Note

1. Address correspondence to J.P. Das, Developmental Disabilities Centre, 6-123 D Education North, University of Alberta, Edmonton, Alberta, Canada T6G 2G5; e-mail: j.p.das@ualberta.ca.

References

Das, J.P. (1999). PREP: PASS Reading Enhancement Program. Deal, NJ: Sarka Educational Resources.

Das, J.P., Divis, B., Alexander, J., Parrila, R.K., & Naglieri, J.A. (1995). Cognitive decline due to aging among persons with Down Syndrome. Research in Developmental Disabilities, 16, 461–478.

Das, J.P., Kar, B.C., & Parrila, R.K. (1996). Cognitive planning. Thousand Oaks, CA: Sage.

Das, J.P., Kirby, J.R., & Jarman, R.F. (1975). Simultaneous and successive syntheses: An alternative model for cognitive abilities. Psychological Bulletin, 82, 87–103.

Das, J.P., Naglieri, J.A., & Kirby, J.R. (1994). Assessment of cognitive processes: The PASS theory of intelligence. Boston: Allyn and Bacon.

Donald, M. (1991). Origins of the modern mind. Cambridge, MA: Harvard University Press.

Frith, C.D. (1997). Linking brain and behavior. In R.S.J. Frackowiak, K.J. Friston, R.J. Dolan, & J.C. Mazziotta (Eds.), Human brain function (pp. 3–23). San Diego: Academic Press.

Gardner, H. (1983). Frames of mind: The theory of multiple intelligences. New York: Basic Books.

Luria, A.R. (1966). Human brain and psychological processes. New York: Harper and Row.

Naglieri, J.A., & Das, J.P. (1997). Das-Naglieri Cognitive Assessment System. Itasca, IL: Riverside Publishing.

Posner, I. (1993). Foundations of cognitive science. Cambridge, MA: MIT Press.

Pugh, K.R., Mencl, W.E., Shaywitz, B.A., Fulbright, R.K., Constable, R.T., Skudlarski, P., Marchione, K.E., Jenner, A.R., Fletcher, J.M., Liberman, A.M., Shankweiler, D.P., Katz, L., Lacadie, C., & Gore, J.C. (2000). The angular gyrus in developmental dyslexia: Task-specific differences in functional connectivity within posterior cortex. Psychological Science, 11, 51–56.

Sternberg, R.J. (1985). Beyond IQ: A triarchic theory of human intelligence. Cambridge, England: Cambridge University Press.

Wagner, R.K., & Torgesen, J.K. (1987). The nature of phonological processing and its causal role in the acquisition of reading skills. Psychological Bulletin, 101, 192–212.

Schizophrenia: A Neurodevelopmental Perspective

Heather M. Conklin and William G. Iacono[1]

Department of Psychology, University of Minnesota, Minneapolis, Minnesota

Abstract

Diverse lines of research suggest that schizophrenia is a genetically influenced neurodevelopmental disorder. Family, twin, and adoption studies suggest that most cases of schizophrenia involve a genetic diathesis that is necessary but not sufficient for development of the disorder. Histological, neuroimaging, and neuropsychological findings converge in providing evidence for medial-temporal and frontal lobe dysfunction that likely predates the onset of psychosis. Behavioral phenomenology and neurobiology suggest that dopamine plays a crucial moderating role between these structural abnormalities and functional impairment. Recently, investigators have used animal models and clinical syndromes to integrate these findings into neurodevelopmental models of schizophrenia that hold great potential for yielding etiological insight.

Keywords

schizophrenia; neurodevelopment; etiology; predisposition

The past decade has seen a proliferation of research findings in the field of schizophrenia, with provocative developments in molecular genetics, neurobiology, neuroimaging, neuropsychology, and studies of high-risk individuals. Although the etiology of schizophrenia remains enigmatic, scientists are gaining ground in developing plausible models of vulnerability to this disorder. In the past, most research findings have provided insights into selected aspects of the disorder without yielding a comprehensive theory that has received broad-based approval. Recently emerging neurodevelopmental models of schizophrenia, however, are capable of accommodating diverse findings and are receiving widespread support among schizophrenia investigators.

