Schizophrenia

Elaine Walker and Kevin Tessner

Emory University

ABSTRACT—*Theoretical conceptualizations of schizophrenia have undergone significant change in the past century. Through the application of behavioral science methodology, psychologists have played a major role in the pivotal scientific advances that have led us to contemporary models. The field has moved from simplistic conceptualizations of mind–brain distinctions to models that encompass complex gene–environment interactions and neural pathways that mediate the relation between psychosocial events and brain dysfunction.*

In this article, we address a challenging behavioral phenomenon with a fascinating scientific history: *schizophrenia*. By definition, schizophrenia is a psychotic disorder and is arguably the most debilitating one (Walker, Kestler, Bollini, & Hochman, 2004). Psychotic symptoms entail a distortion in the apprehension of reality that is so severe it compromises the person's ability to function. Patients with schizophrenia show poorer courses than patients with other psychotic and nonpsychotic disorders (Harrow, Grossman, Jobe, & Herbener, 2005). Moreover, the illness is typically chronic, and the modal age at onset is in late adolescence or early adulthood—a period when most individuals are achieving autonomy (Jobe & Harrow, 2005). Yet there is also considerable variability in the course of the illness. Harrow and colleagues (2005) followed a group of patients diagnosed with schizophrenia for over 15 years and found that approximately 40% of them had one or more periods of intermittent recovery.

The primary domains of psychotic symptoms are perceptual, ideational, and behavioral (Walker et al., 2004). In the perceptual domain, the key symptom is hallucinations: sensory experiences in the absence of any sensory stimulus. The ideational manifestations are thought disorder and delusions. Behavioral abnormalities include bizarre movements, postures, and rituals. In addition, many patients show affective abnormalities, such as blunted or inappropriate emotional expression.

The study of schizophrenia has a fascinating history characterized by major paradigm shifts. Although evidence suggesting

brain abnormality in schizophrenia was revealed in postmortem and pneumoencephalographic studies conducted as early as the late 1800s (see Torrey, 2002, for a review), these findings did not have a significant impact on theorizing about schizophrenia. It was not until the latter half of the 20th century that researchers had relatively noninvasive scientific tools for studying brain structure or function in vivo. Consequently, in the first half of the 20th century, the literature on psychotic disorders was dominated by a brain-versus-mind distinction that fueled many futile debates about whether schizophrenia was a biological or a psychological disorder. In fact, prior to the 1970s, the field of psychiatry distinguished between *organic* and *functional* disorders, with the implicit assumption that only the former were disorders of the brain (Heath, 1952). The psychoses, including schizophrenia, were viewed as functional disorders. If a biological basis (e.g., brain injury or drugs) was suspected, the patient's psychosis was not diagnosed as schizophrenia. This dichotomy presented significant challenges to the field of psychiatry by implying that psychiatry was a medical specialty that dealt with nonmedical conditions (Heath, 1952). But gradually, over the past half century, the functional–organic distinction has been abandoned, giving way to the idea that schizophrenia is a brain disorder. Moreover, decades of research have revealed that schizophrenia is a brain disorder with complex and varied etiologies. This conclusion is a consequence of important scientific developments in which psychologists have played a major role.

There is no disputing the fact that psychologists have been instrumental in moving schizophrenia research through a series of paradigm shifts moving toward a more accurate, albeit more complex, picture of etiology. These shifts are, in part, a reflection of changes in the prevailing theoretical trends in behavioral science. Thus, theories about the nature and origins of psychosis have changed in tandem with developments in our scientific assumptions about the determinants of behavior.

This article examines some important turning points in our scientific understanding of schizophrenia and the contributions that psychologists have made at each juncture. First, there was a shift from conceptualizations of schizophrenia as a disorder of the mind, with primarily psychosocial causes, to the widespread acceptance of the notion that brain abnormalities were involved. A second shift, which overlapped the first, was the transition to theories that encompassed genetic as well as environmental factors. This shift set the stage for the emergence of diathesis-

Address correspondence to Elaine Walker, Department of Psychology, Emory University, 532 North Kilgo Circle, Atlanta, GA 30322; e-mail: psyefw@emory.edu.

stress models of etiology. A third watershed involved broadening the conceptualization of environmental factors to encompass both psychosocial factors and bioenvironmental factors that affect brain development. Finally, the field has recently witnessed a revision in our understanding of the way genetic influences are implicated. Rather than viewing genetics as a blueprint that inevitably translates into behavior, we now recognize that the expression of the genotype is dependent on bioenvironmental triggers. As described later in this article, psychologists have played a major role in all of these critical phases. In fact, one could argue that they have led the way in most of the substantive theoretical shifts in the field.

PSYCHOSOCIAL CONCEPTUALIZATIONS

The early history of ideas about the nature of psychosis is well documented (see Mirsky & Duncan, 2005, for a historical overview). Not more than three centuries ago, the dominant assumption was that psychotic symptoms reflected demonic possession. But by the 20th century, the mental health movement was firmly established in Western nations, and the clinical characteristics of schizophrenia were articulated by Emil Kraepelin and Eugen Bleuler.

