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Mental disorders as a result of gene-environment interaction: A new findings

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Research studies in psychiatry which take into consideration the gene-environment interaction (GEI) are relatively a new research model. The findings coming from recent studies in the field show that gene-environment interactions really exist in nature and significantly influence many mental disorders. This article aims to address several problems. First, the authors explain what is meant by gene-environment interaction. Also we discuss why such interactions are so important in psychopathology, and summarize emerging evidence about gene-environment interactions in development of mental disorders. The article focuses on studies of antisocial behavior, because these have been leading the way in investigating environmental as well as genetic influences on psychopathology. The final part of the article envisages future work on gene-environment interplay, arguing that it is an interesting and profitable way forward for psychopathology research.

Zaburzenia psychiczne jako wynik interakcji geny-środowisko: Nowe odkrycia

Badania naukowe biorące pod uwagę interakcję pomiędzy genami a środowiskiem stanowią stosunkowo nowy model na gruncie psychiatrii. Wyniki najnowszych badań wskazują, że interakcje geny-środowisko (GEI) istnieją w rzeczywistości i w istotny sposób wpływają na występowanie zaburzeń psychicznych. Niniejszy artykuł podejmuje kilka problemów. Po pierwsze, autorzy wyjaśniają, co rozumieją pod pojęciem interakcji geny-środowisko. Uzasadniają także, dlaczego są one tak ważne na gruncie psychopatologii oraz podają fakty świadczące o udziale interakcji typu geny-środowisko w rozwoju zaburzeń psychicznych. Jako przykład mogą tu posłużyć wyniki badań nad zaburzeniami antyspołecznymi, które należą do najlepiej udokumentowanych w literaturze przedmiotu. W końcowej części artykułu autorzy wskazują na możliwości zastosowania paradygmatu GEI w przyszłych badaniach prowadzonych na gruncie psychopatologii.

INTRODUCTION

In recent years psychologists and psychiatrists have come to a deeper understanding of interplay between genetic and environmental risk factors that influence mental disorders. In the professional literature this interplay is referred as gene-environment interaction (GEI). There are some basic forms of that interaction. The first type comprises quantitative models of heritability-environment interaction. These models explain

how the determined balance of heritable versus environmental influence on a phenotype's variation is visible in differences occurring in subgroups of the population [1]. It is represented in twin studies which findings show that heritability estimates are population-specific. The models belonging to the first type involve statistical interaction and concentrate on latent genetic effects in population variation. However, they don't indicate that sensitivity to the environment is moderated by

TABLE 1. Main approaches to psychiatric genetics research

1	Gene	→	Disorder
2	Gene	→	Endophenotype → Disorder
3	Environment	→	Genotype → Disorder
4	Environment → Genotype → Neural substrate reactivity → Disorder		
Ad 1 – assumes direct linear relations between genes and disorder.			
Ad 2 – replaces the disorder outcomes with intermediate phenotypes.			
Ad 3 – assumes that genes moderate the effect of environmental pathogens on disorder.			
Ad 4 – specifies important role of nervous system reactivity in the gene-environment interaction.			

variation in the DNA sequence. The second type of GEI is called as epigenetic programming. It emphasizes that environmental effects on an outcome such as physical health or behavior are moderated by altered gene expression or altered chromosomal structure [2, 3]. Many experimental studies with animals have shown that early-life rearing experiences can change gene expression, and that this expression subsequently can influence a later behavior [4]. The epigenetic programming is mostly a biological process which involves a specific measured genes and a specific environments. In this process the effects don't involve variation in the DNA sequence, and they don't indicate that sensitivity to the environment is moderated by measured genetic variation. It should be said, rather, that the environmental effects are mediated through gene expression. The third type of gene-environment interaction a person's genotype influences his or her probability of exposure to environmental risks [5]. In this model gene-environment interplay is discussed as if the genes have direct biological effects on an environmental risk factor (for instance, it explains that the tendency to specific reaction on stressful life events is partly heritable). However, as it is known now, the genetic effect is mediated through some behaviors that in turn bring about the environment risk (e.g. personality traits influence our reaction on life events). (Basic approaches used in psychiatric genetics research are showed in table 1). Research studies on the GEI have become essential in such sciences as agriculture (how animals' and plants' genotypes moderate the resistance to diseases), and medicine (how hosts' genotypes moderate susceptibility to diseases such as malaria or tuberculosis). Also in social sciences the GEI model, since a long time, is an important theoretical concept. For instance, it plays an essential role in developmental psychology (how it happens that some children have a good mental health despite adversities existing in their families?).