Neurodevelopmental models propose that vulnerability to schizophrenia results from a disruption in forebrain development during the perinatal period. A brain lesion that occurs early in development is hypothesized to lie dormant until normal brain maturational events trigger the appearance of traditional diagnostic signs, typically in adolescence or early adulthood (Weinberger, 1987). Such models are supported by reports of increased intrauterine and perinatal complications among individuals with schizophrenia, as well as by demonstrations that neurological, neuropsychological, and physical abnormalities predate the onset of psychosis. Although this evidence is far from conclusive, neurodevelopmental models hold immense promise as a heuristic for bridging research in multiple domains and posing questions central to discovering the etiology of this disorder.

GENETIC AND ENVIRONMENTAL VULNERABILITY

Well-replicated findings from family, twin, and adoption studies indicate that there is a substantial genetic component to the predisposition for schizophrenia. The likeli-

hood that this genetic predisposition involves multiple genes and the possibility that different genetic variants underlie the risk for schizophrenia have made the search for genes via standard molecular techniques daunting. Although research findings have identified several chromosomal sites where there may be genes that confer susceptibility to schizophrenia (i.e., genetic linkage), a failure to replicate these findings has become the norm rather than the exception. A recent study, which examined the entire genome of individuals in families with high rates of schizophrenia, provided evidence for schizophrenia susceptibility on chromosome 1 (Brzustowicz, Hodgkinson, Chow, Honer, & Bassett, 2000). This finding is promising in that the evidence for genetic linkage was unusually strong, a factor that should facilitate the search for a specific gene on this chromosome in these families.

It is reasonable to propose that alteration of gene expression (i.e., production of proteins coded for by genes), during critical phases of early development, contributes to neurodevelopmental abnormalities seen in schizophrenia. Brain development is a delicate process that requires a precise cascade of events orchestrated by the timing and specificity of gene expression. However, until one or more schizophrenia-susceptibility genes have been identified, the link between genetic variations and neurodevelopmental abnormalities remains largely theoretical. For example, neurodevelopmental disturbances in schizophrenia may result from the improper function of proteins that regulate the movement of neurons to their final destination in the brain (neuronal migration) and the formation of neural connections (synaptogenesis).

If schizophrenia were entirely due to heredity, all identical twins with schizophrenia would have co-twins who also have the disorder because identical twins share all of their genes. In fact, the co-twins of affected identical twins develop schizophrenia only about half the time. Thus, environmental factors must also influence schizophrenia's development. From a neurodevelopmental perspective, events occurring early in life are of greatest interest as potential environmental risk factors. A higher rate of obstetric complications has been found for schizophrenia patients relative to normal comparison subjects, psychiatric comparison subjects, and well siblings. A recent report suggests that the risk for schizophrenia is correlated with the number of hypoxia-associated obstetric complications (i.e., complications that can result in oxygen deprivation) an individual may have experienced (Cannon, Rosso, Bearden, Sanchez, & Hadley, 1999). The risk for schizophrenia appears to be conferred from an interaction between genetic predisposition and obstetric complications, rather than obstetric complications alone. In addition, *in utero* viral exposure has been studied as an environmental risk factor for schizophrenia because of the higher number of winter births than births in other seasons among schizophrenia patients and the increased frequency of viral epidemics in the fall. For example, an increased rate of schizophrenia was demonstrated among individuals who were exposed during their second trimester to an influenza epidemic in Helsinki in 1957 (Mednick, Machon, Huttunen, & Bonett, 1988).