The recognition of psychotic disorders as mental illness set the stage for a new debate that mirrored the ongoing dilemma about the relation between mind and brain (Miller, 2005) and reflected the distinction described earlier between functional and organic disorders. Some people argued that psychosis was the product of disordered mental processes that arose in response to adverse psychosocial factors, whereas others took the position that impaired brain function was the critical and final pathway. Those who focused exclusively on psychosocial determinants implicitly conceived of a disembodied mind by either ignoring or actively resisting notions of brain dysfunction.

Despite early speculations about brain dysfunction in psychosis, biological factors did not figure prominently in the psychological theories of the late 1800s and early 1900s. For example, most early psychodynamic theorists believed that schizophrenia arose from a disturbance in the early formation of *object relations*, or attachments to others (Arlow & Brenner, 1969; Freud, 1920). Freud proposed that psychosocial trauma could disturb personality formation and bring about a mental state of object fragmentation. Psychodynamic theorizing focused on intrapsychic motives and posited that psychosis is attributable to ego weakness and that psychotic symptoms are symbolic representations of repressed unconscious conflicts. Another psychosocial perspective, the *double-bind theory*, posited that psychotic symptoms emerge when a developing child is unable to respond adequately to repeated conflicting injunctions (i.e., double-bind communications) from family members (Bateson, Jackson, Haley, & Weakland, 1956). But the weight of empirical research did not support either the psychodynamic or double-bind theories.

A more fruitful psychosocial perspective focused on the affective component of family communication and its role in precipitating or exacerbating psychosis (Singer & Wynne, 1963; Vaughn & Leff, 1976). The phrase *expressed emotion* came to refer to communication with the patient that is critical, hostile, or emotionally overinvolved. Studies revealed that high levels of expressed emotion were associated with greater risk of relapse (Vaughn & Leff, 1976), suggesting a role for psychosocial factors in the recurrence of psychotic episodes. Other researchers, however, raised questions about the nature of the causal relationship. Do family members' negative communications contribute to relapse, or are family members reacting to the patient's impending relapse, or both? Psychologists have demonstrated that the causal relation between expressed emotion and relapse is bidirectional, but that negative expressed emotion can indeed contribute to patient relapse (Goldstein, 1987; King, Ricard, Rochon, Steiger, & Nelis, 2003). So the psychosocial environment does matter, but in a different way than was originally assumed. As described later, contemporary views of this process include neural mechanisms that can translate stress into brain dysfunction (Walker & Diforio, 1997).

MIND VERSUS BRAIN: THE CONTRIBUTION OF NEUROPSYCHOLOGY

Although the notion that psychotic disorders reflect brain dysfunction was overshadowed by psychosocial theories in the early 1900s, this idea is not unique to 20th-century thinkers. More than 1,000 years ago, Greek and Roman physicians viewed madness as a disease of the brain (see Mirsky & Duncan, 2005, for a review). Ancient Greek and Roman medical writers described internal and external factors that produced an imbalance of bile and phlegm, which led to distinguishable behavioral disturbances. Much later, in *A Treatise on Madness*, Battie (1758) described madness as a disorder that could have physical (possibly hereditary) as well as environmental causes. He observed that madness was frequently viewed as a single disorder, but "when thoroughly examined, it discovers as much variety with respect to its causes and circumstances as any distemper whatever" (Battie, 1758, p. 94). For example, one cause of madness that Battie suggested was pressure on a portion of the brainstem, in particular, the medulla. But the scientific techniques for documenting brain dysfunction were not available to Battie and his predecessors, so their speculations did not garner much attention.

Then the tide turned in the 1960s, and systematic research began to yield evidence that raised questions about the primacy of psychosocial determinants and the nonorganic nature of schizophrenia. During this era, the major line of empirical investigation that pointed to brain dysfunction was neuropsychological research (see Levin, Yurgelun-Todd, & Craft, 1989, for a review). Among the many psychologists who led the way were Allan Mirsky and Robert Heaton.

The field of neuropsychology grew out of the use of psychological test batteries administered to war veterans who had suffered head injuries in combat. Systematic comparisons of the cognitive performance of patients with lesions in various brain regions revealed that damage to specific areas was associated with characteristic deficits on cognitive tasks.

In 1969, Mirsky published a seminal paper entitled *Neuropsychological Bases of Schizophrenia*. On the basis of accumulating neuropsychological data, he proposed what may have been the first neural circuitry model of brain dysfunction in schizophrenia. A subsequent wave of neuropsychological studies revealed that patients with schizophrenia manifested a performance pattern similar to those of certain brain-damaged patients, leading Robert Heaton and his colleagues (Heaton, Baade, & Johnson, 1978) to conclude that patients with schizophrenia were suffering from frontal- or temporal-lobe brain damage. The power of neuropsychological techniques was documented in a recent meta-analysis showing that neuropsychological measures were more effective than most biological measures—including neuroimaging—in differentiating schizophrenia patients from healthy controls (Heinrichs, 2004).

Thus, even before the advent of neuroimaging technology in the form of computerized tomography (Weinberger, Torrey, Neophytides, & Wyatt, 1979), many psychologists believed that schizophrenia involved brain dysfunction. Neuropsychology provided nontechnical but reliable tools for measuring the integrity of brain function and yielded findings that have now been confirmed and extended by hundreds of neuroimaging studies. For example, imaging studies have shown that *hypofrontality*—reduced blood flow in the frontal lobe—is correlated with performance deficits on neuropsychological measures of frontal-lobe function (Davidson & Heinrichs, 2003).