THE IMPLEMENTATION OF THE GEI MODEL IN MENTAL HEALTH

However the research studies on gene-environment interaction in field of mental health are relatively new, they gathered some important amount of knowledge. The GEI approach brings a new opportunities to psychiatric research which extend the range of its field and integrate it with the neuroscience. Moreover, successful collaboration of these two sciences can possibly solve the biggest mystery of human psychopathology: how does an environmental factor, external to the human being, get inside the nervous system and change its elements to generate the symptoms of a mental disorder? An answer on this question would advance our understanding of essence of mental disorders, and subsequently, increase our potential to treat and prevent them successfully.

Like many other illnesses that show frequent prevalence in population and complex etiology, most mental disorders have known environmental risk factors whose causal status is unproven and environmental pathogens being proven causes. For example, an important role of environmental pathogens have been proved for substance-use disorders [6], antisocial disorders [7], depression [8], and also for some disorders belonging to the schizophrenia group [9, 10]. Current investigations show that for other disorders, such as autism, Alzheimer-type dementia and ADHD (*attention deficit hyperactivity disorder*), the pool of environmental factors is significantly limited.

There is a wide array of environmental risk factors related to mental disorders. They include, among others, such as maternal stress and substance abuse during pregnancy, low birth weight, complications during delivery, low quality of parental care during infancy, childhood physical maltreatment and neglect, premature parental loss, exposure to parental conflict, family violence, stressful life events, e.g. head injury and toxic

TABLE 2. Risk for schizophrenia in genetic relatives of schizophrenics

Genetic relation	Type of relation	Risk
General population	–	1 %
Third-degree	Cousins	2 %
Second-degree	Uncles/aunts	2 %
	Nieces/nephews	3 %
	Grandchildren	4 %
	Half-siblings	6 %
First-degree	Children	13 %
	Parents	6 %
	Siblings	9 %
	DZ twins	17 %
Identical	MZ twins	48 %

Source: [16]

exposure. Some of these environmental factors play only a contributory role because exposure to them does not always generate disorder, while others are able to cause a severe psychopathological states. Those differences result from a variability in individual responses to environmental pathogens. Research studies performed both on humans and animals confirm clear heterogeneity of response on all environmental risk factors for psychopathology, even such dangerous like physical traumas. This heterogeneity is moderated by some individual differences in physiology of nervous system, temperament, personality and intelligence, all of which are determined by genetic factors [11]. It implies that differences between individual people, originated in the DNA sequence, are responsible for differences existing between them in their resilience or vulnerability to the environmental causes of mental disorders. This obvious assumption is the subject of studies in relation not only to mental disorders, but also to number of somatic illnesses like diabetes, cancer, respiratory and cardiovascular diseases [12, 13, 14].

Many serious research studies on genetic influence on course of major mental disorders brought about a confusing results. It applies especially to such frequently occurring illness, as schizophrenia (see table 2). However, the results tell us something very important: *there may not be single genes of significant effect for schizophrenia and possibly for most other forms of psychopathology*. Geneticists interpret the data as supporting a polygenic mode of inheritance—several genes contribute to the liability of developing schizophrenia and the effect size for each locus is relatively small. Thus, linkage studies require a very large number of cases in order to detect these loci. The biggest advantage of these confusing results is that they can guide future research re-

quiring a more sophisticated genetic knowledge and technologies. As more and more human genes are identified and characterized at the molecular level, the strategy to detect vulnerability loci will switch from the linkage design to the more powerful association design. Instead of blindly assessing the tens of thousands of human loci for their relevance for schizophrenia, the linkage results point to areas of the genome that should first be explored. For instance, the 6p region potentially implicated in schizophrenia contains several hundreds to perhaps a thousand or so genes [15].

