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Gene–environment interplay in the etiology of psychosis

Alyson Zwicker[1,2,3], Eileen M. Denovan-Wright[4] and Rudolf Uher[1,2,3,5]

[1]Department of Pathology, Dalhousie University, Halifax, NS, Canada; [2]Department of Psychiatry, Dalhousie University, Halifax, NS, Canada; [3]Nova Scotia Health Authority, Halifax, NS, Canada; [4]Department of Pharmacology, Dalhousie University, Halifax, NS, Canada and [5]Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK

Invited Review

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Author for correspondence:
Rudolf Uher,
E-mail: uher@dal.ca

Abstract

Schizophrenia and other types of psychosis incur suffering, high health care costs and loss of human potential, due to the combination of early onset and poor response to treatment. Our ability to prevent or cure psychosis depends on knowledge of causal mechanisms. Molecular genetic studies show that thousands of common and rare variants contribute to the genetic risk for psychosis. Epidemiological studies have identified many environmental factors associated with increased risk of psychosis. However, no single genetic or environmental factor is sufficient to cause psychosis on its own. The risk of developing psychosis increases with the accumulation of many genetic risk variants and exposures to multiple adverse environmental factors. Additionally, the impact of environmental exposures likely depends on genetic factors, through gene–environment interactions. Only a few specific gene–environment combinations that lead to increased risk of psychosis have been identified to date. An example of replicable gene–environment interaction is a common polymorphism in the *AKT1* gene that makes its carriers sensitive to developing psychosis with regular cannabis use. A synthesis of results from twin studies, molecular genetics, and epidemiological research outlines the many genetic and environmental factors contributing to psychosis. The interplay between these factors needs to be considered to draw a complete picture of etiology. To reach a more complete explanation of psychosis that can inform preventive strategies, future research should focus on longitudinal assessments of multiple environmental exposures within large, genotyped cohorts beginning early in life.

Psychosis refers to a subset of severe mental illness marked by delusions, hallucinations, and disorganized behavior. Schizophrenia is the prototypical psychotic disorder and it is defined by the presence of persistent psychotic symptoms and impaired functioning. However, psychosis manifests across a spectrum of conditions including major depressive disorder, bipolar disorder, schizoaffective disorder, delusional and schizophreniform disorder. Over 3% of individuals develop a psychotic disorder at some point during their lifetime but less than 1% are diagnosed with schizophrenia (Perala *et al.* 2007). All forms of psychosis tend to emerge in early adulthood, cause persistent disability, and premature death (Smith, 2011; Reininghaus *et al.* 2015). Psychotic disorders are often preceded by early manifestations of psychopathology, including transitory psychotic symptoms that commonly occur in childhood (Kelleher *et al.* 2012). Childhood psychotic symptoms tend to be transient but they are associated with increased risk of psychotic disorders in adulthood (Poulton *et al.* 2000; Fisher *et al.* 2013) and may be considered antecedents to psychotic illness (Uher *et al.* 2014). Knowledge of mechanisms involved in the etiology of psychosis may inform effective prevention. While a variety of risk factors have been identified, the causation of psychosis is still far from being understood. In this paper, we take stock of genetic and environmental factors associated with psychosis. Since there is substantial overlap of etiological factors across all types of severe mental illness (Uher & Zwicker, 2017), we include evidence on the entire spectrum of psychotic disorders wherever possible. However, the largest body of data has been collected specifically on schizophrenia. We will review genetic and environmental contributions to psychosis separately before examining the joint effects of genetics and the environment. We will conclude by providing suggestions to guide future research.

The role of genetics in the development of psychosis

Psychosis runs in families. The strongest known predictor of risk is having a close biological relative who is affected (Gottesman *et al.* 2010). Results from adoption and twin studies suggest that the familial clustering of psychosis is due largely to genetic factors. Among individuals with schizophrenia who were adopted at birth, increased rates of schizophrenia were found among their biological relatives and not within their adoptive families (Kety *et al.*

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1994). Additionally, twin studies show that monozygotic twins, who are genetically identical, are substantially more similar in their propensity to develop schizophrenia than are dizygotic twins, who share only half of their genetic material. The heritability of schizophrenia derived from twin studies is estimated to be 92% (Polderman *et al.* 2015). Twin and family studies also suggest a substantial genetic contribution to psychotic symptoms in childhood (Zavos *et al.* 2014). Taken together, this information strongly suggests that genetic factors significantly contribute to psychosis.

The last two decades have seen major progress in the identification of specific genetic variants that contribute to the risk of psychosis. To date, most molecular genetic investigations have focused on schizophrenia. Schizophrenia is a complex disorder and no single gene or genetic variant has been implicated as a necessary and sufficient causal factor. In linkage analysis, multiple loci across the genome have met the threshold for genome-wide or suggestive significance for an association with schizophrenia (Ng *et al.* 2009). Due to the cost and difficulty associated with comprehensive genotyping, early investigations into specific molecular genetic contributions to psychosis focused on identifying associations between schizophrenia and a small number of genes thought to play a role in leading etiological hypotheses of psychosis. Using this hypothesis-driven method, associations were identified between several of these biologically plausible genes and schizophrenia. However initial reports often failed to replicate (Farrell *et al.* 2015). The candidate gene era culminated in the finding that associations between single nucleotide polymorphisms (SNPs) in top candidate genes previously reported to be associated with schizophrenia were consistent with chance expectation in the largest sample available at the time (Sanders *et al.* 2008).

