of patients with psychotic disorder, and <i>N</i> = 523 healthy individuals. Mean ages: healthy controls = 31.10 years, siblings = 27.85 years, parents = 54.83 years.	Individuals assessed using self-report CAPE questionnaire (described above) and the structured interview by clinicians using the Structured interview for Schizotypy - Revised (SIS-R) (100, 101). CAPE included positive, negative and depressive symptom subscales. SIS-R contained positive and negative schizotypy subscales.	PRS analysis: Tested for association between schizophrenia (PGC2) (10) PRS and CAPE and SIS-R totals and subscales. IQ included as covariate. Relatives of psychotic individuals and healthy controls were analysed separately. Relatedness between siblings and parents controlled using mixed linear modelling. The independence of associations for each subscale was assessed by covarying for all other subscales. Variance explained by the schizophrenia PRS was not estimated.	<p>Among relatives of patients, significant positive associations between schizophrenia PRS and CAPE total, CAPE depressive, SIS-R total and SIS-R positive scores were identified, but not for CAPE positive, CAPE negative, or SIS-R negative. Secondary analyses showed that only CAPE depressive symptoms were significantly associated with schizophrenia PRS when accounting for all other PENS dimension scores and IQ.</p> <p>Among healthy individuals, significant positive associations between schizophrenia PRS and all SIS-R scores (total, positive, and negative) were identified, but not for any CAPE measures. Secondary analyses showed that only the SIS-R positive subscale showed a significant positive association with schizophrenia PRS when accounting for other scales. Secondary analyses showed a significant negative association between schizophrenia PRS and CAPE negative scores when accounting for covariance with other subscales.</p>

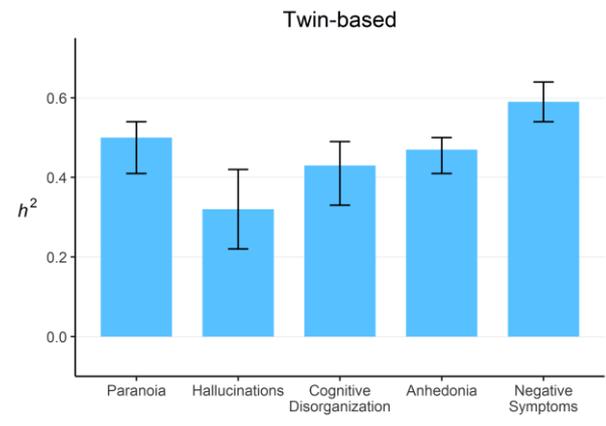
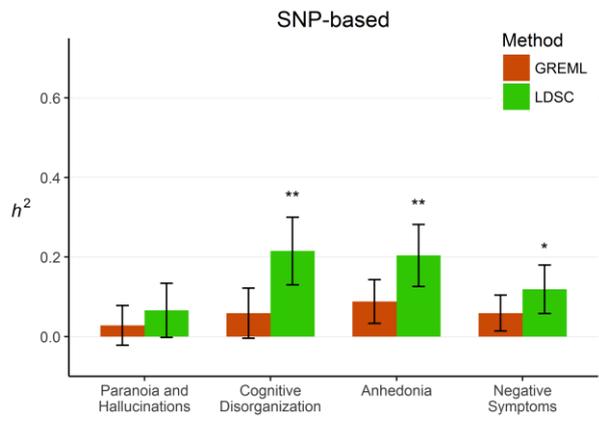
Study	Type	Sample/s	Relevant Measure/s	Key Methods	Key Results
Ortega-Alonso et al., 2017 (2)	GWAS; SNP $h^2$	NFBC66: $N =$ maximum of 4,269 unrelated individuals assessed at age 31.	Self-report psychosis proneness questionnaires were used: Perceptual Aberration Scale (PAS) (102), Hypomanic Personality Scale (HPS) (103), Revised Social Anhedonia Scale (SAS), Revised Physical Anhedonia Scale (PHAS) (78), and the Schizoidia Scale (SCHS) (104).	<p>Estimation of SNP heritability: Performed using GREML in GCTA (84).</p> <p>Estimation of genetic correlation between psychosis proneness scales: Performed using GREML in GCTA. Not performed for Schizoidia scale due to low SNP heritability estimate.</p> <p>GWAS: Univariate and multivariate GWASs. Summary statistics were further analysed using gene-based association testing. Not performed for Schizoidia scale due to low heritability estimate.</p>	<p>SNP heritability estimation: HPS = 27.4%, PAS = 16.6%, PHAS = 26.6%, SAS = 20.4%, and SCHS = &lt;0.1%.</p> <p>Estimation of genetic correlation between psychosis proneness scales: Identified a significant positive genetic correlation between PHAS and SAS scales (<math>r_G = 0.73</math>), and a significant negative genetic correlation between HPS and PHAS scales (<math>r_G = -0.44</math>), both of which are in the same direction as phenotypic and environmental correlations. All other pairwise genetic correlations between the scales were non-significant.</p> <p>Univariate GWAS: Identified a genome-wide significant association for HPS in the <i>TMC7</i> gene, although there was no replication reported. Gene-based analysis of results identified 14 genes at significance after Bonferroni correction across the other four remaining psychosis proneness scales.</p> <p>Bivariate GWAS: Combined analysis of HPS and PHAS identified a locus with borderline genome-wide significance nearest to <i>AR1D1B</i>.</p>