Although schizophrenia is the most studied disorder in the genetics of psychopathology, there have been twin and adoption studies on other disorders. The results are similar to those for schizophrenia in the following ways: (1) MZ twins are never 100% concordant for a disorder; this clearly implicates the environment for all forms of psychopathology studied thus far. This is why statements like „*alcoholism is a genetic disorder*” or „*bipolar manic-depression is due to heredity*” are very misleading. (2) The risks to relatives do not following the pattern of simple Mendelian inheritance, even if that pattern is „souped up” by espousing incomplete penetrance and variable expressivity. The results of almost all forms of segregation analysis (a statistical attempt to find major Mendelian loci for disorders with complex genetics) have been mixed [17]. (3) Hence, all forms of psychopathology studies thus far are DCGs (disorders with complex genetics). (4) Although many researchers suspect heterogeneity, no subdivision of any disorder into „types” has been so compelling as to put them into a handbook. The best example is depression. Despite attempts to classify depression into „*exogenous versus endogenous*,” „*reactive versus nonre*

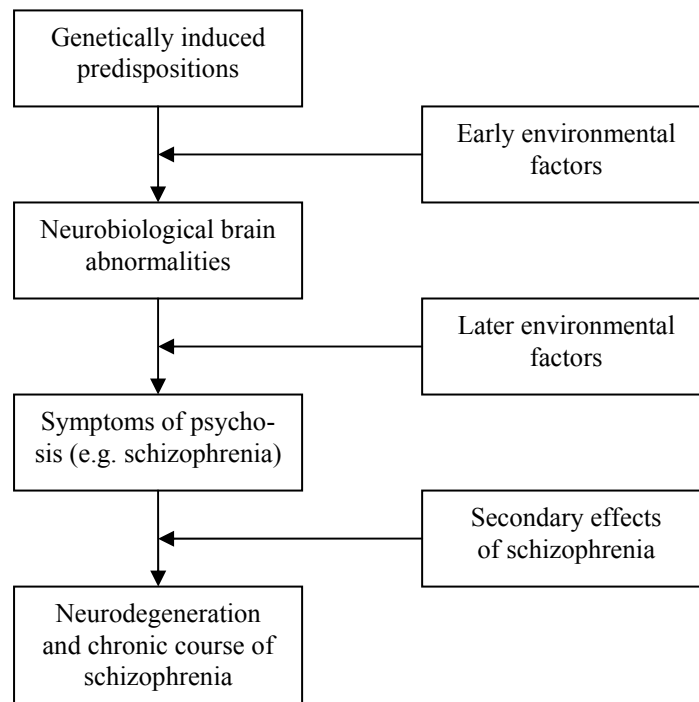


FIG. 1. The GEI model of schizophrenia

active,” and „neurotic versus psychotic,” the data suggest that they do not run true to type within families. (5) To date, no genes of large effect have been reported by a large and replicated body of linkage or association results. To be sure, there are interesting leads here and there, but no single result has passed the crucial test of replication in a large number of independent labs. The reasons for this state of affairs are unclear, but the empirical data have certainly dampened the initial enthusiasm of investigators who hoped to detect such phenomenon as a „chromosome 13 form of schizophrenia.” On the other hand, the confusing results should not lead to a state of despair in which linkage and association studies are abandoned as being unproductive. The puzzling results are telling us *something important* – it is just that we have not been clever enough to figure out what that important something is. Currently the most favored hypothesis is that polygenic transmission is responsible for the lion’s share of the genetic diathesis. Hence, the effect of any single locus will be on the small side and hard to detect in studies that lack very large numbers of cases. Perhaps, as we learn more about the human genome, we will eventually develop more firm generalizations. What we cannot anticipate, however, is *how long* it might take to develop a large body of well-replicated genetic associations with psychopathology. This proposed model of schizophrenia (fig. 1) reflects our theoretical premise that the

neurobiological substrate for the disorder is formed by the joint effect of genes and adverse environmental events. The model also explains how later environmental events (e.g. life events and biological factors) are combined with neurobiological abnormalities to cause schizophrenia. The lower part of the figure indicates that psychosis may lead to neurodegeneration and chronic course of schizophrenia. If the GEI model is accurate, then it follows that psychosis and the subsequent diagnosis (i.e. categorization) of schizophrenia are events that occur well after the first manifestation of the genetic liability to schizophrenia. This view is consistent with the notion of an underlying continuum of genetic liability that has schizophrenia as only one of its possible outcomes.

