Gene-environment interactions in mental disorders

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Research clearly shows that both nature and nurture play important roles in the genesis of psychopathology. In this paper, we focus on 'gene-environment interaction' in mental disorders, using genetic control of sensitivity to the environment as our definition of that term. We begin with an examination of methodological issues involving gene-environment interactions, with examples concerning psychiatric and neurological conditions. Then we review the interactions in psychiatric disorders using twin, adoption and association designs. Finally, we consider gene-environment interactions in selected neurodevelopmental disorders (autism and schizophrenia).

Key words: Genetic factors, environment, interaction, neurodevelopmental disorders

Family, twin, and adoption studies have firmly established the roles of both genes and environment in mental disorders. It remains difficult, however, to find genes for these disorders, and to characterize the particular environmental circumstances under which psychopathology emerges. The reason for this difficulty lies in the complex nature of mental disorders. Many disorders – like many normal physiological conditions (e.g., blood pressure) and cognitive abilities (e.g., intelligence) – probably result from the combined action of multiple genes of small effect together with a variety of environmental factors. In addition, genetic and environmental factors interact with each other in complex ways to influence phenotype (1). In other words, individual genes and environmental factors exert their effects only via interaction with other genes and other environmental factors. The issue is no longer one of nature *versus* nurture; rather, we must ask: how do genes and environment *interact* to produce a behavioral phenotype?

In this paper, we will focus on 'gene-environment interaction' in mental disorders, using genetic control of sensitivity to the environment as our definition of that term (2). Gene-environment interaction occurs when environmental influences on a trait differ according to a person's genetic predispositions, or when a person's genetic predispositions are expressed differently in different environments. Interaction phenomena are important. By ignoring interactions, true genetic and environmental effects can be obscured, which leads to false negative results and, more generally, to inconsistent findings in the literature.

The subsequent discussion begins with a consideration of methodological and measurement issues involving gene-environment interactions, with examples concerning psychiatric and neurological conditions. This will be followed by a representative review of interactions in psychiatric disorders using twin, adoption and association designs. Finally, gene-environment interactions will be considered in selected neurodevelopmental disorders (autism and schizophrenia) to highlight their potential to shed light on underlying etiologic mechanisms in this class of psychiatric conditions.

METHODOLOGY AND MEASUREMENT ISSUES

Several excellent reviews discuss some of the methodological issues and problems involved in assessing gene-environment interaction, and the reader is referred to these for a more detailed discussion (3-7). Some of these problems are ones of definition and assessment, i.e., in order to test for gene-environment interaction, individuals must be classified according to presence or absence of genetic and environmental risk, and the specification of both can be difficult. Environmental exposures are difficult to define and measure precisely, and are understudied in the context of genetic research designs (8). Moreover, putative environmental risk factors may not be truly environmental. This phenomenon is known as gene-environment correlation, in which an individual's genotype influences his exposure to the environment. In other words, 'environmental' factors are themselves attributable to genetic influences. Gene-environment interaction is difficult to measure in the presence of gene-environment correlation (4).

On the other hand, there are several different ways of measuring genotype (3). Unfortunately, because of the lack of well-established candidate genes for mental disorders (and relatively little knowledge of the biological processes that give rise to mental disorders), researchers have to rely on less direct ways of classifying a person according to genetic risk. This point underscores the importance and potential impact of the developments in molecular genetics, which will make it easier to identify genes and genetic markers associated with mental disorders. These ongoing advances will eventually allow the assessment of specific genotypes in specific environments, which will facilitate direct and systematic investigations of gene-environment interactions.

The impact of advances in molecular genetics (i.e.,

identifying genetic variants associated with mental disorders) can be illustrated using the case of Alzheimer's disease (AD). An allelic association exists between AD and the ε4 allele of the apolipoprotein E (APOE) gene (9), which results in a 6-fold risk for AD in individuals with one or two copies of this allele (10). APOE is considered a 'susceptibility gene', because it is neither necessary nor sufficient for the development of AD. Other genes or environmental agents must be present for the ε4 allele to increase risk for AD. One of the earliest environmental risk factors associated with AD was a history of head injury (11,12). Because a positive family history was also a risk factor for the disease (13), attempts were made to find evidence for gene-environment interaction, using family history as an indicator of genetic risk. However, results of early studies failed to demonstrate convincing evidence of interaction (14,15). Mayeux et al (16) then studied the combined effects of head injury and genetic susceptibility on risk for AD, and found no increase in risk associated with head injury in the absence of the ε4 allele, a two-fold increase in risk with ε4 alone, and a 10-fold increase in risk with both ε4 and a history of head injury. These findings and those from subsequent studies examining frequency of the APOE-ε4 allele in patients with head injury have led to hypotheses regarding a biological mechanism whereby head injury contributes to the pathogenesis of AD by increasing beta-amyloid precursor protein (APP) deposition in the cerebral cortex, which exacerbates the effect of the APOE-ε4 allele (which is thought to be related to cerebral beta-APP deposition).