GENETICS OF SCHIZOPHRENIA: THE FIRST PHASE

Overlapping the growing trend toward localizing vulnerability for psychotic disorders in the brain, other investigators were zeroing in on etiologic factors. Paul Meehl was among the many pioneering psychologists in the field of schizophrenia. In 1962, Meehl published a classic paper entitled *Schizotaxia, Schizotypy, Schizophrenia*, in which he proposed a biological predisposition to schizophrenia that he referred to as *schizotaxia*, a genetic defect in neurointegration. He conjectured that schizotaxia does not always lead to schizophrenia and that it has a higher base rate than the population prevalence rate of 1% for schizophrenia. In a highly favorable environment, schizotaxia is not associated with an observable behavioral syndrome. Meehl argued, however, that many schizotaxic individuals develop a syndrome known as *schizotypy*—which involves perceptual abnormalities and cognitive deficits—and that only a minority would develop schizophrenia. In summary, without the benefit of much empirical data, Meehl presaged several key scientific advances in the field. Most notably, he posited that genetic and environmental factors interact in the etiology of schizophrenia and that some vulnerable individuals manifest subclinical signs of psychosis.

Within the same decade, findings from behavioral genetic studies of mental disorders began to accumulate, and they confirmed Meehl's ideas. Three methods dominated this line of investigation (see Gottesman, 1991, for a detailed review of these methods and the research findings). First, the *family history* method examined the occurrence of schizophrenia and other psychoses in patients' biological relatives. The findings showed that the rate of disorder in relatives varied as a function of genetic similarity: First-degree relatives were more likely to be affected than second-degree relatives who, in turn, had higher rates of disorder than the general population.

A second and more powerful method for studying genetic influences on mental disorders is the *twin method*. Because monozygotic (MZ) twins are the product of one zygote that splits after fertilization, the two members of the twin pair have identical genotypes. (Technically, due to postcleavage mutations, the genotypes can be nonidentical.) In contrast, dizygotic (DZ) or fraternal twins share, on average, 50% of their genes. Numerous twin studies have been published, and the results consistently show a higher rate of concordance for schizophrenia in MZ twins than in DZ twins. Lending additional support to the role of genetic factors in the etiology of schizophrenia, adoption studies have shown that the biological offspring of mothers with schizophrenia who are reared in adoptive homes from infancy have a higher rate of schizophrenia than do adoptees with healthy biological parents.

Among the major figures spearheading the application of behavioral genetic approaches to schizophrenia were psychologists Irving Gottesman (Gottesman & Shields, 1966) and Philip Holzman (1977). Gottesman conducted seminal behavioral genetic studies and was among the first to argue for a polygenic mode of transmission for vulnerability to schizophrenia—in other words, that multiple genes are implicated (Gottesman, 1991). A competing model assumed a single major locus, and Holzman was a leading proponent of this position (Holzman, 1977). Ultimately the research results did not support a single major-locus model. By the early 1980s, most people rejected the idea of a single, culpable gene, and the polygenetic model of multiple risk genes acting in concert gained dominance (Faraone & Tsuang, 1985).

Taken together, evidence from behavioral genetics paradigms points to a genetic basis for at least some cases of schizophrenia. But critical questions remain: If there is a genetic predisposition, is it always expressed in behavior, and does it inevitably lead to illness? As Meehl suggested in 1962, the answer to the latter question is "no," given that the concordance rate for MZ twins is 50% or lower. But the absence of clinical illness does not necessarily preclude behavioral abnormalities. Behavioral genetics research has shown that the biological relatives of people with schizophrenia often manifest signs of schizotypy, as

described by Meehl. These signs include subclinical manifestations of psychotic symptoms—such as magical thinking, suspiciousness, and odd beliefs—as well as impairment in cognitive, affective, and social functioning.

Philip Holzman studied the biological relatives of patients and identified several biobehavioral measures that reflected a genetic predisposition for schizophrenia. Holzman referred to these markers as *endophenotypes* for the illness (Gottesman & Gould, 2003). For example, Holzman's studies of patients' relatives revealed abnormalities in visual tracking similar to abnormalities observed in patients with schizophrenia (Holzman, 1977).

Molecular genetics research has recently shed light on the mechanisms that might modulate gene expression. Gottesman and his colleagues have shown that there are differences between members of discordant MZ-twin pairs in the expression of genes due to DNA methylation (Petronis et al., 2003). Their study examined DNA methylation in the dopamine D2-receptor gene and revealed that affected twins from the discordant MZ pairs had methylation patterns more similar to the affected twins in concordant pairs than to their unaffected co-twins. These findings not only highlight the differences between co-twins in MZ-twin pairs, but they also demonstrate that stochastic events and the environment influence the regulation of gene activity.

EMERGENCE OF THE DIATHESIS-STRESS MODEL

Findings from behavioral genetics research served as the impetus for the diathesis-stress model. In this framework, *diathesis* refers to a constitutional vulnerability, and *stress* refers to adverse events that impinge on the vulnerable individual. In the 1960s and 1970s, the diathesis was typically assumed to be genetically determined, and stress stemmed from childhood psychosocial events. Joseph Zubin and Bonnie Spring (Zubin & Spring, 1977) were among the most influential diathesis-stress theorists. They assumed that individuals inherited a diathesis that was expressed behaviorally only when psychosocial stressors exceeded the individual's capacity to cope.