GENE-ENVIRONMENT INTERACTION IN RELATION TO BEHAVIOR DISORDERS

Despite of a relatively short tradition of the GEI studies in mental health science, some of the recent findings are very interesting and promising. For example, Caspi et al. (2002) [18] have found that a functional polymorphism in the promoter region of the gene encoding the neurotransmitter-metabolizing enzyme monoamine oxidase A (MAOA) would moderate the effect of child maltreatment in the cycle of violence. The results indicated that maltreated children, whose genotype conferred low levels of MAOA expression,

more often developed conduct disorder, antisocial personality and adult violent crime than children with a high-activity MAOA genotype. In another study the same group of researchers [19] tested the hypothesis that a functional polymorphism in the promoter region of the serotonin transporter (5-HTT) gene would moderate the influence of stressful life events on depression. The findings have showed that individuals with one or two copies of the 5-HTT „short” allele exhibited more depressive symptoms, diagnosable depression, and suicidality following stressful life events than individuals with two copies of the "long" allele. Examples of those studies convince us of important value of the GEI model to psychiatric epidemiology. First of all, it helps to estimate the involvement of gene-environment interaction in development of mental disorders, and, secondly, to test whether the interaction accounts for a significant proportion of the disorders in a studied population. This kind of information about mechanisms involved in development of mental disorders could be very useful for future construction of adequate theory and treatments.

There are at least three theoretical reasons to support the assumptions that GEI effects are important and consequential for mental health. *First*, the underlying concepts of natural selection dictate that genes are involved in organisms' adaptation to the environment, that all organisms in a species will not respond to environmental change in the same way, and that this within-species variation in response involves individual differences in genetic endowment. Genetic variation in response to the environment is the raw material for natural selection [20]. *Second*, biological development at the level of the individual involves adaptations to prevailing environmental conditions [21]. The literature on biological programming by early experience provides relevant examples [22, 23]. Given that human development is an environment-dependent process, it is implausible that genetic factors do not play a role in moderating the process [24]. It is even more implausible that the process does not include mental health among its outcomes. *Third*, both human and animal studies consistently reveal great variability in individuals' behavioral responses to a variety of environmental hazards. Heterogeneity in response characterizes even the most overwhelming of traumas, including all known environmental risk factors for psychopathology. To argue that such response heterogeneity is not under genetic influence would require the assumption that although

genes influence all other areas of biological and psychological function, responsiveness to the environment is uniquely outside the sphere of genetic influence.

THE GEI CAUSATION IN DEVELOPMENT OF ANTISOCIAL BEHAVIORS

In recent years the research studies on etiology of behavior disorders are stuck on risk factor stage [25]. In order to illustrate how the GEI design is important and promising in field of mental health, we will explain it on examples of the studies of antisocial behaviors. On beginning we take into consideration just one risk factor, *bad parenting*, and one antisocial outcome, *children's aggression*. The bad parenting includes a group of risk factors such as unskilled discipline, child neglect and abuse. The outcome – children aggression – includes such behaviors as fighting, bullying and cruelty in relations with peers and other antisocial behaviors. In many studies it has been confirmed that bad parenting predicts aggressive behavior in children [26]. Assessment of these studies would enable to determine whether the relation between bad parenting and children's aggression is a true cause–effect relation such that interventions that stop bad parenting can reasonably be expected to prevent aggression from emerging. This aim is important meaning because studies of adoptions have documented the dispiriting fact that aggression emerges in adopted children despite the fact that they were separated from their at-risk biological parents at birth and reared by skilled and loving adoptive parents.