Malaspina et al (17) found similar evidence for gene-environment interaction in schizophrenia, another mental disorder that has been associated with head injury. Using membership in multiplex schizophrenia and bipolar pedigrees as proxies for, respectively, greater and lesser genetic loading, they found that schizophrenic subjects from schizophrenic pedigrees were more likely to have experienced a traumatic brain injury (19.6%) than schizophrenic subjects from bipolar pedigrees (4.5%). Within the schizophrenia pedigrees, head injury was associated with a greater risk of schizophrenia (OR = 2.06), consistent with a synergistic effect between genes and environment. While these results are provocative, their implications are limited by the lack of information about schizophrenia susceptibility genes. As was the case with AD, once these have been identified with the aid of advances in molecular genetics, it will be relatively easy to incorporate this information into epidemiological studies, resulting in a rapid increase in knowledge about disease pathogenesis.

Currently, alcohol use provides a paradigm for studying gene-environment interaction similar to AD. Two polymorphisms – in the aldehyde dehydrogenase (ALDH) and alcohol dehydrogenase (ADH) genes – are associated with risk for alcohol dependence in Asian populations (18,19), providing the basis for studies examining the relationship between these genetic risk factors and the effects of known environmental risk/protective factors for alcohol abuse and dependence, such as early family rearing environment.

Until now, however, most knowledge about gene-environment interaction has come from traditional quantitative genetic studies, in which family history and monozygotic/dizygotic (MZ/DZ) concordance are used as indices of genetic risk. While there are methodological limitations to these studies (e.g., the possibility of genetic misclassification), twin and adoption studies have been influential in demonstrating gene-environment interaction effects (3).

TWIN STUDIES

Twins can be a useful tool in the investigation of gene-environment interaction (20). For example, MZ discordant twins can provide evidence for the influence of non-inherited characteristics on a disorder. A greater incidence of obstetric complications (OCs) (21) and of dysmorphological handprint signs suggestive of abnormal fetal development (22) has been observed in MZ twins with schizophrenia than in their unaffected cotwins. A different approach involves comparing heritabilities (i.e., the proportion of phenotypic variance due to genetic variance) according to the presence or absence of identified specific environmental risk factors. In addition to having main effects on rates and/or symptom levels of a disorder, environmental variables may also have moderating effects on the relative magnitude of genetic and environmental influences on the disorder. This is a form of gene-environment interaction: changes in the environment may render genes or environment more or less salient as influences on the behavior. In other words, the amount of variability in a disorder that is due to genetic or environmental influences may differ at different levels of an environmental variable, distinct from any main effect of that variable (i.e., in the absence of phenotypic change).

Several twin studies have examined the impact of broad personal variables on symptoms of mental disorders. Among these, the effects of socioregional variables on adolescent alcohol use were examined in a population-based sample of Finnish twins (23,24). In the first study, Rose et al (24) found that although drinking frequencies were similar for adolescents in urban and rural environments, genetic factors played a larger role in urban areas, whereas shared environment had a greater influence in rural settings. In an effort to better understand the nature of this urban/rural effect, this same group then examined more specific, continuous measures of the environment, and found that the magnitude of genetic influences on drinking frequency was nearly five times greater in environments characterized by a greater percentage of young adults, higher migration rates, and proportionately greater alcohol sales (23).

Marital status has been found to exert moderating

effects on the expression of genetic and environmental influences on alcohol consumption (25) and on symptoms of depression (26) in a sample of female adult Australian twin pairs. Genetic influences accounted for a greater proportion of the variance in both alcohol consumption and symptoms of depression in unmarried twins than in twins involved in a marriage-like relationship. In other words, having a marriage-like relationship reduced the impact of genetic influences on psychiatric symptoms. Religiosity has also been found to have a moderating effect on alcohol use initiation (27) and disinhibition, as measured by the Sensation Seeking Scale (28) in a Dutch twin sample. In both of these studies, while there was no association between religious upbringing and either alcohol use initiation or disinhibition, the influence of genetic factors on these variables was much greater in subjects without a religious background. These results suggest that receiving a religious upbringing, like being involved in a marriage-like relationship, may act as a protective factor in reducing the influence of genetic liability to psychiatric symptoms (26).