Adoption studies have yielded support for the diathesis-stress model. For example, Tienari et al. (1987) examined the diagnostic outcome for the biological offspring of parents with schizophrenia and found that the quality of the rearing environment was a significant determinant of psychiatric outcome; the incidence of schizophrenia was much higher in individuals reared in a disturbed adoptive families. Similarly, in a study of nonadopted offspring of patients with schizophrenia, Walker, Downey, and Bergman (1989) found that individuals exposed to maltreatment were more likely to develop behavioral problems. These and other findings provide an empirical foundation for the diathesis-stress model. Thus, the model's basic assumption—that schizophrenia is the product of an interaction between constitutional vulnerability and environmental factors—continues to dominate theories of etiology.

In recent decades, however, the breadth and complexity of etiological models has changed dramatically. In particular, scientific findings that emerged in the 1970s led researchers to broaden their conceptualization of environmental factors. Thus, in addition to focusing on psychosocial stressors, such as disturbed family environments, researchers began to investigate biological stressors as well.

The Broadened Scope of Environmental Influences: Bioenvironmental Factors

Early diathesis-stress models assumed that psychosocial stress and genetics acted unidirectionally and through nonmediated pathways to determine illness. Until the 1970s, researchers did not generally consider that stress might encompass biological factors, that stress could occur during fetal development, or that psychosocial effects were mediated by neural processes.

As empirical data have accumulated, however, it is increasingly apparent that bioenvironmental insults to the brain must be considered among the environmental factors that contribute to schizophrenia. As early as the 1970s, Sarnoff Mednick, a psychologist and pioneer in schizophrenia research, alerted the scientific community to the role of prenatal factors in the etiology of schizophrenia (Mednick, Mura, Schulsinger, & Mednick, 1971). Mednick later uncovered the link between maternal influenza infection and schizophrenia, and he was the first to suggest the hippocampus as a brain region vulnerable to prenatal complications in schizophrenia (Lyon, Barr, Cannon, Mednick, & Shore, 1989; Mednick, Machon, Huttunen, & Bonett, 1988). Numerous studies have subsequently confirmed the association of prenatal and delivery complications with schizophrenia and other psychoses (Kunugi, Nanko, & Murray, 2001). This work not only broadened our understanding of environmental effects, it also showed that these effects could be traced to the fetal period and could result in compromised fetal neurodevelopment.

The range of potential prenatal insults was further extended by evidence that psychosocial events could also compromise fetal development. In 1978, Huttunen and Niskanen published an important study showing that women who were exposed to psychosocial stress during pregnancy were more likely to give birth to a child who later developed mental illness, such as schizophrenia. At the time this study was published, relatively little was known about the biological processes that could mediate a relation between prenatal maternal stress and the mental health of offspring. But subsequent research with animals has shed important light on these mechanisms by demonstrating that elevated maternal stress hormones (i.e., glucocorticoids) can adversely influence fetal neurodevelopment.

More recently, another bioenvironmental influence has been discovered: Adolescent drug use, specifically marijuana, can contribute to psychosis (Verdoux, Tournier, & Cougnard, 2005). Evidence to support this relation has come from retrospective

and prospective studies. Although the mechanisms involved are not yet known, there is reason to suspect that the principal active ingredient of cannabis, Δ-9-tetrahydrocannabinol (Δ-9-THC), increases the risk for psychosis by augmenting dopamine neurotransmission and stress hormone release (D'Souza et al., 2005; Viveros, Llorente, Moreno, & Marco, 2005).

Neurodevelopmental Perspectives

Evidence suggesting that abnormal fetal brain development can contribute to the risk for schizophrenia converged with other findings that behavioral signs of vulnerability can be present at birth. For example, studies of the infant offspring of patients with schizophrenia (Fish, 1977) and subsequent archival research using home movies (Walker, 1994) revealed that subtle signs of neuromotor and emotional dysfunction were apparent in patients with schizophrenia as early as infancy. These and related reports launched a new conceptual debate. Some researchers began to refer to schizophrenia as a neurodevelopmental disorder, arguing that the illness involves abnormalities in fetal development of the central nervous system (Murray, O'Callaghan, Castle, & Lewis, 1992). Others juxtaposed this idea with the notion that schizophrenia involves a degenerative brain process that begins in young adulthood, when early clinical signs are manifested (Delisi et al., 1997). A debate between neurodevelopmental and degenerative models ensued.

In recent years, new findings on adolescent brain development have provided a basis for reconciling these two perspectives (Walker, 2002). One of the most well-established observations of psychotic disorders is that their clinical onset typically occurs in late adolescence or early adulthood. To be consistent with the modal developmental course of the illness, neurodevelopmental models must account for the dramatic rise in onset during adolescence. Advances in noninvasive neuroimaging have made it possible for researchers to examine brain development. Within the past decade, changes in brain structure and function throughout adolescence have been identified (Walker, 2002). Furthermore, during adolescence, individuals at risk for psychosis show a pattern of gray- and white-matter brain changes that differs from that observed in controls. Healthy adolescents lose gray matter at the rate of 1%–2% per year, whereas adolescents with schizophrenia show a more rapid and progressive loss of gray matter in frontal and temporal cortices (roughly 3%–4% per year; Toga, Thompson, & Sowell, 2006). The cellular mechanisms responsible for the loss of gray matter are unknown, but they are thought to involve neurodegenerative processes that include abnormal increases in apoptosis or neuronal death (Perez-Neri, Ramirez-Bermudez, Montes, & Rios, 2006).