In the past decade, technological advances have enabled large-scale genomic studies and consortia have formed that have brought together sample sizes necessary for adequately powered genome-wide investigations (Sullivan *et al.* 2017). The focus has shifted from candidate gene studies to the exploration of molecular genetic contributions to psychosis on a genome-wide scale. A case-control genome-wide association study (GWAS) conducted by the Schizophrenia Working Group of the Psychiatric Genomics Consortium identified over 100 independent loci that are associated with schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). It is likely that substantially more (thousands) common variants contribute to the genetic liability for psychosis, because the predictive ability of polygenic risk scores (see Table 1 for definition) for schizophrenia improves with the inclusion of weakly associated variants in addition to variants significantly associated with the disorder (see Fig. 1). Some of the variants identified by GWAS fall within predictable genes (e.g. *DRD2* – which encodes the dopamine receptor D_2, the target of most effective antipsychotic medications). However, the strongest association stemmed from variation within the major histocompatibility complex locus on chromosome 6, which is an area of the genome known for its role in immune function. This association is partly due to the many alleles of the complement component 4 (*C4*) genes (Sekar *et al.* 2016). These alleles produce varying levels of *C4A*/*C4B* expression in the brain and alleles producing greater *C4A* expression were more associated with increased risk of schizophrenia. *C4* is expressed in neurons and has been shown to mediate synaptic pruning during brain development in mice (Sekar *et al.* 2016). These results implicate the immune system and complement activity in the causation of schizophrenia.

The results of genome-wide investigations of common SNPs suggest that genetic liability to schizophrenia arises from the accumulation of small effects of hundreds to thousands of variants across the genome. In addition to the cumulative effect of common SNPs, rare copy number variants and disruptive mutations are also enriched among individuals with schizophrenia compared with controls (Purcell *et al.* 2014; Marshall *et al.* 2016). A specific deletion on chromosome 22, leading to 22q11.2 deletion syndrome, is associated with increased risk of psychosis. Approximately one in four individuals with this deletion will develop schizophrenia (Owen & Doherty, 2016). However, 22q11.2 deletion syndrome is not specific to schizophrenia, and is associated with a range of medical and psychiatric phenotypes (Niarchou *et al.* 2014; Owen & Doherty, 2016). More recently, exome sequencing has enabled identification of rare variants that may alter protein function and are associated with schizophrenia (Girard *et al.* 2015; Genovese *et al.* 2016; Singh *et al.* 2016). Psychosis-associated rare variants, including deletions/duplications and copy number variants, are more prevalent in genes involved in neurodevelopment, e.g. neuregulin (Walsh *et al.* 2008). Additionally, rare copy number variants have been identified in individuals with psychosis from densely affected families (Van Den Bossche *et al.* 2013). Rare variants directly

Table 1. Terminology of gene–environment interplay

Differential susceptibility refers to individual differences in the impact of both positive and negative aspects of the environment. The Differential Susceptibility Hypothesis posits that the same individuals who are most negatively affected by exposure to adverse environments also benefit most from enriching environments.
Gene-environment correlation (rGE) occurs when genetic factors are associated with increased likelihood of exposure to an environmental factor.
Gene–environment interaction (G × E) occurs when a genetic factor or genetic factors influence the impact of an environmental exposure on an individual.
Genome-wide association study (GWAS) screens hundreds of thousands to millions of common genetic variants (minor allele frequency typically >1%) across the genome for an association with a phenotype. Each genetic variant is tested separately for an association with the outcome of interest. Due to a large number of statistical tests, the genome-wide significance level is typically defined as $p < 5 \times 10^{-8}$.
Genome–wide environment interaction study (GWEIS) tests statistical interactions between genetic variants across the genome and an environmental exposure on an outcome of interest. If only a single environmental exposure is used, the same genome-wide significance threshold as GWAS is applied.
Mendelian randomization (MR) is a method of using genetic variants associated with an environmental risk factor of interest as a proxy for the exposure. MR is based on the fact that transmission of specific genetic variants from one generation to the next occurs by chance (hence the term 'randomization'). If the assumptions of MR are met, the genetic proxies should be free of confounding factors present in observational studies. When properly used, MR allows for the study of causal effects of environmental exposures that might not otherwise be possible by experimental means.
Polygenic environmental sensitivity score is a polygenic score that indexes genetic sensitivity to the environment. It can be derived from a GWAS of differences between monozygotic twins.
Polygenic risk score (PRS) is a sum of alleles associated with a phenotype, estimated from a GWAS. To calculate a PRS, variants from a GWAS are rank-ordered based on their p value of association with the phenotype and those that fall below a given threshold (e.g. $p < 0.05$) are retained to construct the PRS. Variants are typically weighted by their effect size from the GWAS.

