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Introduction

Jim van Os[1,2] and Robin Murray[3]

[2]Division of Psychological Medicine, Institute of Psychiatry, London, UK, Maastricht University; [3]Institute of Psychiatry

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The search for the molecular genetic basis of schizophrenia has proven much more difficult than was initially thought. Indeed, the field is currently in a state of anxious self-examination with a range of explanations proposed for the failure to consistently replicate the putative susceptibility genes proposed in the early 2000s.[1–4] One explanation that has received scant attention is gene-environment interaction. Molecular genetic studies in schizophrenia to date have rarely attempted to include environmental measures and have instead assumed that if samples were sufficiently large and the number of molecular markers sufficiently numerous, genetic effects would be revealed even if underlying interaction with environmental factors were present. In theory, this strategy is correct, but now that close to 1500 molecular studies in schizophrenia have failed to yield definitive results, it is time to reconsider the role of gene-environment interactions and how examining the joint effects of genes and environment may be more productive than studying either one in isolation.

The hypothesis that multiple gene-environment interactions play a role in the etiology for schizophrenia is attractive. Indeed, brain development itself is characterized by a series of successive gene-environment interactions; critical periods of exposure to the environment are necessary for genetically influenced traits such as speech, vision, and social cognition to be expressed in their correct developmental sequence. Similarly, it is difficult to see how anomalies in the timing, quality, and quantity of environmental exposures involved in brain development could fail to be related to schizophrenia when it is characterized by developmental alterations in cognition, emotion, and salience attribution.

Gene-environment interaction research to date has attracted little funding. One reason, as mentioned above, is that genetic factors may be identified by "brute force" alone,[3] even if the environment is ignored. Recent findings in diabetes involving combined samples of over 70,000 people mostly yielding odds ratios of around 1.1 for susceptibility genes may serve as an example.[5] Thus, while the brute force strategy may also help identify some tiny genetic effects in schizophrenia using, eg, genome-wide association approaches in many thousands of patients, distal tiny genetic contributions by themselves explain little if more proximal interactions with environmental component causes determine the underlying pathophysiology. Therefore, although the brute force approach may be helpful, the more complicated work of identifying underlying gene-environment interactions also needs to be carried out and is currently disproportionably lagging behind. The other reason for lack of funding may be related to the fact that gene-environment interaction research necessarily is multidisciplinary, requiring close collaboration between unlikely partners coming from the fields of epidemiology, psychology, developmental neurobiology, psychiatry, neuroimaging, pharmacology, biostatistics, and genetics. Only by bringing the often dissociated and sometimes frankly antagonistic efforts of these disciplines together does the identification of gene-environment interactions stand a chance. It is not a question whether one "believes" in or perhaps more commonly disbelieves in gene-environment interactions in schizophrenia; the question is that they represent an excellent scientific hypothesis for which major funding is required if they are to be identified. As Rutter[6] recently wrote: "A very large amount of data has shown that all biological features involve substantial genetic influence. Why should sensitivity to the environment be the one and only characteristic that provides a major exception? It just does not seem a plausible supposition."

The European Network of Schizophrenia Networks for the Study of Gene-Environment Interactions[7] has argued that systematic attempts to identify gene-environment interaction cannot be equated with traditional molecular genetic studies with a number of putative environmental variables thrown in. The challenge in the years to come is to go beyond paying lip service to the "stress vulnerability" model of

[1]To whom correspondence should be addressed; Department of Psychiatry and Neuropsychology, Maastricht University Medical Centre, Maastricht, The Netherlands; tel: 31-43-3875443, fax: 31-43-3875444, e-mail: j.vanos@sp.unimaas.nl.

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schizophrenia and bring a variety of disciplines together to jointly work on the identification of gene-environment interactions.

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