Future research in the genetics of schizophrenia may provide insight into the mechanisms underlying neuromaturational changes during critical developmental periods and into the degenerative processes leading to psychosis. Combined with the evidence for fetal neurodevelopmental abnormalities in schizophrenia, these findings suggest that both neurodevelopmental and neurodegenerative processes are implicated. So how can these two processes be reconciled with our understanding of genetic factors in schizophrenia?

THE SECOND GENETIC REVOLUTION IN SCHIZOPHRENIA RESEARCH

As reviewed earlier, the first phase of research on the genetics of schizophrenia firmly established that vulnerability to schizophrenia could be inherited, and the data were most consistent with the hypothesis that multiple genes act in concert (Gottesman, 1991). But, empirical findings that emerged in the 1970s and 1980s made it increasingly apparent that the number of relevant genes was larger than originally assumed.

In the 1990s, a plethora of new genetic methods, including linkage and association studies, was applied to the study of schizophrenia. But the enthusiasm that accompanied the introduction of these methods far exceeded their ability to shed light on the genetics of schizophrenia. Each initially positive finding on a specific gene or chromosome was followed by a series of failures to replicate (Kirov, O'Donovan, & Owen, 2005). When the technology for scanning the human genome was introduced, it yielded some significant findings, but replications were uncommon. A meta-analysis of the results suggested evidence for linkage on at least 12 chromosomes, and many of these had already been implicated in other psychiatric disorders (Lewis et al., 2003). Although the absence of consistent genetic findings has contributed to a pessimistic outlook among some investigators, the results are, in fact, providing us with critical information about the nature of schizophrenia.

Why has it been so difficult to elucidate the genetics of schizophrenia and other forms of psychosis? There are several likely reasons. First, it appears that schizophrenia is a complex syndrome for which there are multiple contributing genes, each with alleles (i.e., variant forms) that have relatively weak effects on their own. Moreover, the relevant genes may produce more than one biobehavioral effect, and they may interact with each other (gene–gene interactions). Second, the behavioral syndrome (phenotype) we now label *schizophrenia* is heterogeneous; its manifestations across patients are highly variable, and it is likely that the genetic determinants also vary across cases. Third, it appears that diagnostic boundaries in the current *Diagnostic and Statistical Manual of Mental Disorders* (*DSM–IV*; American Psychiatric Association, 1994) do not distinguish on the basis of etiology; many of the genes that have been associated with schizophrenia have also been shown to be associated with other forms of psychosis (Craddock, O'Donovan, & Owen, 2005). So it appears that genetic susceptibility overlaps the diagnostic boundaries that differentiate schizophrenia from mood disorders with psychotic features. In addition, we have no biological markers of psychosis to provide clues in the search for

candidate genes. Fourth, currently available genetic analyses are somewhat ineffective at detecting weak effects of single genes and are even less effective at detecting interactions among genes. Finally, the strong evidence that both biological and psychosocial aspects of the environment influence the expression of genetic vulnerability makes it difficult to identify the genetic factors that confer vulnerability. Nonetheless, the enormous body of literature on schizophrenia and other psychoses leads to the inescapable conclusion that they are complex diseases that arise from complex gene–environment interactions.

Gene–Environment Interactions: The Real Nature of Nature–Nurture Interactions

Diathesis-stress models of the etiology of schizophrenia were fueled by the idea of nature–nurture interaction. But it is only recently that scientific research on gene–environment interactions has yielded findings that have given tangible meaning to the concept. Psychologists Avshalom Caspi and Terrie Moffit have led the development of new research approaches to clarify gene–environment interactions in the etiology of mental disorders (Moffitt, Caspi, & Rutter, 2005).

In a seminal study, Caspi et al. (2003) found that 33% of individuals with a specific allele of the serotonin transporter gene became depressed in the presence of severe adverse life events, whereas only 17% of the individuals without this genotype developed major depression. These findings have been replicated by at least one other research group (Wilhelm et al., 2006). At this point, the study of gene–environment interactions in the etiology of psychosis is in its infancy, but there is reason to believe that such interactions exist. As a prime example, in a recent report, Caspi and colleagues found that a functional polymorphism in the catechol-O-methyltransferase (COMT) gene moderated the influence of adolescent cannabis use on risk for adult psychosis. In a large population sample, carriers of the COMT valine158 allele were most likely to exhibit psychotic symptoms and to develop schizophreniform disorder if they used cannabis. Cannabis had no adverse influence on individuals

with two copies of the methionine allele. These findings illustrate a Gene × Environment interaction in the etiology of psychosis and suggest that several susceptibility genes for psychosis influence vulnerability to bioenvironmental factors (Caspi et al., 2005).