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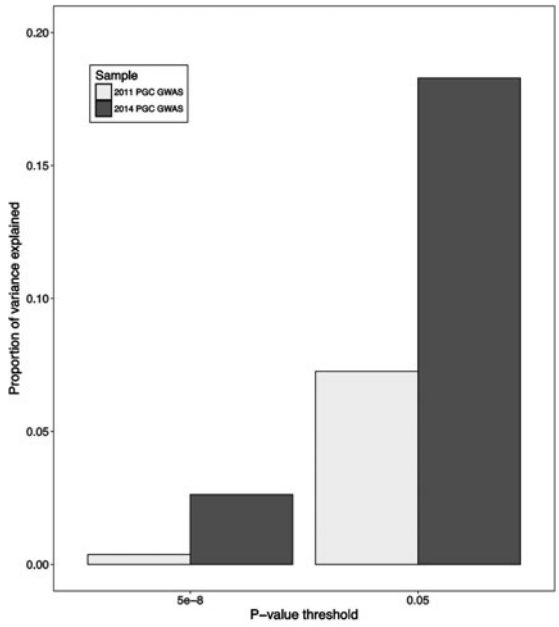

	2011 PGC GWAS	2014 PGC GWAS
Number of Cases	9,320	32,838
Number of Controls	10,228	44,357
Variance explained with $P_T = 5 \times 10^{-8}$	0.04%	3%
Variance explained with $P_T = 0.05$	7%	18%

Fig. 1. The polygenic risk for schizophrenia. The proportion of variance explained by polygenic risk scores for schizophrenia produced using the Psychiatric Genomics Consortium (PGC) sample from 2011 (The Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium 2011) and 2014 (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) as the discovery samples, with p value thresholds (PT) at 5×10^{-8} (genome-wide significance) and 0.05. The proportion of variance explained increases with both sample size and with the inclusion of more, non-significantly associated variants. This suggests that schizophrenia is highly polygenic, and many more genetic loci contribute to disease risk than have been captured by the most recent GWAS.

affecting protein function could individually have larger effects on psychosis risk than the common variants detected by genome-wide SNP analysis. The evidence suggests that genetic risk of psychosis is likely due to a combination of rare and common genetic variation.

The ability to identify and quantify genetic risk for psychosis allows us to investigate how genetic liability for illness manifests before disease onset. Genetic liability for schizophrenia is enriched among individuals with a family history (Bigdeli *et al.* 2016). The genetic burden of both rare and common variants is higher among individuals with early-onset compared with later-onset schizophrenia (Walsh *et al.* 2008; Ahn *et al.* 2014, 2016). In a general population sample, genetic risk for schizophrenia is associated with anxiety, negative symptoms, and worse neurodevelopmental outcomes (e.g. worse language fluency) in childhood and adolescence but, surprisingly, not with adolescent psychotic symptoms (Jones *et al.* 2016; Riglin *et al.* 2016). However, these findings warrant further investigation due to the high and non-random attrition of participants in this particular study (Jones *et al.* 2016; Martin *et al.* 2016; Taylor *et al.* 2017). To find out when in development genetic risk for psychosis first manifests, it is necessary to establish large genotyped cohorts with high retention rates over longitudinal follow-ups with comprehensive phenotyping, including putative developmental precursors of psychotic illness.

Polygenic analyses across multiple disorders suggest that the genetic loci contributing to schizophrenia risk are also implicated in other mental and physical illnesses. There is substantial overlap between genetic liability to schizophrenia and bipolar disorder, major depressive disorder, and autism (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013*b*). To a smaller extent, schizophrenia-associated genetic variants also confer increased risk of inflammatory bowel disease, further supporting a role of the immune system in schizophrenia etiology (Pickrell *et al.* 2016). In summary, the heritable contribution to psychosis is highly polygenic, arises from a combination of rare and common variation, and overlaps with other forms of pathology.

Environmental factors contributing to psychosis

The relative contributions of environmental and genetic factors to psychosis have been debated over time. Twin studies seem to suggest that less than 20% of the variance in liability to schizophrenia is explained by environmental influences unique to the individual and that environment shared between twins plays no role in the causation of schizophrenia (Sullivan *et al.* 2003; Polderman *et al.* 2015). However, other typed of research studies strongly suggest a relatively smaller contribution of genetics and greater role of environment. Epidemiological studies show strong and consistent associations between multiple environmental exposures and psychosis (Marconi *et al.* 2016; Varese *et al.* 2012). Molecular genetic studies in unrelated individuals give substantially lower heritability estimates than twin studies (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013*a*; Sullivan *et al.* 2017). In combination, the results of epidemiological research and the gap between twin and molecular heritability estimates suggest that environmental exposures likely play a more prominent role in the etiology of psychotic illness than was previously thought (Uher & Zwicker, 2017).

The major environmental exposures that have been implicated in psychosis are listed in Fig. 2. They can be clustered based on the stage in development when exposure could influence risk. Complex factors, such as parental socioeconomic status (SES) and income inequality tend to remain constant throughout development and have wide-reaching implications on health across the life course (Adler *et al.* 1994; Kennedy *et al.* 1998). Other factors, including maternal viral infection, influence psychosis risk if individuals are exposed during a 'sensitive' period in development (Brown & Patterson, 2011). Most individuals, with and without psychotic illness, are exposed to at least one risk factor, which complicates the investigation of the roles of individual environmental exposures (Van Nierop *et al.* 2013; Stepniak *et al.* 2014).