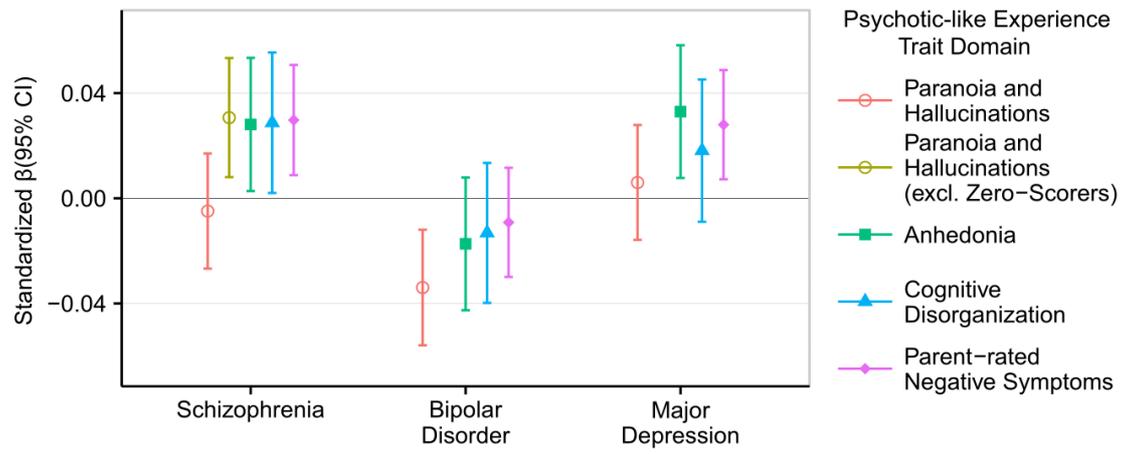
Study	Type	Sample/s	Relevant Measure/s	Key Methods	Key Results
Hatzimanolis et al., 2018 (3)	PRS; GxE	Discovery sample: Athens Study of Psychosis Proneness and Incidence of Schizophrenia (ASPIS) (105): <i>N</i> = 875 unrelated male conscripts (mean age = 20.8) at induction. <i>N</i> = 121 at 18-month follow up.  Replication sample: Learning on Genetics of Schizophrenia Spectrum (LOGOS) replication sample (106): <i>N</i> = 690 unrelated conscript males (mean age = 22.3).	Discovery sample: Self-report Schizotypal Personality Questionnaire (SPQ) (107) and Perceptual Aberration Scale (PAS) (102). Assessed at the time of conscription (see sample) and at follow up 18-months later.  Replication sample: Self-report Schizotypal Traits Questionnaire (STQ) (108) assessed three dimensions of positive schizotypy.	PRS analysis in discovery sample: Tested for association between schizophrenia (PGC2) (10) PRS and four SPQ dimensions (positive, negative, disorganisation, and paranoid), and PAS score at conscription. Years of education included as covariate. Tested for interaction effect between environmental stress (conscription) and schizophrenia genetic risk predicts SPQ factors and PAS score. Achieved by comparing schizophrenia PRS association results at conscription and follow up, and by comparing the difference in SPQ and PAS scores at the two time points, stratified by high and low schizophrenia PRS.  PRS analysis in replication sample: Tested for association between STQ dimensions and schizophrenia genetic risk. An interaction effect between schizophrenia genetic risk and anxiety was assessed.	PRS analysis in discovery sample: Significant negative genetic association identified between schizophrenia genetic risk and PAS scores, and positive, disorganisation and paranoid SPQ dimensions (no significant association found for negative SPQ dimension). In the replication sample, point estimates of association between schizophrenia PRS and STQ dimensions were also negative, although non-significant. One interaction identified, with lower PRS carriers showed higher PAS scores in the stressed condition compared to high PRS carriers (interactions not significant for SPQ dimensions). PRS analysis in replication sample: An interaction between anxiety and schizophrenia risk significantly predicted lower paranoid ideation.