THE NEW CONCEPTUAL FRAMEWORK

We now have a conceptual model of schizophrenia and other psychoses that is undoubtedly more complex than the models envisioned by psychologists who first described the syndrome. The functional versus organic distinction that dominated psychiatry into the 1960s has given way to contemporary models that incorporate multiple levels of analysis. Psychologists have facilitated these advances by applying the tools of behavioral science. First, neuropsychologists moved the field forward by establishing that people with schizophrenia manifest a pattern of cognitive performance suggestive of brain dysfunction. One source of this brain dysfunction, heredity, was demonstrated through the application of behavioral genetics methods. Other sources of constitutional vulnerability—in particular, prenatal influences—were then identified, and the scope of etiologic influences was expanded to include bioenvironmental factors. More recently, psychologists have moved the field forward through innovative studies that illustrate the importance of gene–environment interactions. These scientific advances have been paralleled by the emergence of more sophisticated models of etiology that move far beyond the mind–brain dualism that was evident in early functional–organic distinctions. Again, psychologists have been in the forefront of developing these new models. For example, Walker and Diforio (1997) proposed a neural diathesis-stress model that encompasses genetic, bioenvironmental, and psychosocial factors (see Fig. 1). This model assumes that constitutional vulnerability to psychotic disorders is determined by genetic (inherited) and prenatal (acquired) factors and that adult psychiatric outcome is determined by the cumulative effects of exposure to environmental stressors that act through the neural circuitry that subserve the biological
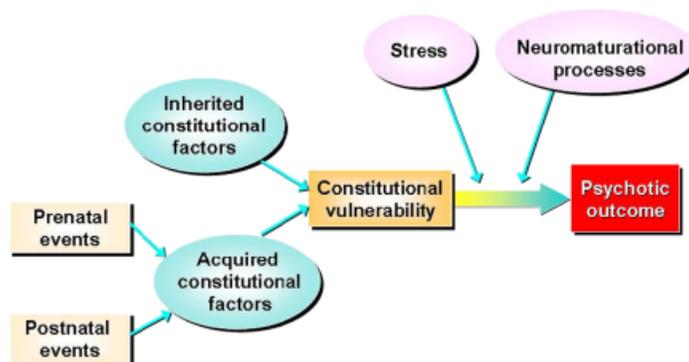
Fig. 1. A contemporary neural diathesis-stress model of the etiology of psychosis.

stress response. The model also emphasizes the role of neuro-maturational processes that unfold during adolescence. With regard to the latter, it is assumed that hormonal changes during adolescence can trigger the expression of liability genes and the neural circuitry malfunction that underlie psychotic symptoms. Along these same lines, Nuechterlein and Dawson (1984) have presented a model that emphasizes the cumulative interactions among biological and environmental vulnerability factors, as well as the modulating effect of protective factors such as patients' coping mechanisms.

THE NEXT FRONTIERS

Empirical research has shown that schizophrenia is not the consequence of a single genetic or environmental factor. The contemporary view is that schizophrenia is a heterogeneous disorder and that its polygenic etiology overlaps with other psychotic disorders. This view does not exclude the possibility that psychosis is the product of a singular neuropathological process—perhaps an abnormality in a specific neural circuit or set of circuits.

Current approaches to the treatment of schizophrenia include both psychotropic medications and psychotherapeutic techniques (Walker et. al., 2004). But antipsychotic medications are considered the first line of intervention, and many patients do not have access to other forms of treatment. Furthermore, although the newer atypical antipsychotics have fewer adverse side effects than first-generation drugs, they control symptoms rather than curing the disorder, and most patients face a lifetime of disability. Major advances in treatment will undoubtedly follow advances in our understanding of the neural mechanisms that give rise to psychotic syndromes.

Future research on the etiology of schizophrenia will be characterized by two major thrusts. First, there will be a more intense focus on the developmental period immediately prior to the clinical onset of the illness. The period of subclinical behavioral dysfunction that precedes the onset of schizophrenia has been referred to as the *prodrome*. As mentioned, most individuals who develop the disease show prodromal signs during adolescence. This well-documented fact is leading researchers to intensify their efforts to chart postpubertal biological and psychological changes. As yet, there is no better predictor of impending psychosis than prodromal behavioral signs. It is therefore likely that behavioral measures will be the primary tool for identifying persons at highest risk, so psychologists will play an even greater role.

Second, there will be intensified focus on studies of gene–environment interactions with the aim of elucidating mechanisms through which genetic vulnerabilities are translated into clinical disorder. Included in this will be the burgeoning field of *epigenetics*, the study of changes in gene expression that occur without a change in DNA sequence. Research has shown that epigenetic mechanisms influence both the normal and abnormal

(e.g., cancer, autoimmune diseases) development and survival of cells and that they are altered by hormones, including stress hormones.

Finally, it is likely that adolescence will prove to be a critical period for preventive intervention for psychosis. Some psychologists have speculated that hormonally driven neuromaturational processes play a role in triggering the onset of the prodrome in adolescence. Hormonal factors may, in fact, trigger the expression of disease-related gene patterns. It is possible, therefore, that preventive interventions will entail psychological or pharmacological techniques that change the hormonal milieu and thereby prevent aberrant brain changes that contribute to psychosis.