In terms of pre- and perinatal risk factors, exposures that influence immune function have been linked to the development of psychotic illness (Mednick *et al.* 1988; van Os & Selten, 1998; Brown *et al.* 2000, 2001; Buka *et al.* 2008; Khashan *et al.* 2008; Malaspina *et al.* 2008; Torrey *et al.* 2012; Fineberg *et al.* 2016). It has been suggested that immune activation and subsequent inflammation could mediate the effects of pre- and perinatal insults, such as stress or infection, on psychosis risk by contributing to abnormal neurodevelopment (Deverman & Patterson, 2009; Holloway *et al.* 2013; Miller *et al.* 2013; Ménard *et al.* 2017). Individuals exposed to high levels of inflammation *in utero* are at increased risk of developing schizophrenia in adulthood (Canetta & Sourander, 2014). Conversely, elevated levels of anti-inflammatory molecules *in utero* lower the risk of developing psychosis in adulthood (Allswede *et al.* 2016). Results from

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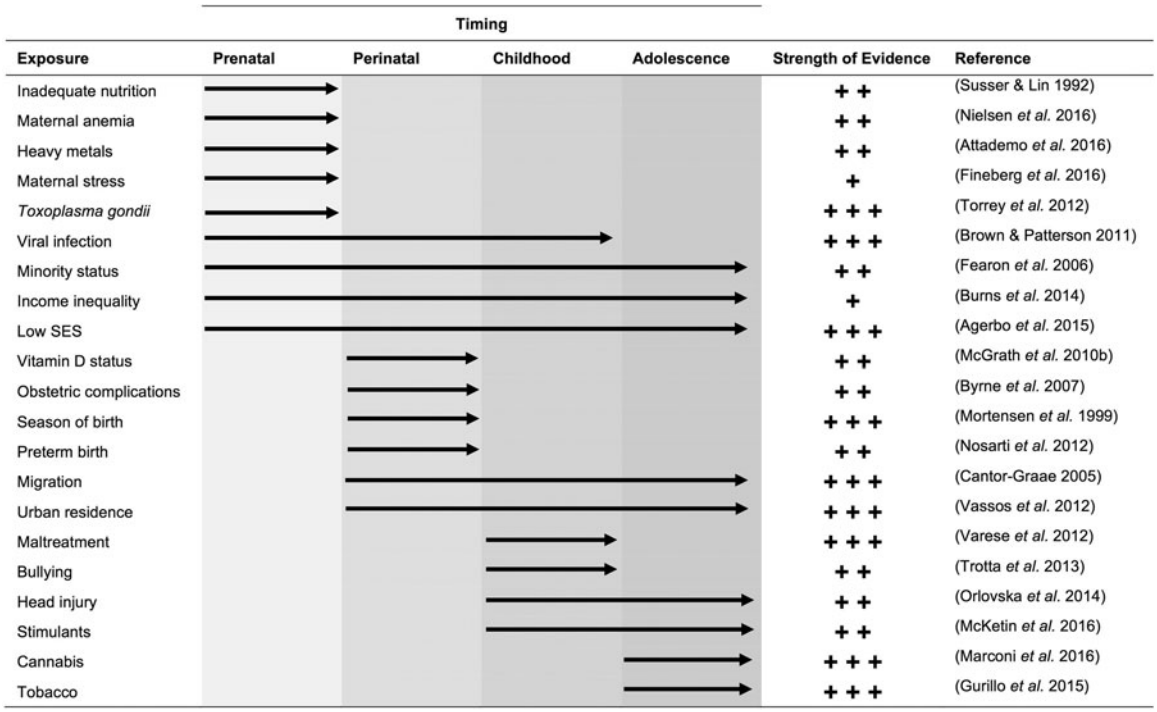

Fig. 2. Environmental factors associated with psychosis. The number of plus signs denotes the strength of evidence for the association: +++ indicates consistent evidence from multiple large-scale studies or a meta-analysis; ++ indicates evidence from multiple smaller studies or a strong association in a high-quality study; + indicates evidence from a single study, multiple small/low-quality studies, or few studies with conflicting reports. The reference provided for each exposure reflects a meta-analysis (where available) or the largest study available. The list is limited to environmental exposures and excludes risk factors that reflect conditions of the individual (e.g. inflammation).

animal studies suggest that the unfavorable effects of prenatal immune activation may extend across multiple generations. For example, using a mouse model, some pathological traits (e.g. reduced sociability) resulting from *in utero* exposure to immune activation were observable for up to three generations (Weber-Stadlbauer *et al.* 2017). This suggests that epigenetic mechanisms or learned behavioral transmission may influence these traits.

Early adversities occurring in childhood, including physical, sexual, and emotional abuse, neglect and exposure to violence have been strongly implicated in the development of psychotic illness (Varese *et al.* 2012). More recently, involvement in bullying, both as a victim and as a bully, has been recognized as a contributor to both psychotic illness in adulthood and subclinical psychotic symptoms in adolescence (Schreier *et al.* 2009; Trotta *et al.* 2013; Wolke *et al.* 2014). Childhood trauma is associated with increased levels of inflammatory markers in adulthood, which provides a possible mechanism through which childhood adversities could impact the development of psychosis (Baumeister *et al.* 2016).

Exposures associated with psychosis that occur later in development are largely substance use-related. Abuse of psychostimulants is typically associated with acute psychosis, however, individuals with a family history of mental illness who use stimulants recreationally appear to be more vulnerable to persistent psychotic symptoms (Curran *et al.* 2004; Li *et al.* 2014; Hajebi *et al.* 2016; McKetin *et al.* 2016). Interestingly, the link between stimulants and psychosis extends to children with a family history of mental illness taking stimulants to treat attention-deficit/hyperactivity disorder (MacKenzie *et al.* 2016). The risk of experiencing psychotic symptoms is more than four times higher among children taking prescribed stimulant medication compared with those who have never taken stimulants (MacKenzie *et al.* 2016). Regardless of family history status, cannabis use has been strongly and consistently associated with psychotic disorders (Moore *et al.* 2007; Gage *et al.* 2015). In the case of cannabis exposure, many criteria of causality are met including a positive dose–response relationship between cannabis use and psychotic outcomes (Marconi *et al.* 2016), the temporal sequence of cannabis use preceding the onset of psychosis (Arseneault *et al.* 2002; Stefanis *et al.* 2013; Kelley *et al.* 2016), and consistent evidence for an association (Hill, 1965). Additionally, a Mendelian randomization study (see Table 1) found that use of cannabis is causally associated with risk of schizophrenia and that cannabis users had a 37% increased risk of developing schizophrenia (Vaucher *et al.* 2017). There is also evidence that tobacco use could play a role in the development of psychosis (van Gastel *et al.* 2013; Gurillo *et al.* 2015; McGrath *et al.* 2016). The fact that cannabis and tobacco are often used by the same individuals complicates the investigation into the nature of the individual relationships between cannabis and tobacco use and psychosis (Gage *et al.* 2014). This highlights the necessity of gathering information on exposure to multiple factors when examining environmental contributors to psychosis.

