Schizophrenia Bulletin Advance Access published May 24, 2014

Schizophrenia Bulletin
doi:10.1093/schbul/sbu069

Identifying Gene-Environment Interactions in Schizophrenia: Contemporary Challenges for Integrated, Large-scale Investigations

European Network of National Networks studying Gene-Environment Interactions in Schizophrenia (EU-GEI)*

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Recent years have seen considerable progress in epidemiological and molecular genetic research into environmental and genetic factors in schizophrenia, but methodological uncertainties remain with regard to validating environmental exposures, and the population risk conferred by individual molecular genetic variants is small. There are now also a limited number of studies that have investigated molecular genetic candidate gene-environment interactions (G × E), however, so far, thorough replication of findings is rare and G × E research still faces several conceptual and methodological challenges. In this article, we aim to review these recent developments and illustrate how integrated, large-scale investigations may overcome contemporary challenges in G × E research, drawing on the example of a large, international, multi–center study into the identification and translational application of G × E in schizophrenia. While such investigations are now well underway, new challenges emerge for G × E research from late-breaking evidence that genetic variation and environmental exposures are, to a significant degree, shared across a range of psychiatric disorders, with potential overlap in phenotype.

Key words: schizophrenia/gene-environment interaction/psychosis/epidemiology/genetics

The Environment and Schizophrenia: Evidence Beyond Reasonable Doubt?

Over the past decades, substantial and consistent evidence has accrued that implicates environmental factors in the development of schizophrenia. Numerous studies have consistently reported an increased incidence of schizophrenia in urban areas[1–8] as well as in migrant and minority ethnic groups.[4,7,9–12] Evidence further suggests cannabis use[13–17] and childhood adversity[18–20] confer substantial risk for psychotic disorder. For these environmental factors, pooled effects sizes from meta-analyses in the range of a 2- to 4-fold increase in risk,[4,5,8–10,13–17,20] evidence of dose-response gradient,[10,20–26] and population attributable risk fractions of 20%–35%[20,27] have been reported. These advances notwithstanding, a number of methodological uncertainties remain in validating environmental exposures, including risk of systematic information bias, confounding by genetic and other factors, and possible reverse causality.[19,28–32]

Recent Gene Discoveries in Schizophrenia: (Some) More Light in the Dark

While the initial surge for the molecular genetic basis of schizophrenia was characterized by slow progress and methodological concerns,[32,33] recent years have seen more rapid advances through large-scale collaboration in genome-wide association studies (GWAS), which have generated replicated findings on a number of common risk alleles.[34–38] Recent advances have further produced consistent findings that rare copy number variants (CNVs) increase schizophrenia risk substantially and to a greater extent than individual common risk alleles identified by GWAS.[39–42]

However, the common variants identified to date explain only a small proportion of the genetic risk of schizophrenia and a large number of common risk alleles (with small effects) remain to be identified.[35,41,43] Also, heritability estimates of the overall contribution of common genetic variants based on molecular genetic data are considerably smaller (ie 23%–33%)[38,44] than heritability estimates from twin studies (ie 81%).[45,46] What is more, while the reported effect sizes for CNVs tend to be much larger, they are rare and therefore contribute even less to total risk.[40–42] There are several potential explanations that may account for this pattern in molecular genetic findings, but, given the consistent evidence that environmental factors confer substantial, and much greater risk than individual common genetic risk variants, it seems reasonable that gene-environment interactions (G × E) play an important role.

Gene-Environment Interactions: Contemporary Challenges

The G × E approach posits that the effect of an individual's genotype depends on environmental exposure

and, vice versa, the effect of environmental exposure on risk depends on an individual's genotype.[32,47] Since both environmental and genetic factors have consistently been implicated in etiology, but there is considerable variation in phenotype, in so far as not all individuals exposed to environmental risk or carrying genetic risk variants go on to develop the disorder, G × E appears to be particularly relevant in schizophrenia.[29,48] G × E would also plausibly account for the large discrepancy in heritability estimates from twin and molecular genetic studies.[44–46] This heritability gap may come about because G × E involving shared environmental factors within families are included in heritability estimates of twin studies, but not molecular genetic studies of unrelated subjects.[46]