NEUROLOGICAL ABNORMALITIES

The longest-held finding in support of the neurodevelopmental model is the increased size of fluid-filled spaces (lateral ventricles) in the brain that is present in first-episode schizophrenia patients and appears to remain static over time. It appears, then, that brain abnormalities are not just an index of the disorder's progression, but more likely constitute a preexisting vulnerability to the disorder. Post mortem histological studies have produced convergent evidence for neurological anomalies at the cellular level. Cellular abnormalities in the brain, such as increased neuronal spacing and altered arrangement of neuronal layers in temporal and frontal lobes areas,[2] have suggested that the predisposition for schizophrenia may involve disruption in neuronal migration. Furthermore, histological studies have failed to find signs of gliosis (a neuronal indicator of injury to a mature brain or of a neuropathological process), again suggesting the cellular deviations occurred early in life.

Neuroimaging studies have demonstrated structural and metabolic abnormalities in the medial-temporal lobe and frontal lobe of schizophrenia patients. For example, reduced frontal cerebral blood flow (hypofrontality) during tasks that require frontal activation has been observed, with the degree of frontal blood flow correlating with task performance. Although a review of recent neuroimaging findings in schizophrenia is beyond the scope of this article, there have been increasing efforts to parse out specific areas within the medial-temporal and frontal lobes that may be compromised in schizophrenia. Temporal lobe dysfunction likely contributes to positive symptoms, consisting of delusions and hallucinations, and frontal lobe dysfunction likely contributes to negative symptoms, such as impoverished thought, lack of goal-directed activities, and social withdrawal.

The performance of schizophrenia patients on neuropsychologi-

cal tasks has been used to elucidate cognitive deficits that may be secondary to brain abnormalities in these patients, as well as to develop hypotheses about the location of their neuropathology. Schizophrenia patients have been found to be impaired on a range of tasks, including ones purported to measure abstraction, sustained attention, language, and memory. Recently, Bilder et al. (2000) evaluated the performance of first-episode schizophrenia patients using a comprehensive neuropsychological test battery. They reported a large generalized deficit in schizophrenia patients with additional specific deficits in memory and executive functions. These results are not open to previous criticisms that cognitive deficits in schizophrenia merely reflect factors associated with chronic mental illness (e.g., long-term treatment) or depict global impairment. The findings are consistent with histological and neuroimaging findings that implicate temporal and frontal lobe involvement in schizophrenia.

Although it is now recognized that multiple neurotransmitters likely contribute to the etiology of schizophrenia, dopamine continues to be the primary neurotransmitter of interest.[3] The dopamine hypothesis, which originally asserted that schizophrenia results from a diffuse excess of dopamine in the brain, has been revised to suggest a dysregulation of dopamine resulting in an excess of dopamine in temporal areas and a depletion of dopamine in frontal areas. Further, it has now been proposed that the alteration in dopamine neurotransmission may not result from a primary deficit in dopamine neurons or receptors, but rather may result from abnormalities in the regulation of dopamine by limbic (medial-temporal lobe structures responsible for motivated and emotional behaviors) and frontal regions (More, West, &

Grace, 1999). These are the same brain areas implicated by histological, neuroimaging, and neuropsychological studies. The dysregulation of dopamine neurotransmission that appears to occur in schizophrenia corresponds with behavioral and cognitive processes that are altered in this disorder. For example, within the frontal lobe, dopamine appears to specifically mediate aspects of working memory and motor planning that are impaired in schizophrenia (Goldman-Rakic, 1996). Dopamine and its interaction with other neurotransmitters, such as glutamate and gamma amino butyric acid (GABA), continue to be central to etiological models of schizophrenia.

Animal models[4] of schizophrenia hold promise for testing etiological theories, including neurodevelopmental models. Administration of neurotoxins in developing animals has been used to create disruptions in prenatal neuronal migration, perinatal oxygen deprivation has been used to imitate hypoxia associated with obstetric complications, and neonatal lesions to the hippocampus have been used to re-create structural brain abnormalities. To date, animal models have been able to reproduce a surprisingly broad range of neurobiological, behavioral, and cognitive aspects of schizophrenia. For example, some models have reproduced schizophrenia-like post mortem histological changes, impairment on working memory tasks, and withdrawn social behavior. In addition, animal models have demonstrated that some deficits are specific to neonatal rather than adult lesions, some symptoms show delayed emergence in adulthood, and some functions are returned to normal with the administration of drugs used to treat schizophrenia (neuroleptics). Behavioral outcomes can also vary with the genetic strain of an animal, suggesting an interac-

tion between genes and environment. Although animal models integrate findings across research areas well, they have obvious limitations, including the fact that animal behaviors may be insufficient proxies for certain complex human behaviors.