REFERENCES

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Arlow, J.A., & Brenner, C. (1969). The psychopathology of the psychoses: A proposed revision. *International Journal Psychoanalysis*, *50*, 5–14.

Bateson, G., Jackson, D.D., Haley, J., & Weakland, J. (1956). Toward a theory of schizophrenia. *Behavioral Science*, *1*, 251–264.

Battie, W. (1758). *A treatise on madness*. Retrieved February 21, 2007, from http://er.library.northwestern.edu/detail.asp?id=310227&pn=1

Caspi, A., Moffitt, T.E., Cannon, M., McClay, J., Murray, R., Harrington, H., et al. (2005). Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: Longitudinal evidence of a gene × environment interaction. *Biological Psychiatry*, *57*, 1117–1127.

Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., et al. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science*, *301*, 386–389.

Craddock, N., O'Donovan, M.C., & Owen, M.J. (2005). The genetics of schizophrenia and bipolar disorder: Dissecting psychosis. *Journal of Medical Genetics*, *42*, 193–204.

Davidson, L.L., & Heinrichs, R.W. (2003). Quantification of frontal and temporal lobe brain-imaging findings in schizophrenia: A meta-analysis. *Psychiatry Research*, *122*, 69–87.

Delisi, L.E., Sakuma, M., Tew, W., Kushner, M., Hoff, A.L., & Grimson, R. (1997). Schizophrenia as a chronic active brain process: A study of progressive brain structural changes subsequent to the onset of schizophrenia. *Psychiatry Research*, *74*, 129–140.

D'Souza, D.C., Abi-Saab, W.M., Madonick, S., Forselius-Bielen, K., Doersch, A., Braley, G., et al. (2005). Delta-9-tetrahydrocannabinol effects in schizophrenia: Implications for cognition, psychosis, and addiction. *Biological Psychiatry*, *57*, 594–608.

Faraone, S.V., & Tsuang, M.T. (1985). Quantitative models of the genetic transmission of schizophrenia. *Psychological Bulletin*, *98*, 41–66.

Fish, B. (1977). Neurobiologic antecedents of schizophrenia in children. Evidence for an inherited, congenital neurointegrative defect. *Archives of General Psychiatry*, *34*, 1297–1313.

Freud, S. (1920). *Beyond the pleasure principle* (Vol. 18, pp. 1–64). London: Hogarth Press.

Goldstein, M.J. (1987). The UCLA high-risk project. *Schizophrenia Bulletin*, *13*, 505–514.

Gottesman, I.I. (1991). *Schizophrenia genesis: The origins of madness*. New York: W.H. Freeman/Times Books/Henry Holt & Co.

Gottesman, I.I., & Gould, T.D. (2003). The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry*, *160*, 636–645.

Gottesman, I.I., & Shields, J. (1966). Schizophrenia in twins: 16 years' consecutive admissions to a psychiatric clinic. *British Journal of Psychiatry*, *112*, 809–818.

Harrow, M., Grossman, L.S., Jobe, T.H., & Herbener, E.S. (2005). Do patients with schizophrenia ever show period of recovery? A 15-year multi-follow-up study. *Schizophrenia Bulletin*, *31*, 723–734.

Heath, R.G. (1952). The concept of functional versus organic disease: A critique. *Medical Clinics of North America*, *36*, 305–310.

Heaton, R.K., Baade, L.E., & Johnson, K.L. (1978). Neuropsychological test results associated with psychiatric disorders in adults. *Psychological Bulletin*, *85*, 141–162.

Heinrichs, R.W. (2004). Meta-analysis and the science of schizophrenia: Variant evidence or evidence of variants? *Neuroscience Biobehavioral Review*, *28*, 379–394.

Holzman, P.S. (1977). Abnormal-pursuit eye movements in schizophrenia: Evidence for a genetic indicator. *Archives of General Psychiatry*, *34*, 802–805.

Huttunen, M.O., & Niskanen, P. (1978). Prenatal loss of father and psychiatric disorders. *Archives of General Psychiatry*, *35*, 429–431.

Jobe, T.H., & Harrow, M. (2005). Long-term outcome of patients with schizophrenia: A review. *Canadian Journal of Psychiatry*, *50*, 892–900.

King, S., Ricard, N., Rochon, V., Steiger, H., & Nelis, S. (2003). Determinants of expressed emotion in mothers of schizophrenia patients. *Psychiatry Research*, *117*, 211–222.

Kirov, G., O'Donovan, M.C., & Owen, M.J. (2005). Finding schizophrenia genes. *Journal of Clinical Investigation*, *115*, 1440–1448.

Kunugi, H., Nanko, S., & Murray, R.M. (2001). Obstetric complications and schizophrenia: Prenatal underdevelopment and subsequent neurodevelopmental impairment. *British Journal of Psychiatry*, *178*(Suppl. 40), 25–29.

Levin, S., Yurgelun-Todd, D., & Craft, S. (1989). Contributions of clinical neuropsychology to the study of schizophrenia. *Journal of Abnormal Psychology*, *98*, 341–356.

Lewis, C.M., Levinson, D.F., Wise, L.H., DeLisi, L.E., Straub, R.E., Hovatta, I., et al. (2003). Genome scan meta-analysis of schizophrenia and bipolar disorder: II. Schizophrenia. *American Journal of Human Genetics*, *73*, 34–48.

