Developmental gene-environment interactions: A model for psychosis

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The incidence of psychotic disorders varies greatly across places and demographic groups, as do symptoms, course, and treatment response across individuals. High rates of schizophrenia in large cities, and among immigrants, cannabis users, and traumatised individuals reflect the causal influence of environmental exposures. This, in combination with progress in the area of molecular genetics, has generated interest in more complicated models of schizophrenia aetiology that explicitly posit gene-environment interactions.

Unravelling the causes of psychotic disorders

Schizophrenia and related psychotic disorders have a complex aetiology. Research has attempted to determine the role of specific biological variables, such as genetic and biochemical factors and subtle changes in brain morphology. Genetic vulnerability in schizophrenia is shared in part with bipolar disorder and recent molecular genetic findings also indicate an overlap with developmental disorders such as autism (Van Os & Kapur, 2009). According to twin and family studies more than half of the vulnerability for schizophrenia is of genetic origin. However, attempts to discover genes that relate directly to psychotic disorder have been frustrating and often disappointing, and despite enormous investments, the identification of actual molecular genetic variants underlying schizophrenia liability has proven extremely difficult. This difficulty is mainly due to the phenomenon of gene-environment interaction, which is defined as genetic control of sensitivity to the

environment.

Exciting findings in other areas of psychiatry have motivated researchers to turn their attention to better understanding the complex ways in which genetic factors interact with non-genetic factors to produce psychosis. Biological vulnerability factors with a genetic background interact with complex physical, psychological and environmental vulnerability factors. Conceptualised in a model, gene-environment interaction proposes that genes influencing risk for schizophrenia may not do so directly (the dominant model until recently), but indirectly by making individuals more sensitive to the effects of causal environmental risk factors.

The 'genotype x environmental interaction' approach differs from the linear gene-phenotype approach by positing a causal role not for either genes or environment in isolation but for their synergistic co-participation in the cause of psychosis where the effect of one is conditional on the other (Van Os et al., 2008). Gene-environment interaction seems a particularly suitable approach for understanding the development of psychosis because this phenotype is known to be associated with environmentally mediated risks, yet people display considerable heterogeneity in their response to those environmental exposures.

In the framework of gene-environment interaction, research is focussing on subclinical symptoms that can be traced to prior persistence of clinically relevant symptoms. For example, in a substantial proportion of patients with bipolar disorder, onset of illness may be seen as the poor outcome of a developmentally common and usually transitory non-clinical bipolar phenotype (Tijssen et al., 2010).

In schizophrenia and related psychotic disorders, the median prevalence of subclinical psychotic experiences is reported to be around 5% and the median incidence rate to be around 3%. The difference between

prevalence and incidence rates, together with data from follow-up studies, indicates that approximately 75□□% of developmental psychotic experiences are transitory and disappear over time. There is evidence, however, that transitory developmental expression of psychosis ('psychosis proneness') may become abnormally persistent ('persistence') and subsequently clinically relevant ('impairment'), depending on the degree of environmental risk the person is additionally exposed to (Van Os et al., 2009; Dominguez et al., 2009). According to the model of psychosis proneness - persistence - impairment, genetic background factors impact on a broadly distributed and transitory population expression of psychosis during development. Hence, poor prognosis, in terms of persistence and clinical need, can be predicted by environmental exposure interacting with genetic risk.

Environmental risk factors

According to findings from epidemiological research, rates of schizophrenia and related psychotic disorders are substantially influenced by a spectrum of environmental risk factors with significant impact on children and adolescents growing up in European societies.

- Urbanicity

  Growing up in an urban area has been shown to be associated with an increased risk of developing psychotic disorder in later life (Spauwen et al., 2004). For children growing up in big cities a more than twofold risk compared to children in rural environments has been shown, independent of other risk factors. According to latest research findings up to 25% of all schizophrenia cases can be attributed to this effect.

- Migration

  Migration presents an increasing challenge to European countries. In immigrant populations the risk of developing psychotic disorders is much higher compared to the risk in both the host country and the country of origin. These findings point to a significant impact associated with the often problematic social interaction between migrants and majority populations.