Broad characteristics of the physical environment during development have also been associated with psychotic illness. Upbringing in an urban center is associated with increased risk of psychosis compared with rural upbringing (Vassos *et al.* 2012). Risk increases with total time spent living in an urban setting (Pedersen & Mortensen, 2001). This finding is not exclusive to adult illness; psychotic symptoms among children and adolescents are more frequent and more likely to progress to a first

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episode of psychosis among youth living in an urban environment (Polanczyk *et al.* 2010; Dragt *et al.* 2011). The exact components of the urban environment that contribute to psychosis are not well-defined. Air pollution and toxins, such as heavy metals, are not likely to play a substantial role (Attademo *et al.* 2017). A deficiency or excess of Vitamin D, which is produced in the skin when exposed to sunlight and may play a role in the regulation of gene expression, could explain a proportion of psychosis (McGrath, 1999; McGrath *et al.* 2004, 2010*a*, 2010*b*). It has been suggested that vitamin D deficiency is more prevalent in urban centers, possibly due to less sun exposure (Holick, 1995). In the case of childhood and adolescent psychotic symptoms, neighborhood factors including low social cohesion and high crime rate partially explain the elevated risk for psychotic symptoms among children living in urban areas (Polanczyk *et al.* 2010; Newbury *et al.* 2016).

Although some environmental risk factors for psychosis have been identified, it is difficult to separate the effects of individual factors because exposures often cluster within the same person (Gage *et al.* 2014; Sideli *et al.* 2015). Similar to the notion of many genetic factors of small effect sizes contributing to the genetic risk of psychosis, it has been suggested that environmental risk is also attributable to the cumulative contribution of many exposures (Van Nierop *et al.* 2013). Exposure to a greater number of environmental risk factors was associated with earlier age at onset of psychotic symptoms and first-episode of psychosis (Stepniak *et al.* 2014; O'Donoghue *et al.* 2015). An aggregate 'polyenviromic' score predicted the onset of psychosis among youth with a family history of psychotic illness (Padmanabhan *et al.* 2017). Although exposure to certain environments increases the risk of psychosis, only a minority of individuals exposed to these factors will become ill. Genetic differences may render some individuals more vulnerable or resilient to the impact of environmental exposures.

Gene–environment interplay

Psychotic illness in a given individual arises due to a combination of genetics and environment. The term gene–environment interplay captures the combined contributory effects of both genetics and environment to psychosis. Gene–environment interplay encompasses gene-environment correlation (rGE) and gene–environment interaction (GxE; see Table 1 for definitions).

Gene-environment correlation

Exposure to specific environments is not random. Gene-environment correlation (rGE) refers to this non-random relationship between genotype and exposure. It is important to assess the possible contribution of rGE when investigating causal contributors to psychosis. Three forms of rGE have been widely described: passive rGE, evocative (or reactive) rGE and active rGE (Plomin *et al.* 1977), see Fig. 3.

Passive gene-environment correlation

Passive rGE describes the association between genotype and rearing environment, both of which are influenced by an individual's parents' genes. For example, the association between childhood abuse and genetic risk for psychosis represents a potential passive rGE. Children of parents with psychosis are at increased risk of experiencing childhood maltreatment and individuals who experience abuse are more likely to develop psychosis (Walsh *et al.* 2002; Fisher *et al.* 2014). However, it is unclear whether the association between childhood maltreatment and psychosis arises because abuse directly causes psychosis or because genetic factors increase both the likelihood of experiencing abuse and the propensity to develop psychosis. If the latter is true, the association between childhood abuse and psychotic illness represents a passive gene-environment correlation. Adoption studies provide a useful design to tease apart passive rGE from G × E. Using this methodology, it has been possible to demonstrate that individuals with a family history of schizophrenia are truly more vulnerable to the psychosis-inducing effects of childhood adversity than are individuals without a family history (Tienari *et al.* 2004).