These studies are consistent with a sociological perspective that regards heritability as representing an individual's proportion of actualized genetic potential (29). According to this definition, the reason that heritability varies across environmental contexts is because different environments provide different opportunities for genetic potentials to be actualized. Structured situations are those that provide relatively unambiguous cues to guide behavior. Conversely, less structured situations are more ambiguous (30,31). Because there are few salient cues in the environment, individuals must rely to a greater extent on their own disposition to guide behavior. It follows that the causes of behavior in structured situations should be more situational than dispositional, whereas individual differences are more likely to be the causes of behavior in less structured situations. Consistent with this prediction, in the above studies, heritabilities for various clinical problems increased in environments that were less controlling, i.e., in subjects living in urban areas, in subjects who were unmarried, and in subjects without a religious upbringing, and the impact of shared environmental influences was greater in environments that theoretically provided a narrower range of opportunities to express individual differences in behavior. Results such as these, demonstrating differences in genetic and environmental influences in differing environmental circumstances, provide one explanation for the heterogeneity among heritability estimates for the same disorder, and point to the need to incorporate measures of the environment into genetically informative designs.

Kendler and colleagues have also used large population-based twin samples to study the impact of life events on depression and anxiety in women. Studies investigating the comorbidity of generalized anxiety disorder (GAD) and major depression (MD) in female twins found that all of the genes that influenced lifetime risk for GAD and MD appeared to be completely shared between the two disorders (32-34). Common or familial environment was not a factor in the etiology of either disorder. Some non-shared or unique environmental factors, however, may be relatively specific to either GAD or MD (e.g., stressful life events), while others may be both depressogenic and anxiogenic. These results suggest that it is likely that environmental factors are largely responsible for whether a female expresses genetic vulnerability as anxiety or depression. Roy et al (35) replicated these results in a clinical twin sample that included both male and female subjects and suggested that MD may be associated with stressful life events that involve loss, while GAD may be primarily related to life events that involve danger, consistent with the fact that MD and GAD have been associated with different sociodemographic predictors (36).

Following these results, Kendler et al (37) set out to investigate the relationship between stressful life events and the onset of depression in this sample. They found that the risk of onset of a major depressive episode in the month following the occurrence of any of four types of severe life events (death of a close relative, assault, divorce or marriage breakup, serious marital conflict) was highest in those at greatest genetic risk (as gauged by twin concordance). The one-month probability of onset of MD in individuals at lower genetic risk (i.e., with an unaffected cotwin) was 0.5% and 6.2%, respectively, depending on the absence or presence within that month of a severe life event. For individuals at high genetic risk (i.e., with an affected cotwin), the probabilities were 1.1% and 14.6%, respectively. These results are indicative of a gene-environment effect, in which genetic susceptibility increases an individual's sensitivity to the psychological impact of stressful life events.

Genetic factors, however, play a role in individual exposure to life events (37) and, moreover, the genetic liability to experience stressful life events overlaps with the genetic liability for depression (i.e., gene-environment correlation) (38). Thus, Silberg et al (39) conducted a more rigorous test of this gene-environment interaction effect by examining the relationship between risk for anxiety and depression and independent life events, i.e., those life events involving no genetic mediation, in a sample of adolescent female twins. They found a gene-environment effect similar to that of Kendler et al (37), in which the occurrence of an independent stressful life event in the past year (a new stepbrother/stepsister, brother/sister leaving home, father losing his job) had no effect on the depression scores of girls at low genetic risk (as indexed by the absence of parental emotional disorder), but significantly increased the scores of girls who had a parent with a history of depression or anxiety. In addition, life events exerted a moderating effect on the genetic and environmental influences on depression and anxiety, such that genetic variance increased with increasing exposure to

stressful life events, a result in accord with the hypotheses regarding protective environments advanced in the studies discussed above (23,26). This study illustrates just one of the difficulties in finding evidence for gene-environment interaction in complex disorders: genes influence both exposure and susceptibility to environmental risk factors. Gene-environment correlation and gene-environment interaction both operate to influence phenotype, and disentangling the two will require conceptual advances such as that illustrated by this study.