- Cannabis use

  Apart from alcohol, cannabis is the most widely used drug in Europe. Although its effects were considered to be harmless compared to other drugs until recently, many studies have shown that cannabis use, in particular heavy use during adolescence, increases the risk of psychotic disorders such as schizophrenia.

- Childhood victimisation

  In European countries at least 15% of populations are the victims of significant abuse, neglect or bullying during childhood. Evidence from epidemiological research pointing to a link between childhood trauma and psychotic disorders is remarkably consistent in showing strong effects on disease vulnerability.

Measuring schizophrenia vulnerability caused by gene-environment interaction

Given substantial gene-environment interaction underlying schizophrenia and related psychotic disorders, the most promising approach to

elucidate the causes of schizophrenia is to focus on both genes and environments in the same research project. The study of gene-environment interaction is a multidisciplinary exercise involving epidemiology, psychology, psychiatry, neuroscience, neuro-imaging, pharmacology, biostatistics, and genetics. However, it has proven extremely difficult to bring together these disciplines. Now for the first time in the European Union a rational strategy of focused research collaboration has been devised with a unique, large-scale project, which aims to unravel the causes of schizophrenia and related psychotic disorders (EU-GEI project, see below).

The EU-GEI project

This multidisciplinary project, involving more than 7,500 patients and their families from 15 countries, is the largest effort to date to find gene-environment interactions underlying schizophrenia risk. It is designed to focus on the effects of gene-environment interactions on brain pathways and psychological vulnerability, and to elucidate how subtle, but measurable, behavioural expressions of vulnerability for psychotic disorder are mediated by cerebral and psychological pathways. Follow-up research in the project is expected to establish why, in some individuals, expression of vulnerability will never progress to overt illness, while in others, schizophrenia will manifest in clinical expression.

Psychopathological experiences show essential features such as variability over time and dynamic patterns of reactivity to the environment that need to be captured for a better understanding of their underlying mechanisms. Behavioural expression of vulnerability, occasioned by gene-environment interactions, is best captured as subtle alterations in mood, perception, volition and thought in response to minor stressors in the flow of daily life. Since to date no tools exist to adequately monitor these alterations, European enterprises and start-ups

in the EU-GEI project will develop new technology allowing for adequate assessment.

Today a prototypic device (PSYMATE) has been designed which can be carried during the day for easy data input concerning mental state, context and activities at random moments in the stream of consciousness. This new method will enable clinicians to capture the 'film' rather than a 'snapshot' of daily life reality of patients, fuelling new research into the gene -environment - experience interplay underlying psychopathology and its treatment (Myin-Germeys et al., 2009).

Clinical implications

Given the evidence for detrimental effects of big cities on mental health and a wide range of somatic disorders, the impact of the increasing urbanisation and other environmental risk factors in European countries (e.g. migration) should be prioritized in scientific research.

Since genetic factors impact on a rather common, transitory expression of psychosis during development, poor prognosis in terms of clinical need can be predicted by environmental exposure interacting with genetic risk.

The current development of tools allowing the actual measurement of vulnerability caused by gene-environment interaction will enable clinicians to monitor, and possibly modify, vulnerability at the behavioural level.

The findings of the EU-GEI project are promising with regard to preventing transition from subclinical psychosis to overt illness.

Conclusion

Until recently, researchers found it difficult to unveil the causes of schizophrenia and related psychotic disorders. 100 years after the modern definition of schizophrenia, research is beginning to understand the biological mechanisms underlying the symptoms of this most mysterious of mental disorders and the psychosocial factors that moderate their expression.

Recent research findings in psychiatry indicate that genes are likely to influence disorder mostly indirectly, via their impact upon physiological pathways, and work by increasing the likelihood of developing a psychiatric disorder, rather than as direct causes of disorder per se (Van Os et al., 2008).

A significant proportion of psychotic disorder may be understood as the rare poor outcome of a common developmental phenotype characterized by persistence of detectable subclinical psychotic experiences.

The current model of gene-environment interaction is nurturing promising approaches to understand the symptoms of schizophrenia and related psychotic disorders and improve treatment.

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