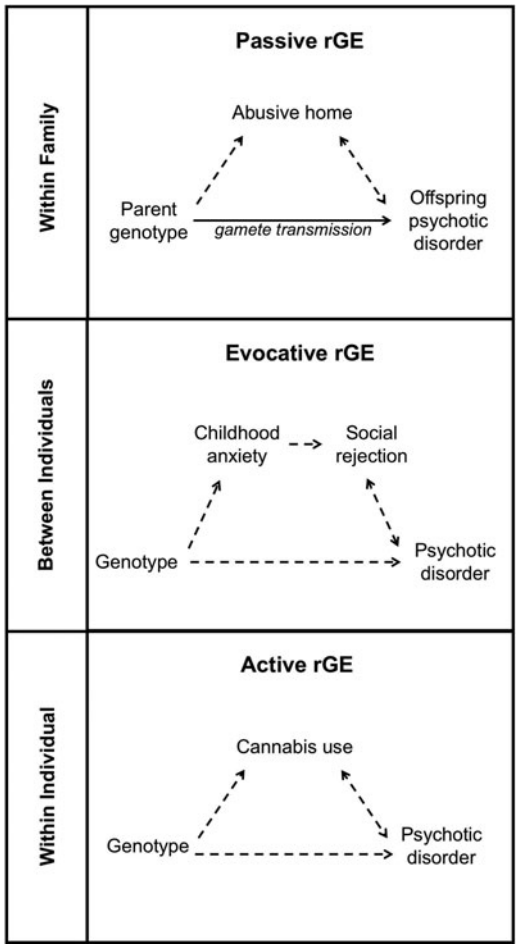

Fig. 3. Gene-environment correlations and psychosis. The three panels illustrate passive, evocative and active gene-environment correlations (rGE), base on specific examples that are relevant to the etiology of psychosis. The same examples are described and referenced in the text section Gene-Environment Correlation.

Evocative gene-environment correlation

Personal characteristics determine how individuals interact in social situations, and as a result, influence the responses they will elicit from others. Evocative rGE describes how differences in genotype will evoke different reactions. As an example, genetic risk of schizophrenia is associated with the presence of childhood anxiety disorders (Jones *et al.* 2016). Anxious children may evoke a different response from peers than their less anxious counterparts, resulting in an evocative rGE. Thus, anxious children may face rejection in social interactions with peers, which could, in

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turn, increase their risk of developing psychosis (Collishaw *et al.* 2007).

Active gene-environment correlation

Individual behaviors and preferences are also partially determined by genetics. By influencing these factors, genotype also influences the experiences that people will seek out. Active rGE describes how genetic variation can contribute to differences in the likelihood of exposure to environments. For example, individuals at high genetic risk for schizophrenia are more likely to use cannabis (Verweij *et al.* 2017). Genotype, therefore, influences both the propensity to develop psychosis and the likelihood of being exposed to cannabis. Active rGE could account for a portion of the association between cannabis use and psychosis. However, genetic risk for schizophrenia only explains a small proportion (0.5%) of the variance in cannabis use (Verweij *et al.* 2017). Therefore, it is unlikely that rGE fully explains the association between cannabis use and psychosis. It does, however, bring attention to the need to consider rGE before making causal interpretations that assume relative independence of genetic and environmental factors.

Gene–environment interaction

Exposure to certain environmental factors increases the risk of psychosis, however, these adverse environments do not affect everyone equally. Some individuals remain healthy even when exposed to multiple known risk factors whereas others will go on to develop a psychotic disorder (Collishaw *et al.* 2007; Tottenham, 2013). Genetic factors may render certain individuals more vulnerable to the impact of environmental exposures, resulting in a gene–environment interaction. Two sets of findings suggest that G × E plays a substantial role in the development of psychosis. First, much larger heritability estimates of schizophrenia have been obtained from twin studies than from molecular genetic studies using unrelated individuals (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013*a*). Second, despite the fact that epidemiological studies have robustly demonstrated that risk factors shared within families (such as minority status, urbanicity, or low SES) are among the top environmental contributors to psychosis, twin studies suggest that shared environment plays a very minor or no role (Polderman *et al.* 2015). The best estimate of shared environment contribution across twin studies is actually a negative number (Polderman *et al.* 2015). These implausible findings can be explained by the manner in which heritability is calculated in twin studies: the interplay between genetic factors and environmental variables shared within a family are attributed to genetics and inflate heritability estimates while reducing the estimated contribution of shared environment (Taylor, 2007; Uher & Zwicker, 2017). Therefore, G × E offers a plausible explanation for these discrepant findings.

In addition to providing an explanation for the conflicting heritability estimates from twin studies, molecular genetic studies and epidemiology, identification of G × E could offer additional insight into both genetic and environmental contributions to psychosis. First, G × E research can lead to the identification of novel genetic contributors to psychosis that may not otherwise be identified in case-control studies (Børglum *et al.* 2013). Additionally, identification of G × E is valuable because unlike genetics, environment is malleable and can be modified selectively among those at high genetic risk. Therefore, identifying G × E could provide the opportunity for targeted interventions to minimize or eliminate exposure to environmental contributors to psychosis, particularly exposures that are under the control of the individual, such as cannabis, tobacco and stimulant use. Despite the significant role of G × E in psychosis and the potential value of G × E knowledge, identification of G × Es to date has been slow.

Gene–environment interaction by proxy

Initial investigation of G × E in psychosis relied on the family history of severe mental illness as a proxy fo genetic risk. Using this method, interactions between 'genetic liability' for psychotic illness and exposure to environmental factors have been identified. Individuals with a family history of psychotic illness appear to be particularly sensitive to the effects of multiple environmental contributors to psychosis including cannabis use (GROUP investigators, 2011; van Winkel & GROUP investigators, 2015), urban upbringing (Van Os *et al.* 2003, 2004), and maternal infection (Clarke *et al.* 2009). There have also been reports in which no interaction was found between family history and known environmental risk factors, such as childhood maltreatment (Fisher *et al.* 2014; Trotta *et al.* 2015). Other factors, such as maternal depression during pregnancy, selectively increases the risk of psychosis among those with at least one parent affected by psychotic illness (Mäki *et al.* 2010). However, since there is overlap in the genetic factors contributing to depression and psychosis, this result could also reflect a gene-environment correlation or interaction between multiple genetic factors (Han *et al.* 2016). Gene-environment studies using proxy measures are inherently limited because a family history of illness is not equivalent to the genetic contribution to psychosis and because genetic variants that increase sensitivity to the environment may be distinct from genetic variants that directly increase the risk of illness. The applicability of findings using proxy measures of genetic contribution to illness is also limited because the comprehensive family history of mental illness is not always known.