More than 100 studies have addressed the question of genetic influence on antisocial behavior, and meta-analyses conclude that genes influence 40% to 50% of population variation in antisocial behavior [27, 28]. This research unequivocally proves that environmental influences account for variation. This fact constitutes a remarkable contribution to the understanding of causation [29]. In addition, it is recognized that the heritability coefficient indexes not only the direct effects of genes but also the effects of interactions between genes and family-wide environments [30, 5]. In such interactions, the effect of an environmental risk may be even larger than previously reported among the subgroup of individuals having a vulnerable genotype. This is the case for antisocial behaviors.

One useful feature of behavioral–genetic research designs is that they offer two powerful

methods for documenting the importance of environmental effects [11]. One of these methods of detecting environmental influence tests whether any of the family members in a study sample are more similar than can be explained by the proportion of genes they share. For instance, in monozygotic (MZ) twins' genetic similarity is twice that of dizygotic (DZ) twins and, therefore, if nothing but genes influenced antisocial behavior, MZ twins' behavior ought to be at least twice as similar as that of DZ twins. If that is not the case, then it can be assumed that something environmental has influenced the twins and enhanced their similarity. For almost all human behavioral traits studied thus far, environmental factors shared by family members have not been found to make family members similar [31]. Antisocial behavior is a significant exception. A comparison of shared environment effects across 10 psychiatric disorders revealed that such effects were stronger for antisocial personality and conduct disorder than for affective disorders, anxiety, or substance dependence disorders [32]. Estimates of shared environment effects on population variation in antisocial behavior are about 15% to 20%, as reported by meta-analyses [27, 28]. The small size of this shared environment estimate should not be too surprising, because the twin-study coefficient indexing the shared environment does not include environmental effects involved in gene-environment interactions. The shared environment coefficient can be thought of as a residual effect of shared environment that remains after controlling for gene-environment interactions. As most human behavior involves nature-nurture interplay, it is remarkable that as much as 20% of the population variation in antisocial behavior can be attributed to direct environmental effects not conditional on genetic vulnerability. The second method of detecting the presence of environmental influence is to test whether family members are less similar than expected from the proportion of genes they share [33]. For instance, if twins in an MZ pair are not perfectly identical in antisocial behavior, despite sharing all their genes, this indicates that different social experience has reduced their behavioral similarity. After estimates of the influences of heritability (50%) and shared family environment (20%) on antisocial behavior are calculated, the remainder of population variation (30%) is assumed to reflect environmental influences not shared by family members (variously labeled „unique”). These experiences might in-

clude criminogenic experiences unique to the individual and not shared with his or her sibling, such as sustaining a head injury, being the unique target of sexual abuse, or living with an antisocial spouse.

Thus, some portion of the non-shared environment effect is attributable to error or genes, and the size of this portion is unknown. It is highly unlikely that any behavior disorder is wholly determined by genes, but it is important to begin any program of research into causal processes by ascertaining what effect sizes can be expected for both genetic and environmental influences under natural conditions, in the absence of intervention. For overall population variation in antisocial behavior, these effects are 50:50. Therefore, quantitative behavioral-genetic research has shown that the answer to question „Does children's aggression have any non-genetic causes?” is a definite „yes”; there is strong evidence that environmental causes must exist.

The GEI research methodology is useful for revealing the contribution of environmental factors to antisocial outcomes in humans. This is a priority for future research because it may indicate the possibility of strategies for prevention. Researchers in behavioral genetics are beginning to include in their research, measures of the environmental factors that are thought to contribute to antisocial behavior, such as the maltreatment of children, poverty and inconsistent discipline. Studies will hope to ascertain how the environments of young people interact with their genetic vulnerabilities, to exacerbate or protect against their risk for antisocial behavior. Longitudinal research will follow samples of twins and adoptees as they age, to explore the changing balance between genetic and environmental factors that influence antisocial behavior over the course of an individual's life. Because ‘crime’ itself is not inherited, researchers are working to investigate which features of personality and cognitive function may be associated with antisocial behavior. With regard to molecular research techniques, research into MAOA related genotypes is likely to continue, along with research into other genes identified in research involving animals, and genes known to have functional significance in the brain. Importantly, quantitative and molecular work is converging on the possibility that genes act to augment the resistance of young people to environmental factors that would otherwise increase the likelihood of antisocial behavior.