While long ignored in molecular genetic analyses, and still an emerging field, the beginning of this century has seen a limited number of G × E studies on candidate genes in schizophrenia.[29,49,50] These studies have tested individual, a priori selected single-nucleotide polymorphisms (SNPs), with very few attempts at replication[49–52] and limited evidence on the potential mechanisms underlying G × E in schizophrenia.[31,32] Indeed, there remain a number of conceptual and methodological challenges in contemporary molecular G × E research. These include (a) the validation of environmental exposures, consistently measured in sufficiently large, epidemiologically characterized samples for G × E analysis[33,46]; (b) selecting optimal strategies for (1) the use of complex GWAS data, (2) a priori, hypothesis-based vs exploratory approaches, and (3) the type of genetic variation to be used in G × E analysis; (c) a relative paucity of validated and scalable experimental methods for investigating modifiable mechanisms underlying G × E in schizophrenia; (d) the different phenotypic levels of schizophrenia at which G × E may impact, including intermediate phenotypes, prodrome, onset, severity, and course of schizophrenia; (e) statistical modeling of the likely simultaneous presence of G × E, G × G and E × E interactions; (f) ethical issues that may arise if G × E analyses produce evidence of substantial risks to be leveraged in risk assessment and early prediction; and (g) the need for translation of G × E findings to clinical practice.

It has repeatedly been noted that current challenges in molecular genetic G × E research warrant integrated, large-scale investigations that bring together international experts at the forefront of research in epidemiology, genetics, experimental psychiatry, statistics, social psychiatry, brain imaging, and clinical psychiatry.[31–33,47,50,53] While in molecular genetic research large-scale collaborations such as the International Schizophrenia Consortium[35] or the Psychiatric Genomics Consortium[54] are increasingly common, there are only few examples in G × E research; one is "The European Network of National Networks studying Gene-Environment Interactions in Schizophrenia" (EU-GEI)[32,47] (see also www.eu-gei.eu).

The European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI)

EU-GEI is a large, international, multi–center study of G × E in schizophrenia using family-based, multidisciplinary research paradigms in more than 15 countries (the Netherlands, the UK, Germany, Turkey, Spain, France, Belgium, Greece, Austria, Switzerland, Hong Kong (China), Brazil, Australia, Ireland, Italy, and other European and non-European countries represented by EU-GEI affiliated centers) for testing a priori G × E hypotheses. The overall aim of EU-GEI is the identification and translational application of clinical, genetic, and environmental interactions in the development, severity, and course of schizophrenia in patients and their families. To this end, several work packages are currently underway that amalgamate expertise from multiple disciplines for addressing contemporary challenges in G × E research (see figure 1).

The "Functional Enviromics" work package has developed and currently applies methods for the detailed assessment of candidate, individual- and area-level environmental exposures of public health relevance (ie with the largest attributable fractions and most relevant to the EU study population).[12] The work package employs a number of strategies for validating environmental exposures by using an optimum, family-based, case-control design in a diverse range of settings across Europe, drawing on corroborative sources of information in the assessment of childhood and adult adversity to minimize recall bias, and taking account of potential confounding by direct and indirect measures of genetic risk as well as other relevant factors. In doing so, "Functional Enviromics" aims to investigate the impact of hypothesized individual- and area-level environmental exposures on risk of first episode psychosis and to identify proximal explanatory factors that account for high rates of psychotic disorder in urban areas and in migrant and ethnic minority groups. The work package further aims, together with "Discovery Genetics" and "G × E Data & Statistics," to examine evidence for hypothesized G × E and environment × environment (E × E) interactions.

The "Discovery Genetics" work package aims to identify novel genes and biological pathways and implement new approaches for CNVs that will allow, jointly with all other work packages, to test specific, a priori G × E hypotheses. Specifically, this work package combines available with newly generated GWAS data to identify common variants, showing robust genome-wide evidence for association, to test specific, a priori SNP-based G × E hypotheses. "Discovery Genetics" further constructs, in collaboration with "G × E Data & Statistics," polygenic pathway scores based on pathway-wide evidence for association of SNPs in genes that are involved in specific biological pathways underlying environmental risks.