Gene–environment interactions involving molecular genetic variants

The search for gene–environment interactions involving specific molecular genetic variants began by testing the interaction between environmental risk factors for psychosis and variants within candidate genes. These studies faced the same challenges as candidate gene association studies discussed earlier. This approach relies on correctly selecting both the genetic variant and environmental exposure of interest based on prior knowledge. Surprisingly, this approach has led to the identification of interactions between variants in a handful of genes and environmental factors influencing the risk of psychosis (see Table 2). Replication of results, however, has been inconsistent. For example, carriers of the methionine-encoding allele of *BDNF* [Val66Met (rs6265)] have been shown to be at increased risk of experiencing psychotic symptoms after being exposed to childhood trauma (Alemany *et al.* 2011), but attempts to replicate this finding have either found no interaction between genotype and exposure to trauma (Ramsay *et al.* 2013), or found discordant results regarding which allele (valine-encoding *v.* methionine-encoding) increases psychosis risk following exposure (de Castro-Catala *et al.* 2016). More systematic searches, involving screening hundreds of polymorphisms across functionally defined groups of genes, have been carried out in search of a G × E. This methodology led to the identification of an interaction between cannabis use and a SNP in *AKT1*, a gene encoding a serine/threonine kinase involved in the transduction of signal

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Table 2. Molecular gene–environment interactions in psychosis

Gene Selection Strategy	Gene	Variant	Exposure	Outcome	Original report	Replication	
					Reference	Result	Reference
Candidate Gene	*BDNF*	rs6265	Childhood trauma	Psychotic symptoms	Alemany *et al.* (2011)	N	Ramsay *et al.* (2013)
						N*	de Castro-Catala *et al.* (2016)
	COMT	rs4680	Childhood trauma	Psychotic symptoms	Ramsay *et al.* (2013)	N*	Green *et al.* (2014)
		rs4680	Childhood abuse + cannabis use	Psychotic symptoms	Vinkers *et al.* (2013)	Y	Alemany *et al.* (2014)
		rs4680	Cannabis use	Psychotic symptoms	Caspi *et al.* (2005)	N	Zammit *et al.* (2011)
		rs4680	Stress (army induction)	Psychotic symptoms	Stefanis *et al.* (2007)	Y*	Collip *et al.* (2011)
	FKBP5	rs1360780	Childhood trauma	Psychotic symptoms	Collip *et al.* (2013)	Y	Alemany *et al.* (2016)
Function-informed systematic search	*AKT1*	rs2494732	Cannabis use	Psychotic disorder	van Winkel (2011)	Y	Di Forti *et al.* (2012)
						Y*	Morgan *et al.* (2016)
Genome-wide systematic search	*CTNNA3*	rs7902091	Cytomegalovirus *in utero*	Schizophrenia	Børglum *et al.* (2013)	Y	Avramopoulos *et al.* (2015)

The table lists specific molecular gene–environment interactions for which there is at least one published replication attempt. The first column classifies the G × Es based on the initial search strategy into G × Es identified based on focused candidate gene testing, systematic searches including polymorphisms that tag genetic variation in a functionally defined group of genes and genome-wide systematic search. For replication results, 'Y' denotes a replication, 'Y*' denotes a replication with a different but similar exposure or outcome from the original report, 'N' denotes a failed replication attempt, and 'N*' denotes a replication attempt where an interaction between the variant and the environment of interest was found but the sensitive allele differed from the original report.

following cannabinoid receptor activation (van Winkel, 2011). Homozygous carriers of the C allele at rs2494732 in *AKT1* appear to be more vulnerable to the psychosis-inducing properties of cannabis. In a replication study, individuals with the C/C genotype at rs2494732 who used cannabis daily were found to be at 7-fold increased risk of developing psychotic illness compared with T allele homozygotes (Di Forti *et al.* 2012). This finding has been replicated in two independent samples since the original report and therefore likely represents a true G × E (Di Forti *et al.* 2012; Morgan *et al.* 2016).

Comprehensive genome-wide search strategies, referred to as genome–wide environment interaction studies (GWEIS), have also been conducted to systematically search for G × E. The first GWEIS in psychosis found a significant interaction in a genome-wide test examining the interaction between *in utero* exposure to cytomegalovirus (CMV) infection and hundreds of thousands of common SNPs across the genome (Børglum *et al.* 2013). This led to the identification of a single G × E between CMV infection and a variant within a gene (*CTNNA3*) not previously associated with psychosis (Børglum *et al.* 2013). Carriers of the minor allele at rs7902091 in *CTNNA3* exposed to CMV *in utero* are at increased risk of developing schizophrenia compared with those who do not carry the minor allele and those who were not exposed to CMV. A genome-wide approach to G × E research is likely to be superior to hypothesis-driven approaches, as many schizophrenia-associated genetic loci that have been identified to date are found within genes that were not previously suspected to be implicated in psychosis (Collins *et al.* 2012). Due to a large number of loci being tested, GWEIS require very large samples to be adequately powered – even when examining interactions between common variants and common exposures. Although it is likely that G × Es play a significant role in the development of psychosis, no individual G × E identified thus far explains a substantial proportion of cases. The potential gene–environment interactions involved in the early manifestation of psychosis in childhood and adolescence remain to be examined.