PROSPECTIVE AND HIGH-RISK STUDIES

Neurodevelopmental models implicitly predict that signs of disorder predate the onset of florid psychosis. Indeed, research has demonstrated that individuals who later develop schizophrenia exhibit motor, cognitive, and behavioral abnormalities during childhood. In an innovative archival study, Walker and Lewine (1990) showed that preschizophrenic children could be reliably differentiated from their well siblings in home videos taken during early childhood, primarily on the basis of abnormal movements and reduced facial expression. Jones, Rodgers, Murray, and Marmot (1994) studied a British cohort of 4,746 children born in 1946, of which 30 later developed schizophrenia. The preschizophrenic individuals were more likely than control subjects to have exhibited delayed early motor development; obtained low educational test scores at ages 8, 11, and 15; preferred solitary play at ages 4 and 6; and been rated by teachers as anxious in social situations at age 15.

Researchers have also investigated abnormalities in the unaffected first-degree relatives of schizophrenia patients. These individuals are at genetic risk because they share on average half of their genes with schizophrenia patients. Healthy relatives have been observed to demonstrate both behavioral and neurobiological impairments that are similar to those seen

in affected patients. For nearly a century, higher rates of schizophrenia-related disorders, such as schizotypal personality disorder,[5] have been seen in these relatives compared with the general population. The most consistent finding in relatives has been eye movement dysfunction, a finding consistent with frontal involvement in the genetic diathesis for schizophrenia. The impaired performance of relatives on certain neuropsychological measures, such as working memory tasks, provides further convergent evidence for frontal lobe dysfunction. Relatives who are deviant on more than one of these measures may be at the greatest risk for schizophrenia and may be most informative when included in genetic studies of this disorder. Associations among schizophrenia-related disorders, cognitive task performance, and the quality of eye movements in relatives of schizophrenia patients are being investigated (for discussion, see Iacono & Grove, 1993).

VELOCARDIOFACIAL SYNDROME (VCFS) AS AN INTEGRATIVE EXAMPLE

VCFS is a congenital syndrome that affects multiple body systems and is associated with a small deletion of genetic material in a specific area of chromosome 22. The symptom profile of individuals with VCFS is variable but commonly includes facial malformations, oral palatal anomalies, nasal voice, and cardiac abnormalities. Various studies have demonstrated that the rate of schizophrenia among individuals with VCFS is approximately 25 times the rate found in the population overall (i.e., 1%), leading investigators to suggest that VCFS is a genetic subtype of schizophrenia (Bassett et al., 1998). The inverse relationship also holds,

with multiple studies demonstrating that the rate of this deletion on chromosome 22 in schizophrenia patients is approximately 80 times the general-population rate of 1 in 4,000. VCFS and preschizophrenic individuals show strikingly similar developmental characteristics. Specifically, children with VCFS exhibit delayed motor development, below-average IQ, a tendency toward concrete thinking, bland affect, and lowered levels of social interaction.