Lyon, M., Barr, C.E., Cannon, T.D., Mednick, S.A., & Shore, D. (1989). Fetal neural development and schizophrenia. *Schizophrenia Bulletin*, *15*, 149–161.

Mednick, S.A., Machon, R.A., Huttunen, M.O., & Bonett, D. (1988). Adult schizophrenia following prenatal exposure to an influenza epidemic. *Archives of General Psychiatry*, *45*, 189–192.

Mednick, S.A., Mura, E., Schulsinger, F., & Mednick, B. (1971). Perinatal conditions and infant development in children with schizophrenic parents. *Social Biology*, *18*, S103–S113.

Meehl, P.E. (1962). Schizotaxia, schizotypy, schizophrenia. *American Psychologist*, *17*, 827–838.

Miller, G. (2005). What is the biological basis of consciousness? *Science*, *309*, 79.

Mirsky, A.F. (1969). Neuropsychological bases of schizophrenia. *Annual Review of Psychology*, *20*, 321–348.

Mirsky, A.F., & Duncan, C. (2005). Pathophysiology of mental illness: A view from the fourth ventricle. *International Journal of Psychophysiology*, *58*, 162–178.

Moffitt, T.E., Caspi, A., & Rutter, M. (2005). Strategy for investigating interactions between measured genes and measured environments. *Archives of General Psychiatry*, *62*, 473–481.

Murray, R.M., O'Callaghan, E., Castle, D.J., & Lewis, S.W. (1992). A neurodevelopmental approach to the classification of schizophrenia. *Schizophrenia Bulletin*, *18*, 319–332.

Nuechterlein, K.H., & Dawson, M. (1984). A heuristic vulnerability/stress model of schizophrenic episodes. *Schizophrenia Bulletin*, *10*, 300–312.

Perez-Neri, I., Ramirez-Bermudez, J., Montes, S., & Rios, C. (2006). Possible mechanisms of neurodegeneration in schizophrenia. *Neurochemical Research*, *31*, 1279–1294.

Petronis, A., Gottesman, I.I., Kan, P., Kennedy, J.L., Basile, V.S., Paterson, A.D., et al. (2003). Monozygotic twins exhibit numerous epigenetic differences: Clues to twin discordance? *Schizophrenia Bulletin*, *29*, 169–178.

Singer, M., & Wynne, L. (1963). Differentiating characteristics of parents of childhood schizophrenics, childhood neurotics, and young adult schizophrenics. *American Journal of Psychiatry*, *120*, 234–243.

Tienari, P., Sorri, A., Lahti, I., Naarala, M., Wahlberg, K.E., Moring, J., et al. (1987). Genetic and psychosocial factors in schizophrenia: The Finnish adoptive family study. *Schizophrenia Bulletin*, *13*, 477–484.

Toga, A.W., Thompson, P.M., & Sowell, E.R. (2006). Mapping brain maturation. *Trends in Neuroscience*, *29*, 148–159.

Torrey, E.F. (2002). Studies of individuals with schizophrenia never treated with antipsychotic medications: A review. *Schizophrenia Research*, *58*, 101–115.

Vaughn, C., & Leff, J. (1976). The measurement of expressed emotion in families of psychiatric patients. *British Journal of Social and Clinical Psychology*, *15*, 157–165.

Verdoux, H., Tournier, M., & Cougnard, A. (2005). Impact of substance use on the onset and course of early psychosis. *Schizophrenia Research*, *79*, 69–75.

Viveros, M.P., Llorente, R., Moreno, E., & Marco, E.M. (2005). Behavioural and neuroendocrine effects of cannabinoids in critical developmental periods. *Behavioural Pharmacology*, *16*, 353–362.

Walker, E. (1994). Developmentally moderated expressions of the neuropathology underlying schizophrenia. *Schizophrenia Bulletin*, *20*, 453–480.

Walker, E. (2002). Role of endogenous and exogenous risk factors in the genesis of schizophrenia. In R.J. McMahon & R.D.V. Peters (Eds.), *The effects of parental dysfunction on children* (pp. 3–16). New York: Kluwer Academic.

Walker, E., & Diforio, D. (1997). Schizophrenia: A neural diathesis-stress model. *Psychological Review*, *104*, 667–685.

Walker, E., Downey, G., & Bergman, A. (1989). The effects of parental psychopathology and maltreatment on child behavior: A test of the diathesis-stress model. *Child Development*, *60*, 15–24.

Walker, E., Kestler, L., Bollini, A., & Hochman, K. (2004). Schizophrenia: Etiology and course. *Annual Review of Psychology*, *55*, 401–430.

Weinberger, D.R., Torrey, E.F., Neophytides, A.N., & Wyatt, R.J. (1979). Lateral cerebral ventricular enlargement in chronic schizophrenia. *Archives of General Psychiatry*, *36*, 735–739.

Wilhelm, K., Mitchell, P.B., Niven, H., Finch, A., Wedgwood, L., Scimone, A., et al. (2006). Life events, first depression onset and the serotonin transporter gene. *British Journal of Psychiatry*, *188*, 210–215.

Zubin, J., & Spring, B. (1977). Vulnerability: A new view of schizophrenia. *Journal of Abnormal Psychology*, *86*, 103–126.