ADOPTION STUDIES

More than twin and family studies, adoption studies allow for the separation of genetic and environmental effects, because children do not share home environments with their biological parents. The major drawback to this type of design is that adoptive homes underrepresent high-risk environments, i.e., those at the extremes of poverty and deprivation (see Rutter and Silberg (4) for additional limitations). This is especially important because it has been suggested that gene-environment interactions may only exist at the extremes of genetic and environmental variation, hence adoption studies may underestimate the effects of environmental risk and protective factors and may not always detect true gene-environment interactions (40).

For the most part, adoption study investigations of gene-environment interaction have used biological family history of mental disorder as an indicator of genetic risk, and examined its relationship to psychosocial risk and protective factors in the adoptive family. Results from studies investigating the effects of family variables such as family conflict, poor cohesion, and deviant communication indicate that a wide range of mental disorders, including alcoholism, antisocial behavior (ASB), depression, and schizophrenia share these risk factors and that, for each disorder, these environmental influences interact with genetic risk to exacerbate psychiatric symptoms.

An early adoption study found that male (but not female) adoptees with an alcoholic biological parent were more likely to develop certain types of alcoholism if they were also at environmental risk, based on adoptive family characteristics, pre-placement conditions, and age at adoptive placement (41). Cutrona et al (42) found evidence for gene-environment interaction in alcoholism in a US sample of adoptees. Neither a biological background of alcoholism nor any family environmental variables increased risk for alcohol abuse or dependence in female adoptees. However, women (but not men) with at least one alcoholic biological parent who also experienced early-life family conflict and/or adoptive family psychopathology were more likely to become alcoholic than those with low levels of family conflict. In other words, neither a biological background of alcoholism nor environmental stress alone was sufficient to lead to alcoholism in the adoptees, but a combination of the two increased the risk.

Adoption studies have also found evidence for a gene-environment effect on ASB, such that individuals at high genetic risk are more sensitive to adoptive family conflict. Cloninger et al (43) found a synergistic effect for genetic and environmental risk factors in a Swedish sample, such that adoptees at both genetic risk (i.e., criminal biological parents) and environmental risk (i.e., adverse rearing experiences and poor quality adoptive placements) had significantly higher rates of petty criminality than adoptees at either biological or environmental risk alone. In other words, adoptees with genetic predispositions towards criminality also were more likely to be affected by negative environmental experiences. Rutter (44) noted that a problem with this type of study involved the use of parental criminality as a measure of genetic risk, both because it was crude, and also because it did not provide information on the mechanism of the genetic effect. Parental criminality could be an index of any of a number of psychopathological, physiological, or cognitive risk factors in the child.

Cadoret and colleagues conducted a series of adoption studies investigating ASB and consistently found evidence for an interaction between a genetic background of ASB and an adverse adoptive home environment (45-48). In the most recent study, antisocial personality disorder (ASPD) and substance abuse/dependence in the biological parent were used as indicators of genetic risk, and environmental risk was indexed by a composite measure of marital, legal, and psychological problems in the adoptive parents (48). These family environmental factors increased the risk for childhood aggression, adolescent aggression, and conduct disorder (but not adult ASB), but only in the presence of a biological background of ASPD. There was virtually no effect of the environment on those adoptees not at genetic risk. Unlike the earlier studies which combined ASB and substance abuse as an index of genetic risk (46), this study was able to separate the genetic influences associated with both. The results showed that a biological background of alcohol abuse did not interact with adverse adoptive home environment to increase risk for ASB, which demonstrates the specificity of the genetic diathesis for ASB.

Not all adoption studies, however, replicated the observed gene-environment interaction between a biological background of antisocial behavior/traits and environmental risk, in the form of adoptive parent antisocial behavior/traits (49,50). Moreover, evidence for gene-environment correlation in adoptee ASB demonstrates that additional factors may be operating to influence child ASB, and that care must be taken when conducting studies investigating gene-environment interaction. Both Ge et al (51) and O'Connor et al (52) found an association between a biological background of antisociality and adoptive parenting behavior that was mediated by the child's behavior, such that adoptee antisociality led to harsh and inconsistent behaviors on the part of the adop-

tive parents, which increased the child's own antisocial behaviors.