Research has begun to suggest potentially shared pathophysiology for VCFS and schizophrenia that may stem from the deletion on chromosome 22. One theory proposes that both VCFS and schizophrenia are neurodevelopmental disorders that affect midline body structures, an idea consistent with the physical abnormalities seen in VCFS. It may be that the pathology also includes migration of cells destined to be midline brain structures, including medial-temporal lobe structures. VCFS and schizophrenia have been associated with similar neuropathology (e.g., enlarged ventricles and an underdeveloped cerebellum), as revealed by magnetic resonance imaging; these structural changes may play a role in predisposing individuals to psychosis (Vataja & Elomaa, 1998). Another potential mechanism stems from the observation that the chromosomal area deleted in VCFS is close to the catechol-O-methyl transferase (COMT) gene (Dunham, Collins, Wadey, & Scambler, 1992). COMT is an enzyme that metabolizes certain neurotransmitters, including dopamine. It has been proposed that a predisposition to psychosis could arise through either a decrease in the metabolism of these neurotransmitters in the brain or an increase in exposure to them during neurodevelopment. Although there are limitations to the notion that VCFS is a schizophrenia sub-

type, the case of VCFS illustrates how research can be integrated to handle multiple aspects of schizophrenia, including genetic predisposition to illness, presence of signs of disorder that predate psychosis, neurochemical deviations, and developmental brain abnormalities.

FUTURE DIRECTIONS

As much as schizophrenia research is yielding provocative findings, there continue to be important unanswered questions regarding etiology. To date, investigators have not been able to reliably identify susceptibility genes for schizophrenia, precluding mapping the pathway from genetic vulnerability to brain abnormalities. A better understanding of the dormancy period between early brain lesions and adult onset of the disorder is needed. Animal models have failed to support the idea that hormonal changes in puberty may trigger the appearance of symptoms, and theories suggesting that the onset of diagnostic symptoms coincides with ongoing frontal lobe development need to be more adequately investigated. The identification of environmental stressors that contribute substantially to risk for schizophrenia is required. Perinatal complications, such as obstetric complications and viral exposure *in utero*, are some of the leading risk contenders; however, they are likely insufficient to account for the 50% of identical twins who have schizophrenia but whose co-twins do not. In addition, these environmental events make different theoretical predictions based on their timing, the stage of brain development implicated, and the mechanism of action.

Although the neurodevelopmental model is making great strides in integrating diverse re-

search findings, it may be but one of several useful models that ultimately characterize schizophrenia's multiple etiologies. The lack of cohesion of some of the research evidence may be due to schizophrenia resulting from different etiologies in different individuals. Such etiological heterogeneity confounds research into the cause (or causes) of schizophrenia, as study samples likely include individuals for whom the underlying cause of the disorder is not the same. One way to obtain samples with greater etiological homogeneity would be to supplement traditional diagnostic systems with measurement of traits that are likely more direct manifestations of the biological predisposition. For example, an investigator could select study samples of individuals who not only meet current diagnostic criteria for schizophrenia, but also demonstrate signs of neurodevelopmental origin for this disorder, such as those reviewed in this article. Research using a selection procedure such as this, one that is theoretically driven and also supported by recent research findings, likely holds the greatest promise for yielding etiological insight.

Recommended Reading

Cannon, T.D., Rosso, I.M., Bearden, C.E., Sanchez, L.E., & Hadley, T. (1999). (See References)
Iacono, W.G. (1998). Identifying psychophysiological risk for psychopathology: Examples from substance abuse and schizophrenia research. *Psychophysiology, 35,* 621–637.
Lillrank, S.M., Lipska, B.K., & Weinberger, D.R. (1995). Neurodevelopmental animal models of schizophrenia. *Clinical Neuroscience, 3,* 98–104.
Raedler, T.J., Knable, M.B., & Wein-

berger, D.R. (1998). Schizophrenia as a developmental disorder of the cerebral cortex. *Current Opinion in Neurobiology, 8,* 157–161.
Weinberger, D.R. (1987). (See References)