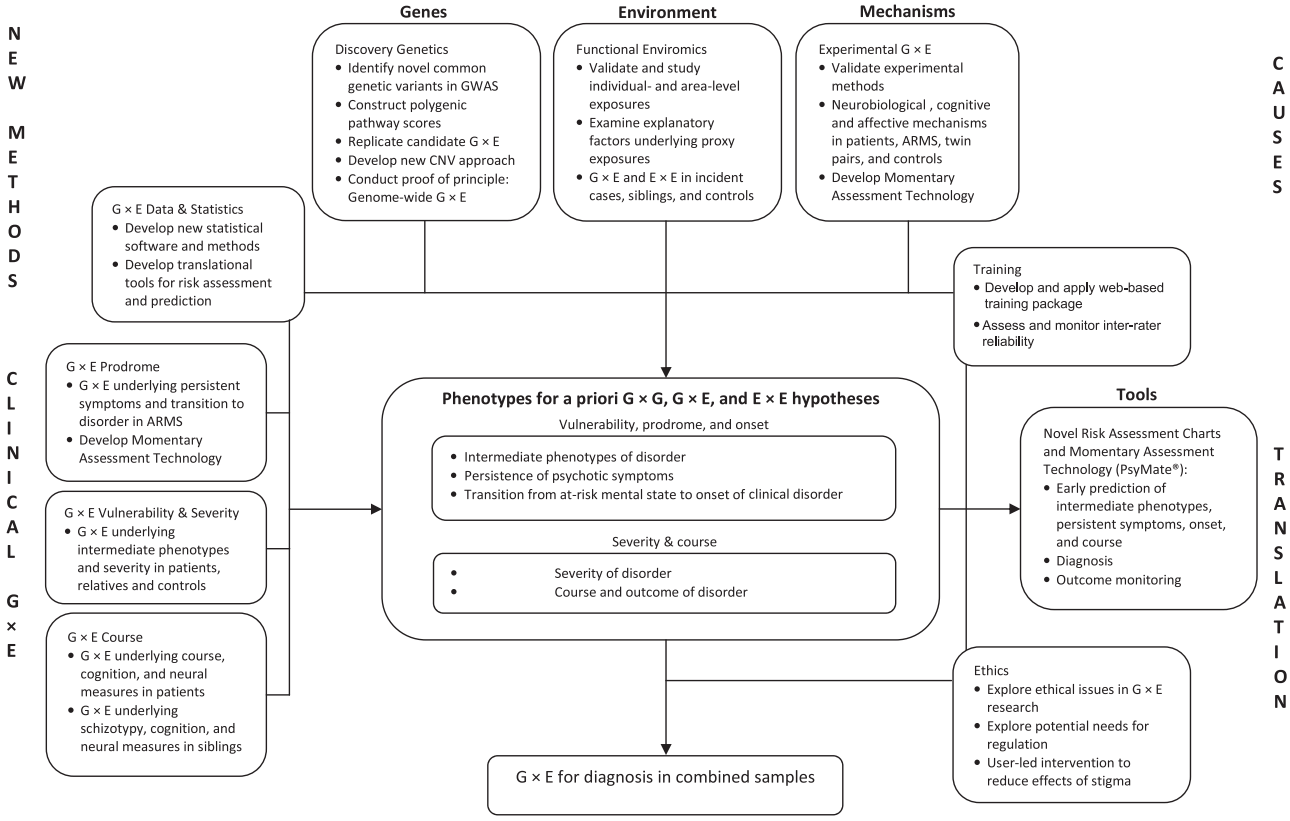

Fig. 1. General approach and overview of European Network of National Networks studying Gene-Environment Interactions in Schizophrenia.

In addition, this work package targets previously identified candidate G × E for replication, develops and implements new approaches to G × E analysis with CNVs, and conducts proof of principle for genome-wide G × E analysis, with the aim of identifying novel risk-environment interplays that are not predicated upon the existence of observed genetic main effects.