The same disturbed adoptive parent variable examined in Cadoret et al (48) also interacts with genetic risk factors to influence MD in women. In another study, for instance, Cadoret et al (53) showed that females (but not males) with a genetic background of alcoholism are at increased risk for MD if they live in an adoptive family with a high number of disturbed behaviors. There was no effect of environmental stress in the absence of an alcoholic background. This finding is in accord with theories suggesting that alcoholism is a marker for genetic risk that leads to depression and alcoholism in females, but only alcoholism in males (54).

An adverse adoptive home environment has also been implicated as a source of potential risk for schizophrenia. Findings from the Finnish adoption studies show an increased risk for schizophrenia in the biological offspring of schizophrenic versus non-schizophrenic parents, but only for those high-risk adoptees who were also exposed to a dysfunctional family rearing environment (55,56). Wahlberg et al (57), also using the Finnish sample, demonstrated that symptoms of thought disorder (i.e., an indicator of schizophrenia vulnerability) in offspring of schizophrenic mothers were more probable when they were raised by adoptive mothers who themselves showed elevated levels of 'communication deviance'. In contrast, offspring of schizophrenic mothers, raised by adoptive parents with low communication deviance, were less likely to show thought disorder. There was no relationship between thought disorder in control adoptees and communication deviance in the adoptive parents. In other words, this gene-environment interaction effect suggests that adoptees without a pre-existing genetic liability were not vulnerable to the effects of a disturbed family environment (at least with respect to thought disorder), and individuals with a pre-existing genetic liability expressed this liability only in the presence of additional adverse environmental factors.

Rutter and Silberg (4) suggested that results such as these from twin and adoption genetic studies, i.e., demonstrating gene-environment interaction, have so far been supportive of the hypothesis that the impact of environmental risk factors on psychopathology is slight in the absence of genetic risk. It is likely that research into gene-environment interaction will progress once genetic marker information can be incorporated into quantitative genetic studies, so that subjects with known genotypes can be exposed to environmental manipulations, allowing for a more experimental approach to the investigation of nature-nurture interplay in human beings. One method of incorporating genotypes into studies of gene-environment interaction is considered in the following section.

ASSOCIATION STUDIES

Association studies provide a potentially useful approach to the detection of gene-environment interactions in mental disorders (i.e., controlling and manipulating both genes and environment). They do provide clues about the interaction in various (non-human) animal protocols (58,59). The risk and protective effects of perinatal rearing experiences (e.g., maternal separation or loss, abuse or neglect, social deprivation) on anxiety- and depression-like behaviors have been demonstrated in both rodents and nonhuman primates (60,61). For example, genetically different strains of rodents that vary in their response to stress show additional differences in gene expression and in behavior when exposed to adverse rearing experiences.

Gene-environment interaction effects might thus provide one explanation for inconsistent findings among association studies between genetic markers and mental disorders, just as they may explain the variability in heritability estimates for the same disorder. For example, the role of the serotonin transporter gene (5-HTT) in anxiety in humans is controversial. While some studies have reported an association between a functional polymorphism in the regulatory region of this gene (5-HTTLPR) and anxiety-related behavior (62,63), others did not replicate the finding (64). Similar contradictory findings have been reported between this polymorphism and both MD and bipolar disorder (64). Studies in rhesus monkeys, however, have demonstrated the role of gene-environment interaction in the association between this polymorphism and anxiety-related behavior (65,66). Monkeys at greater genetic risk (i.e., with a greater number of the high-risk, low-activity allele) show differences in measures of 5-HTT expression that are associated with various adverse behavioral outcomes (e.g., lower rank within a social group, less competent social behavior, and greater impulsive aggression), as well as greater anxiety- and depression-related behavior (e.g., diminished orientation, lower attentional capabilities, and increased affective responding). These genotype effects are more pronounced for peer-raised (i.e., separated at birth from mothers) than for mother-raised monkeys.

Another gene whose association with human behavior is controversial is the dopamine D2 receptor gene (DRD2). Associations have been reported between DRD2 variants and several psychological disorders and traits, including alcoholism and other substance use disorders, schizophrenia, post-traumatic stress disorder, and certain personality traits, although, with the exception of schizophrenia (67), none of these associations has been replicated with enough consistency (68). However, some recent studies using human subjects have demonstrated evidence for association, and for gene-environment interaction, by taking account of environmental measures.