Study	Type	Sample/s	Relevant Measure/s	Key Methods	Key Results
Liuhanen et al., 2018 (47)	PRS; GxE	Discovery Sample: NFBC66 (109): <i>N</i> = maximum of 4,223 unrelated individuals assessed at age 31 years.  Replication sample: The Schizophrenia Family sample: <i>N</i> = 144 (including relatives), 31.2% with schizophrenia.	Discovery sample: Self-report Revised Social Anhedonia Scale (described above).  Replication sample: Self-report Revised Social Anhedonia Scale (described above).	Genome-wide significant variation risk scoring: Genetic risk scores for schizophrenia were calculated based on 8 genome-wide significant SNPs identified in the PGC1 schizophrenia GWAS (80), and separately a 'broader genetic risk score' was calculated using the 128 SNPs identified as genome-wide significant in the PGC2 schizophrenia GWAS (10). Only the PGC1 selected risk score was calculated in the replication sample due to limited genome coverage.  Linear regression was used to assess the relationship between genetic risk, birth weight and social anhedonia.  Individuals with low birth weight (<2.5 kg) were excluded.	Genome-wide significant variation risk scoring: In NFBC66, no association between selected genetic risk score for schizophrenia and social anhedonia. Interaction analysis showed that high genetic risk of schizophrenia in combination with high birth weight predicted high social anhedonia. In the replication sample with schizophrenia this interaction effect was in the same direction but not significant.
Taylor et al., 2017 (46)	PRS	The Child and Adolescent Twin Study in Sweden (CATSS) (110). Relevant measures were completed at age 18 years.  <i>N</i> = 5,368 individuals (including cotwins) assessed for parent-report positive psychotic experiences.  <i>N</i> = 5,518 individuals (including cotwins) assessed for self-report positive psychotic experiences.	Self- and parent-report positive psychotic experiences were assessed using the self- and parent-report versions of the Adolescent Psychotic-Like Symptom Screener (APSS) questionnaire (111).	PRS analysis: Tested for association between schizophrenia PRS (PGC2) (10) and positive experiences (self- and parent-report) using linear regression with a Generalised Estimating Equation (GEE) to account for the presence of twin-pairs.	PRS analysis: a significant association between schizophrenia genetic risk and self- ( $r^2 = 0.15\%$ ) and parent-reported ( $r^2 = 0.17\%$ ) positive psychotic experiences.

Study	Type	Sample/s	Relevant Measure/s	Key Methods	Key Results
Pain et al., 2018 (1)	GWAS; PRS; SNP $h^2$	Discovery sample: TEDS (82), ALSPAC (81) and CATSS (110) assessed for self-reported Paranoia and Hallucinations ( $N = 8,665$ ), Anhedonia ( $N = 6,579$ ), Cognitive Disorganisation ( $N = 6,297$ ), and parent-reported Negative Symptoms ( $N = 10,098$ ). Individuals were assessed between 16-18 years. Sample sizes include cotwins.  Replication sample: Independent subset of TEDS genotyped at a later stage than the TEDS sample above. $N = 2,359$ individuals (including cotwins) assessed for self-reported Anhedonia at age 16.	Common measures of self-report Paranoia and Hallucinations, Cognitive Disorganisation, Anhedonia, and Parent-report Negative Symptoms were derived across three samples to allow combined analysis of these four PENS domains.  In TEDS items came from the SPEQ (see above).  In ALSPAC and CATSS, items came from a selection of psychopathology questionnaires that mirrored items from SPEQ.  Replication sample: Anhedonia assessed with SPEQ Anhedonia subscale.	GWAS of 4 PENS domains using linear regression and GEE to account for the presence of twin-pairs.  Estimation of SNP heritability: SNP heritability of the four PENS domains estimated using GREML in GCTA (84) and LD-Score regression (53).  PRS analysis: Tested for association between schizophrenia (PGC2) (10), bipolar disorder (86) and major depression (PGC1) (85) PRSs, and the four PENS domains using linear regression with a GEE to account for twin-pairs. Post-hoc analysis of the association between schizophrenia PRS and Paranoia and Hallucinations when excluding zero-scorers was also performed.  Genetic covariance estimation: Genetic covariance between schizophrenia, bipolar disorder, major depression, and the four PENS domains was estimated using AVENGEME analysis (112) of PRS association results, and LD-Score Regression (113).	GWAS: Genome-wide association analysis of four PENS domains returned 1 locus achieving genome-wide significance and 37 loci at suggestive significance ( $p < 1 \times 10^{-5}$ ). The genome-wide significant association was for Anhedonia and was within the <i>IDO2</i> gene, a key enzyme in the kynurenine pathway.  Estimation of SNP heritability from GREML: Paranoia and Hallucinations = 2.8%, Anhedonia = 8.8% Cognitive Disorganisation = 5.9%, and Negative Symptoms = 5.9% (Figure 1). LD-score estimates ranged from 6.6%-21.5% (Figure 1).  PRS analysis: Significant association between the schizophrenia PRS and Anhedonia ( $r^2 = 0.08\%$ ), Cognitive disorganisation ( $r^2 = 0.08\%$ ), and Negative Symptoms ( $r^2 = 0.09\%$ ) but not (initially) for Paranoia and Hallucinations. Post-hoc analysis showed a significant association between schizophrenia PRS and Paranoia and Hallucinations when excluding individuals scoring zero on that domain ( $r^2 = 0.09\%$ ). PRS analysis also identified an association between major depression PRS and Anhedonia ( $r^2 = 0.11\%$ ) and Parent-report Negative Symptoms ( $r^2 = 0.08\%$ ). A negative association between Paranoia and Hallucinations and genetic risk for bipolar disorder was identified ( $r^2 = 0.12\%$ ).  Genetic covariance estimation: AVENGEME analysis confirmed the significant associations identified by PRS analysis and identified other additional significant genetic covariance estimates.