In the "Experimental G × E" work package, validated and scalable experimental methods have been developed for investigating neural, cognitive, and affective mechanisms underlying the interplay of genetic and environmental factors under experimental conditions, controlling for measured and unmeasured confounding factors, including genetic factors (and, thereby, gene-environment correlation). Work by the experimental G × E work package also supports the view that epidemiologically validated risk factors such as migration or urban living and upbringing have a social component, as proposed by the social defeat hypothesis.[55] Specifically, findings from this work package suggest a specific impact of social stress on activation in a perigenual cingulate-amygdalar circuit in healthy populations exposed to urban living and upbringing[56] and migration.[57] This suggests that this circuit may be a core convergence region for risk of mental disorders arising through social stressors.[58] The experimental G × E approach is also of considerable potential value for generating translational knowledge. Therefore, this work package has developed innovative Momentary Assessment Technology (ie the PsyMate) to investigate stress sensitivity in daily life as an important affective mechanism underlying environmental and genetic risk in the development of schizophrenia.[59]

The "G × E Prodrome," "G × E Vulnerability and Severity," and "G × E Course" work packages take into account the different phenotypes and clinical stages of disorder at which gene-environment interactions may impact, including intermediate phenotypes, prodrome, onset, severity, and course of schizophrenia. These work packages aim to investigate clinical, environmental, and genetic determinants as well as G × E at all these levels, with initial evidence of candidate SNP × cannabis interaction for psychosis liability.[60,61] The "G × E Data & Statistics" work package provides coordination and support for statistical methodology to examine, jointly with all other work packages, G × E, G × G, and E × E interactions underlying disease risk, course, and outcome of schizophrenia. The work package further develops novel statistical software and methodology for examining G × E interactions. In the "Training" work package, a web-based training environment has been developed for addressing a key issue in large multi–national collaborations, i.e. inter-rater reliability in the assessment of environmental exposures, diagnosis, intermediate phenotypes, prodrome, onset, severity, and course. Given the potential

ethical issues raised by G × E research in schizophrenia, the "Ethics" work package explores these, detects potential needs for regulation and, in collaboration with the "Dissemination" work package, will include ethical and legal perspectives in the dissemination activities. Lastly, the entire project is coordinated by the "Management" work package.

Evidence on G × G, G × E, and E × E generated by EU-GEI will aggregate in the development of risk prediction algorithms that will be implemented in innovative, translational risk assessment charts and momentary assessment technology for early prediction of intermediate phenotypes, persistent symptoms, transition to, as well as onset, severity, course, and outcome of, schizophrenia. Application of these tools will allow the targeting of prevention, treatment and resources to modifiable mechanisms as well as subgroups of individuals with the greatest vulnerability, highest risk of developing persistent symptoms and psychotic disorder and, once diagnosed, to those with greatest severity and highest risk of poor course and outcome.

Conclusion and Future Prospects

Recent years have seen significant advances in epidemiological and molecular genetic research, consistently implicating environmental and genetic factors in the etiology of schizophrenia. However, methodological uncertainties remain with regard to validating environmental exposures and the population risk conferred by the molecular genetic variants identified to date remains small. While G × E may account for the latter, so far, replication of the limited number of molecular genetic candidate G × E findings is rare. Important conceptual and methodological challenges of G × E research in schizophrenia are currently being addressed in integrated, large-scale investigations, such as EU-GEI.

While EU-GEI is now well underway, new challenges emerge at the horizon of G × E research. It now appears increasingly likely that genetic variation[44] and environmental exposures (such as childhood adversity)[18] are, to a significant degree, shared across a range of psychiatric disorders, with some emerging evidence of overlap in phenotypes.[62] Therefore, as for mono-disciplinary, epidemiological and molecular-genetic research, the study of G × E needs to be extended beyond individual disorders to investigations of all major psychiatric disorders in order to unpick the complex interplay of genes, environment, and underlying mechanisms that push some people along a pathway to psychosis, whilst others to non-psychotic or no disorder. Not only cross-discipline, but also large-scale cross-disorder investigations are now required to more fully realize the potential of G × E research in elucidating the etiology of, and, ultimately, improving prevention and treatment for, schizophrenia.

Funding

European Community's Seventh Framework Program under grant agreement (HEALTH-F2-2009–241909, Project EU-GEI).

Acknowledgment

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

European Network of National Networks studying Gene-Environment Interactions in Schizophrenia (EU-GEI)

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