An association between the DRD2 Taq1 polymorphism on chromosome 11 and alcoholism was first reported in 1990 (69). Since that time, many attempts at replication have taken place, with variable results (70). Meta-analyses of DRD2/alcoholism studies found that, overall, alco-

holics had a higher prevalence of the high-risk allele than controls, and that the prevalence was higher in more severe alcoholism than it was in less severe alcoholism (71). Still, the association remains controversial (72-74).

Madrid et al (75) measured alcoholism and stress exposure in a sample of Honduran males, and found that neither was related to DRD2 genotypes. They did find, however, a significant interaction between genotype and stress score, such that individuals homozygous for the low-risk allele had similar alcoholism scores regardless of level of stress exposure. Alcoholism scores for heterozygous individuals increased modestly with increasing stress, and alcoholism scores for individuals homozygous for the high-risk allele increased greatly with stress. These results suggest that: a) individuals at genetic risk have a greater sensitivity to stress than those not at genetic risk; and b) the presence of environmental stress may be necessary for the development of alcoholism in this population.

Similar relationships between DRD2 genotype and environmental stress occur with regard to both cognitive markers and the personality trait of extraversion. Berman and Noble (76) found no relationship between family stress and cognitive markers (including visuospatial ability and event-related potentials, both of which have been linked to alcoholism (77, 78)) in preadolescent boys lacking the Taq1 high-risk allele. However, in boys with one or two copies of this allele, cognitive scores were negatively correlated with family stress scores. There were no differences in performance scores between boys from low-risk and high-risk family environments, regardless of genotype. Ozkaragoz and Noble (79) measured extraversion in a sample of children of alcoholic or control parents, under the hypothesis that children growing up in an alcoholic home would experience more environmental stress than those growing up in a non-alcoholic home. While there were no significant main effects of DRD2 genotype or family environment on extraversion, there was a significant gene-environment interaction such that children with the high-risk allele displayed greater levels of extraversion when living in an alcoholic than in a non-alcoholic home, again suggesting an increased sensitivity to stress in those indidivuals at high genetic risk.

Interestingly, among Honduran males living in a less stressful environment, subjects at low genetic risk (i.e., with no copies of the high-risk allele) received higher alcoholism scores than subjects at high genetic risk (75), and the adolescent boys at low genetic risk received higher extraversion scores when living in a non-alcoholic family than an alcoholic family (79). In other words, results from these studies suggest that greater psychopathology is associated with a less stressful environment in subjects who do not possess the high-risk DRD2 Taq 1 allele. One potential explanation for this phenomenon is that individuals with different DRD2 genotypes might respond to stressors in different ways. For example, Ozkaragoz and Noble (79) suggest that boys possessing the high-risk allele might cope with stress by increasing their level of activity, whereas boys with the low-risk allele might cope with stress by decreasing their activity. Thus it would be that, in a less stressful environment, boys at low genetic risk would appear to be more active than boys at high genetic risk.

GENE-ENVIRONMENT INTERACTION IN NEURODEVELOPMENTAL DISORDERS

Neurodevelopmental disorders are particularly likely to express gene-environment interactions, because development itself is a dynamic process that results from a constant interplay between genetic and environmental determinants. The combination of these etiologic factors begins early in development, with a greater liability for psychopathology arising when genetic susceptibility interacts with adverse biological consequences of untoward environmental events in the pre- or perinatal period. This etiology may result in a variety of outcomes based on the severity of both genetic and environmental 'loadings' for a particular disorder, and also on the presence or absence of other genetic and environmental 'protective factors', which may lower the risk for subsequent psychopathology. Two examples of neurodevelopmental disorders, autism and schizophrenia, will be reviewed for evidence of gene-environmental interactions.

While twin studies provide clear evidence of a genetic basis for autism (80,81), environmental factors also play a major role, although convincing evidence for any particular environmental factor is lacking (82). For example, twin studies show evidence of increased OCs among autistic members of discordant MZ twin pairs (80,83), but perinatal adversity may be a consequence, rather than cause, of autism (84). The work of Pletnikov et al (85,86) provides an example of how animal models may be used to test hypotheses about gene-environment interactions. Viral infections have been hypothesized to play a role in autistic disorders (87,88), and neonatal Borna disease virus (BDV) infection has been used as an experimental teratogen in animal studies to induce neurodevelopmental damage and behavioral deficits similar to those found in autistic spectrum disorders. In one study, Pletnikov et al (85) exposed different strains of rats to BDV neonatally to study potential gene-environment interactions. Significant strain differences were evident in brain pathology, behavior, neurochemistry (monoamine brain systems), and in the response to pharmacological treatments. For instance, one strain displayed a significantly greater thinning of the neocortex compared to the other, which was associated with greater novelty-induced hyperactivity and impaired habituation of the acoustic startle response in a prepulse inhibition paradigm. Results such as these provide support for an interaction between specific environmental risk factors (i.e., viral infection) and genetic liability (i.e., the strain of mouse) in the etiology of a neurodevelop-

mental disorder, and suggest novel avenues for research into other putative disorders of neurodevelopment.