*Note.* Type column shows which methods were included in study. AVENGEME, Additive variance explained and number of genetic effects methods of estimation; LD, linkage disequilibrium; PGC, Psychiatric Genomics Consortium; PRS, polygenic risk scores; SNP, single nucleotide polymorphism; PENS, psychotic experiences and negative symptom traits; IQ, intelligence quotient; GCTA, Genome-wide Complex Trait Analysis; GREML, genomic-relatedness-matrix restricted maximum likelihood; ADHD, attention deficit hyperactivity disorder; GWAS, genome-wide association study; SNP  $h^2$ , SNP heritability; GxE, genome-wide gene-environment interaction analyses.





## Abbreviations

PENS, psychotic experience and negative symptom traits; WHO, World Health Organisation; UK, United Kingdom; PE, psychotic experience; NS, negative symptom; TEDS, Twins Early Development Study; ALSPAC, Avon Longitudinal Study of Parents and Children; CATSS, Child and Adolescent Twin Study in Sweden; SNP, single nucleotide polymorphism; GREML, genomic-relatedness-matrix restricted maximum likelihood; LD, linkage disequilibrium; MAF, minor allele frequency; ERP, event-related potential; EEG, electroencephalogram; GWAS, genome-wide association study; NFBC, Northern Finland Birth Cohort; PGC, Psychiatric Genomics Consortium; PRS, polygenic risk scoring; rGE, gene-environment correlation; GxE, gene-environment interaction; ASD, autism-spectrum disorders; ADHD, attention deficit hyperactivity disorder; AVENGEME, Additive variance explained and number of genetic effects methods of estimation; NFBC66, Northern Finland Birth Cohort 1966; SAS, Revised Social Anhedonia Scale; PHAS, Revised Physical Anhedonia Scale; CASH, Comprehensive Assessment of Symptoms and History; PLIKSi, Psychosis-like Symptoms interview; SCAN, Schedule for Clinical Assessment in Psychiatry; PLIKS-Q, Psychosis-like Symptoms Questionnaire; CAPE, Community Assessment of Psychotic Experiences; DAWBA, Development and Well-Being Assessment; GROUP, Genetic Risk and Outcome of Psychosis; SIS-R, Structured interview for Schizotypy – Revised; PAS, Perceptual Aberration Scale; HPS, Hypomanic Personality Scale; SCHS, Schizoidia Scale; GCTA, Genome-wide Complex Trait Analysis; ASPIS, Athens Study of Psychosis Proneness and Incidence of Schizophrenia; LOGOS, Learning on Genetics of Schizophrenia Spectrum; SPQ, Schizotypal Personality Questionnaire; STQ, Schizotypal Traits Questionnaire; APSS, Adolescent Psychotic-Like Symptom Screener; GEE, Generalised Estimating Equation.