Notes

1. Address correspondence to William G. Iacono, Department of Psychology, University of Minnesota, N218 Elliott Hall, 75 East River Rd., Minneapolis, MN 55455; e-mail: wiacono@tfs.psych.umn.edu.
2. The temporal lobe is located laterally in the brain, near the temples. A primary ability supported by medial-temporal lobe structures (e.g., the hippocampus) is memory. In addition, individuals with damage to the temporal lobe may experience hallucinations. The frontal lobe is located in the most anterior part of the brain. Primary abilities supported by the frontal lobe include attention, as well as higher-level planning and organizing skills sometimes referred to as executive functions. Individuals with damage to the frontal lobe may demonstrate working memory impairment (i.e., an inability to temporarily store and manipulate information needed to execute a task) and eye movement dysfunction (i.e., an inability to produce certain kinds of eye movements in experimental paradigms).
3. Dopamine is one of many identified neurotransmitters, chemicals that allow for communication between nerve cells (neurons). Neurotransmitters are typically released into the space between neurons (a synapse), where they may exert their effect by binding to specific neuroanatomical sites (receptors) of adjacent neurons. In this manner, neurotransmitters may serve to propagate electrochemical signals throughout the nervous system.
4. Animal models attempt to imitate or re-create some aspect of human functioning in animals in order to study specific processes under greater experimental control. For example, animal models of schizophrenia may create any combination of signs and symptoms of the disorder in order to gain better understanding of its etiology or treatments.

5. Schizotypal personality disorder is characterized by disturbances in interpersonal relationships, distorted thoughts or perceptions, and odd speech or behavior. These symptoms are generally believed to be similar, but subthreshold, to schizophrenia symptoms.

References

Bassett, A.S., Hodgkinson, K., Chow, E.W.C., Correia, S., Scutt, L.E., & Weksberg, R. (1998). 22q11 deletion syndrome in adults with schizophrenia. *American Journal of Medical Genetics, 81,* 328–337.

Bilder, R.M., Goldman, R.S., Robinson, D., Reiter, G., Bell, L., Bates, J.A., Pappadopulos, E., Wilson, D.F., Alvir, J.M.J., Woerner, M.G., Geisler, S., Kane, J.M., & Lieberman, J.A. (2000). Neuropsychology of first-episode schizophrenia: Initial characterization and clinical correlates. *American Journal of Psychiatry, 157,* 549–559.

Brzustowicz, L.M., Hodgkinson, K.A., Chow, E.W.C., Honer, W.G., & Bassett, A.S. (2000). Location of a major susceptibility locus for familial schizophrenia on chromosome 1q21-q22. *Science, 288,* 678–682.

Cannon, T.D., Rosso, I.M., Bearden, C.E., Sanchez, L.E., & Hadley, T. (1999). A prospective cohort study of neurodevelopmental processes in the genesis and epigenesis of schizophrenia. *Development and Psychopathology, 11,* 467–485.

Dunham, I., Collins, J., Wadey, R., & Scambler, P. (1992). Possible role for COMT in psychosis associated with velo-cardio-facial syndrome. *The Lancet, 340,* 1361–1362.

Goldman-Rakic, P.S. (1996). Regional and cellular fractionation of working memory. *Proceedings of the National Academy of Sciences, USA, 93,* 13473–13480.

Iacono, W.G., & Grove, W.M. (1993). Schizophrenia research: Toward an integrative genetic model. *Psychological Science, 4,* 273–276.

Jones, P., Rodgers, B., Murray, R., & Marmot, M. (1994). Child developmental risk factors for adult schizophrenia in the British 1946 birth cohort. *The Lancet, 344,* 1398–1402.

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.

Moore, H., West, A.R., & Grace, A.A. (1999). The regulation of forebrain dopamine transmission: Relevance to the pathophysiology and psychopathology of schizophrenia. *Biological Psychiatry, 46,* 40–55.

Vataja, R., & Elomaa, E. (1998). Midline brain anomalies and schizophrenia in people with CATCH 22 syndrome. *British Journal of Psychiatry, 172,* 518–520.

Walker, E., & Lewine, R.J. (1990). Prediction of adult-onset schizophrenia from childhood home movies of the patients. *American Journal of Psychiatry, 147,* 1052–1056.

Weinberger, D.R. (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Archives of General Psychiatry, 44,* 660–669.