The importance of both genetic and environmental factors in schizophrenia is well-established in behavioral genetic and, more recently, molecular genetic studies (89). While the risk of developing schizophrenia is associated strongly with the number of shared genes between a family member and an individual with schizophrenia, no degree of shared genes results in a certainty of developing the illness. For example, having two parents or an MZ twin with schizophrenia results in a risk of approximately 50% for developing the disorder. If having the same genes were the only etiological factor, then the risk should be close to 100% in these cases (1). Instead, the interaction between genetic liability and environmental factors plays an important role in determining outcome. Environmental factors implicated in the development of schizophrenia range from biological to psychosocial in nature and include, among others, pregnancy and birth complications, location of birth/residence, and family environment (90).

Recently, we modified Paul Meehl's use of the term 'schizotaxia' (91) to describe the liability to schizophrenia or schizophrenia-like conditions based on the theoretical premise that the neurobiological basis for schizophrenia is formed by the integrated effect of genes and adverse environmental risk factors. Our reformulation (92) describes genetically vulnerable individuals who are probably exposed to early adverse events (e.g., OCs) that result in abnormal development of certain brain structures. This liability presents from childhood as schizotaxia, which is expressed through a combination of cognitive, neurobiological and social skill deficits that vary in severity. For most individuals, the condition remains stable throughout their lifespan, but for some, a combination of the liability with later adverse environmental events (e.g., substance abuse, or stressful psychosocial circumstances) may predispose to the development of psychosis and chronic schizophrenia.

Consistent with the view of schizotaxia as resulting from a combination of genetic and environmental factors, several studies demonstrate evidence for an interaction between neonatal insults and genetic susceptibility to schizophrenia. For example, these insults likely include OCs and exposure to viral infections (including herpes simplex) (93). The times of greatest vulnerability to the developing brain may include the 2nd and 3rd trimester of pregnancy. During this period, for example, environmental factors may disrupt neuronal migration of cells to the cortex, which results in abnormal development of the prefrontal cortex, the entorhinal cortex, and the hippocampus (94).

Delivery complications associated with increased risk for schizophrenia include fetal hypoxia, ischemia, extreme prematurity, low birth weight, and post-term birth. Overall, pre-eclampsia is the most significant individual obstetric risk factor for schizophrenia (95). Pre-eclampsia, leading to hypoxia during pregnancy, results in fetal malnutrition including lack of oxygen, iodine, glucose, and iron. Chronic hypoxia can result in restricted fetal growth and subtle damage to brain regions. Moreover, blood and oxygen deprivation due to pre-eclampsia during delivery can also result in injury to the hippocampus and cortex (96). Seidman et al (97), utilizing the New England cohort of the National Collaborative Perinatal Project, demonstrated a relationship between obstetrical complications and neuropsychological deficits in children at 7 years of age. Low birth weight had the strongest association with neuropsychological impairments, followed by an index of inferred hypoxic insults, and then by maternal conditions suggesting chronic hypoxia.

Zornberg et al (98) reported results from a 19-year follow-up study of a large sample of individuals with a previously documented history of birth complications, and of matched controls. The individuals with a history of birth complications were classified according to whether or not the complications were hypoxic-ischemia-related. A significant relationship occurred between hypoxic-ischemia-related complications and increased risk for schizophrenia. These data thus suggested that pregnancy and birth complications interacted with genetic liability to increase the likelihood of subsequently developing schizophrenia. Consistent with these findings, Cannon (99) reported a dose-dependent relationship between risk of schizophrenia and severity of perinatal hypoxia in offspring of schizophrenic parents. In contrast, birth complications were unrelated to the development of schizophrenia in a control, low-risk group whose parents did not have schizophrenia. Similarly, Parnas et al (100) followed up offspring of mothers with severe schizophrenia and found the risk of developing the illness was highest for those who were exposed to perinatal complications. Pregnancy and birth complications themselves occur more frequently in schizophrenic mothers compared to normal controls (93), which raises the level of risk for their (already vulnerable) children further.