Gene–environment interactions and polygenic scores

It is possible to summarize the effects of hundreds to thousands of variants across the genome as a single polygenic score. Polygenic risk scores calculated based on the most recent case-control GWAS for schizophrenia have been used to test G × E across the genome. One study derived a score from a few thousand schizophrenia-associated genetic variants located within coding and regulatory regions and found that this score interacted with winter birth to increase the risk of developing schizophrenia (Hong Lee *et al.* 2015). Another study found no interaction between polygenic risk score for schizophrenia and childhood adversity (Trotta *et al.* 2016). The authors of this study concluded that their results support a model whereby genetic and environmental factors contribute independently to psychosis risk.

Polygenic risk scores for schizophrenia may not be the ideal method to detect G × E because sensitivity to the environment and risk of illness may be determined by distinct subsets of genetic variants. It has been suggested that the individuals who are most severely impacted by adverse environments may also benefit most from positive ones. This is referred to as differential susceptibility (Belsky & Pluess, 2009). The differential susceptibility hypothesis

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posits that the genetic variants that render individuals sensitive to environmental influences may be distinct from genetic factors that directly influence the risk of psychopathology (Belsky & Pluess, 2009). Therefore, G × E involving variants contributing to differential susceptibility will not be captured when using a polygenic risk score for schizophrenia (Belsky & Pluess, 2009). A 'polygenic sensitivity score' indexing overall sensitivity to the environment (both positive and negative) predicted both the effects of parenting on emotional problems and response to psychological treatment among children with anxiety disorders (Keers *et al.* 2016). This sensitivity score did not, however, predict psychopathology directly, thus providing evidence that environmental sensitivity is genetically distinct from illness (Keers *et al.* 2016). Like polygenic risk scores for schizophrenia, the predictive ability of the polygenic sensitivity score improved with the inclusion of a greater number of less significantly associated variants, suggesting that genetic contribution to environmental sensitivity is also dispersed over a large number of loci across the genome. A polygenic sensitivity score has yet to be tested in the etiology of psychosis or its early developmental antecedents.

Conclusions, gaps in evidence and future directions

The findings of the past decade have led to a better understanding of the etiology of psychosis but also highlight a need to shift the direction of future research. Advances in the availability of genome-wide technology have uncovered the massively polygenic nature of psychosis. Epidemiological investigations have identified many environmental exposures that are associated with psychosis, however, the effect of these exposures differs between individuals. It is likely that genetic factors influence the impact of environmental exposures, and that genetic sensitivity to the environment is also highly polygenic. Identification of specific gene–environment interactions has proven to be difficult and has been hindered by lack of environmental measurement in large genetic studies. GWEIS can detect multiple gene–environment interactions in a systematic manner, but this methodology is limited in terms of statistical power. Polygenic environmental sensitivity scores may facilitate future genome-wide investigation of G × E in moderately large samples.

Despite the progress of the past decade, there remain important gaps in knowledge. Although genotyping technologies have improved in efficiency and affordability, the commonly used genome-wide genotyping methods do not provide full coverage of the genome. Thus, despite their names, genomic methods such as GWAS, GWEIS, and polygenic risk scores -environment interaction studies still leave a proportion of genetic variation unexplored. Additionally, most investigations of the genetic contribution to psychosis have been performed by comparing the genotypes of individuals diagnosed with schizophrenia to controls who do not have schizophrenia. This approach, though a necessary first step, limits the generalizability of polygenic risk scores from schizophrenia to other forms of psychosis. Indeed, a polygenic risk score for schizophrenia may predict other psychotic disorders less accurately than narrowly defined schizophrenia (Vassos *et al.* 2017). Additionally, most large-scale investigations of the genetic contribution to schizophrenia have relied on ethnically homogenous samples of white individuals of European descent. This limits the generalizability to other ethnicities. In a sample of individuals of African descent, the proportion of variance in psychosis case-control status explained by polygenic risk scores for schizophrenia is approximately 1/9th of the proportion of variance explained in a European sample (1.1% *v.* 9.4%; Vassos *et al.* 2017). To improve the utility of genetic risk information, future gene-environment investigations should cover a broader range of psychosis phenotypes in ethnically diverse samples.

Samples with a thorough assessment of both psychopathology and environment at multiple points in development will likely provide the most valuable information on gene-environment causation. Psychosis typically emerges in the second decade of life and it is often preceded by different and milder forms of mental illness. It is therefore essential to examine environmental exposures and psychopathology earlier in life, prior to disease onset. These studies should begin as early as during pregnancy or infancy and continue longitudinally across development. Regular assessment across development will allow us to establish true age at onset and track the development of psychosis over time. Large cohorts with genome-wide SNP genotyping and/or whole genome sequencing and comprehensive assessment of exposures and psychopathology across development are needed for this investigation. Important steps towards establishing such cohorts are currently underway (Korver *et al.* 2012; Uher *et al.* 2014; Thorup *et al.* 2015; Kooijman *et al.* 2016). To expand and combine information from these cohorts, future work should focus on the formation of large-scale, transparent collaborations and data sharing mechanisms.

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