THE FUTURE OF GENE-ENVIRONMENT RESEARCH STUDIES

At the moment psychiatric genetics has earned pretty bad reputation for its methodological problems, but this reputation should not discourage neuroscientists from bringing genetics into their laboratories to study the genetic moderation of environmental pathogens' effects on neural substrates. It should be stressed that many previously published reports on gene-to-disorder associations proved to be false positives, prompting the publication of methodological warnings [34, 35]. However, most of the methodological problems arise from the fact that genetic epidemiology is an observational discipline that measures genotypes, environmental risk conditions and disorder outcomes as they naturally occur. This observational method involves several compromises to validity, but the same problems do not refer to the experimental method. Therefore, experimental neuroscience paradigms will benefit gene-environment interaction research by addressing some of the methodological concerns that are now disturbing genetic epidemiology, as it is explained below:

1. In case-control studies carried out in genetics research, large samples are needed because genetic effects are expected to be very small. In cohort studies, small effects are also a problem, and there is the additional need for large samples due to the fact that the environmental exposure and/or the disorder might have a low prevalence in cohorts [36]. By contrast, experimental studies have more control over the group sizes and intensity of environmental stimulus needed to obtain a detectable effect [37]. Moreover, unlike mental disorders, neural substrate outcome measures (such as emotional arousal or adrenocorticotrophic hormone responses) tend to be quantitatively distributed such that low prevalence is not a concern.
2. Some researchers express their concern about gene-environment correlation [38, 39]. When genes influence the probability of subjects' exposure to an environmental pathogen, this results in the contamination of measures of environmental exposure with genetic variation, thereby blurring interpretation of the findings. For example, the probability of experiencing certain stressful life events is known to be under partial genetic influence, as is the tendency to expose oneself to environmental pathogens such as cannabis or nicotine. By contrast, experimental random assignment of subjects to the environmental risk condition rules out this type of self-selection. For example, epi-

demologists study self-initiated tobacco smoking, while neuroscientists can study participants that are randomly assigned to nicotine exposure.

3. There are some problems connected with the difficulty of achieving precise and reliable measures of environmental exposure, particularly if the exposure typically occurs over extended periods of the life course [40]. For example, it is very difficult to determine the frequency, timing and extent of the trauma that is involved in stressful life events. Likewise, it is notoriously difficult, using survey methods, to measure the amount of active drug that is ingested during recreational cannabis use over many years. Experimental administration of the environmental pathogen or stimulus with standardized dosage and timing rules out this concern.

4. Also there is concern about the low prior probability of a true association between a disorder and any one among many thousands of genetic polymorphisms [41]. If little or nothing is known prior to a statistical test of association between a gene and behavior, then this results in a low prior probability of the hoped-for association, and any association uncovered could easily be a chance false positive result. Neuroscience research enhances the prior probability of a candidate gene being associated with disorder by connecting that genotype with brain responsiveness to a known environmental cause of the disorder. Thus, a key contribution from experimental neuroscience is evidence and theory that supports the biological plausibility of genetic hypotheses, which helps to prevent false positives. Consider research in cognate medical fields, where caffeine consumption has been linked to the risk of myocardial infarction. Caffeine is metabolized by an enzyme (CYP1A2) in the liver, knowledge that allowed researchers to test (and confirm) the hypothesis that carriers of the slow metabolizer variant of the CYP1A2 gene are at a heightened risk of myocardial infarction [42]. As researchers learn more about genes, the brain and environmental pathogens, the prior probability of hypotheses will become stronger, and false positive gene findings fewer.

After all, some more limitations must be mentioned. Experiments that randomly assign subjects to environmental pathogens will inevitably be limited to using substitutes analogous to the environmental pathogens that cause mental disorders. Real environmental pathogens are not approachable to experimental administration for three reasons: 1. ethics prohibit exposing humans to risk; 2.

animal-model exposures cannot be equated with human exposures; and 3. harm from naturally occurring environmental pathogens often accumulates for months or years longer than a laboratory experiment. These limitations of experimental gene-environment interaction studies must be acknowledged. However, the limitations are diminished where a chain of inference can link experimental findings involving an analogue pathogen to epidemiological findings involving its counterpart natural environmental pathogen.

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