Other studies also examined relationships between OCs and structural brain abnormalities in individuals with schizophrenia and their relatives (95,101). Among these relationships, ventricular enlargement in individuals at increasing genetic risk for schizophrenia interacted with OCs, with the association between ventricular enlargement and OCs increasing with the degree of genetic risk. Suddath et al (102) reported larger ventricles and greater temporal lobe volumes in the affected cotwin of MZ pairs discordant for schizophrenia. These structural differences were associated with higher rates of OCs in the affected cotwins (103). Cannon et al (104) reported that fetal hypoxia was associated with reduced cortical gray matter and increased cerebrospinal fluid among patients with schizophrenia and their non-psychotic siblings, but not among controls. Effect sizes were greatest for low birthweight subjects, consistent with other find-

ings showing higher rates of subsequent schizophrenia in individuals subjected to prenatal underdevelopment (105-107). The relationship between hypoxia and brain abnormalities was stronger among patients than siblings, and hypoxia was related to ventricular enlargement only among patients, both findings consistent with a gene-environment interaction model in which the liability to schizophrenia is increased in the presence of environmental risk factors. While hypoxia did not occur more frequently among patients than among their unaffected siblings in this study, Rosso et al (108), using the same sample, found a greater number of hypoxic-associated OCs among early-onset than among late-onset cases or siblings, as well as an almost three-fold increased risk of early-onset schizophrenia per hypoxic OC.

Seasonality of birth is another possible environmental risk factor for schizophrenia, with winter-spring births being associated with increased risk (95). The increase could be due to a higher incidence of maternal infection (e.g., influenza), and the cumulative evidence from many studies suggests that maternal influenza infection in pregnancy, leading to fetal brain damage, is associated with an increased risk for schizophrenia (109). Support for a gene-environment interaction effect involving winter birth comes from a study by Pulver et al (110), in which winter birth was associated with a positive family history in schizophrenic probands, although associations in the absence of family history occur as well (111,112).

CONCLUSIONS

The nature-nurture controversy is far less germane than it once was for understanding psychiatric disorders. Research clearly shows that both nature and nurture play important roles in the genesis of psychopathology. As the preceding discussion showed, gene-environment interactions are evident both in a broad variety of mental disorders, and also in a wide range of experimental methodologies used to assess the relative contributions of genes and environment in mental disorders.

The salience of this issue will only increase as advances in neuroscience and molecular biology identify new potential sources of gene-environment interaction. For example, while many studies have focused on relationships between specific alleles and clinical diagnoses, or between independent measures of clinical function and clinical diagnoses, there is a growing focus on 'endophenotypic' expressions of mental disorders. Endophenotypes are features that are somewhat intermediate between the genotype and phenotype for a particular disorder (113), and often involve cognitive or neurobiological functions. Because endophenotypes may be closer to their underlying etiologies, they open windows on the mechanisms involved in both normal and abnormal mental functions. For example, in both patients with schizophrenia and normal controls, Egan et al (114) showed that a common polymorphism in the catechol-O-methyltransferase (COMT) gene produced a four-fold range in COMT activity and dopamine catabolism. The range of COMT activity in both groups was associated with a related range of performance on a neuropsychological test of executive function, and of the efficiency of prefrontal and cingulate cortical function during an information processing test. Because many mental functions and mental disorders are complex, multifactorial, polygenetic conditions (1,89,115), results from studies like that by Egan et al clarify specific mechanisms that likely contribute to efficient and inefficient biological function, and thus to mental function and dysfunction. This in turn provides increasing opportunities to specify environmental contingencies that interact with these mechanisms to increase or decrease the liability for mental disorders.

Ultimately, then, the study of gene-environment interactions will further our understanding of how to identify, diagnose and treat mental disorders. As the pool of potential treatment targets increases, so will opportunities for the development of early intervention strategies for many common but difficult to treat mental disorders (116-118). While the study of gene-environment interactions is but one of several promising ways to approach that goal, it is one whose potential warrants additional attention.

Acknowledgements

The preparation of this chapter was supported in part by the National Institute of Mental Health grants 1R37MH4351801, R01 MH50647, R01 MH59624, R01-DA12846 and R25 MH 60485 to Dr. Tsuang, by a NARSAD Distinguished Investigator Award to Dr. Tsuang, and by a NARSAD Young Investigator Award to Dr. Stone.

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