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Neurodevelopment and Schizophrenia: Broadening the Focus

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Abstract
Developmental changes in the brain are now a central feature of most etiological theories of schizophrenia. From the fetal period, in which vulnerability is presumed to originate, to the emergence of clinical illness in adolescence, brain changes are setting the stage for the first episode of psychosis. A host of factors that have the ability to alter fetal brain development have been linked with schizophrenia. Heritable genetic factors may increase risk for aberrant fetal brain development, and molecular genetic studies are now revealing mutations and epigenetic events that can also derail normal developmental processes. Prenatal complications also are now known to be associated with vulnerability. Later, adolescence and early adulthood are the critical periods for the onset of the prodrome, the period of decline before illness onset, and then the clinical syndrome. Here we summarize hypothesized elements of the neurodevelopmental process in schizophrenia in a model that spans both the prenatal and adolescent/young-adult periods. It is likely that future models will be much more complex as epigenetic processes and gene–environment interactions are incorporated.

Keywords
schizophrenia, neurodevelopment, prenatal, adolescent

The idea that *neurodevelopment* is associated with risk for schizophrenia has become widely accepted among researchers in the field. Over the past three decades, however, conceptualizations of neurodevelopmental mechanisms in schizophrenia have been broadened to encompass a larger portion of the life span. Neurodevelopmental models have also become increasingly complex as theorists incorporate findings from the burgeoning fields of neuroscience and molecular genetics.

The term *neurodevelopment* emerged in the literature on schizophrenia in conjunction with scientific evidence that prenatal complications were linked with risk for the disorder. Thus the term was initially used to refer to abnormalities in fetal brain development that were presumed to set the stage for vulnerability (Murray, Jones, & O'Callaghan, 1991). In fact, a Medline search revealed no publications containing the terms *neurodevelopment* and *schizophrenia* prior to 1989 but showed a steady increase in subsequent years. In 1989 there was only one such publication (Green, Satz, Smith, & Nelson, 1989), while in 2009 more than 30 were documented.

In the late 1990s, a short-lived controversy arose between researchers arguing that schizophrenia has a neurodevelopmental origin and those arguing that the disorder is "neurodegenerative" in nature (Lieberman, 1999). However, it is now generally accepted that these are not mutually exclusive and that both may characterize schizophrenia (Ikeda et al., 2008; Velakoulis, Wood, McGorry, & Pantelis, 2000). This conceptual shift was associated with a broadening of the notion of neurodevelopmental models to include brain development in adolescence and young adulthood (Walker, 1994). This broadening was partly a consequence of advances in neuroimaging technology. Prior to the advent of neuroimaging, it was generally assumed that the development of the human brain primarily occurred during the prenatal period. While it is certainly true that all of the regions of the human brain are formed prenatally, we now know that neurodevelopment extends throughout the life span (Walker, Mittal & Tessner, 2008), and this knowledge has served as the impetus for researchers to modify their conceptual frameworks.

There are three general sources of evidence suggesting that the development of the nervous system is linked with

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schizophrenia. These are bodies of research indicating that risk for the disorder (a) appears to be linked with genes that play a role in the development of the central nervous system (Arnold, Talbot, & Hahn, 2005); (b) is associated with prenatal complications (Clarke, Harley, & Cannon, 2006); and (c) is characterized by changes in brain structure prior to the onset of illness, typically in adolescence/young adulthood (Pantelis et al., 2005).

Neurodevelopmental Mechanisms in the Origins of Vulnerability

Heritable genetic risk factors

During the 1960s and extending through the 1980s, behavioral genetic paradigms provided clear evidence that vulnerability to schizophrenia could be inherited. Although the magnitude of the heritability estimates varied, findings from family, twin, and adoption studies all yielded support for the hypothesis that genes that confer risk for schizophrenia could be passed from one generation to the next. While some researchers were optimistic that one or a few genes would be identified as major risk factors, subsequent studies using sophisticated molecular genetic techniques failed to provide consistent support for the influences of any single gene or even subgroup of genes as major risk factors. Instead, the findings from genome-wide association studies (GWASs) have led to the conclusions that (a) there are likely many genes, perhaps thousands, that are capable of contributing to risk; and that (b) risk genes act in additive or interactive ways to set the stage for schizophrenia (International Schizophrenia Consortium et al., 2009; St. Clair, 2009). Moreover, among the genes that have been implicated in multiple studies, such as *DISC1, dysbindin*, and *neuregulin 1*, many play a role in brain development and neuronal connectivity. Thus, risk genes may be disrupting the complex process of fetal brain development (Arnold et al., 2005).

Mutations

Within the past few years, GWASs have revealed another likely source of vulnerability. There are now numerous reports showing that, when compared to healthy controls, schizophrenia patients manifest significantly more abnormalities in their DNA—abnormalities that entail mutations in the form of deletions or duplications of DNA sequences (referred to as ''microdeletions'' and ''copy number variations''; St. Clair, 2009). Again, the affected genes tend to be those that are involved in the development of the nervous system, although any single mutation likely contributes only slightly to risk for schizophrenia. Further, differences in such mutations are even observed in monozygotic twins who are discordant for schizophrenia, with the discordant twin manifesting more of them (Singh & O'Reilly, 2009). Thus, while mutations can be inherited, these findings indicate that de novo (noninherited) changes in DNA can also contribute to vulnerability.

Epigenetics

The term *epigenetic* (i.e., in addition to genetic) refers to changes in the expression of genes that can affect the biological and behavioral phenotype (i.e., manifest characteristics) of an organism—that is, genes, located in the nucleus of cells, can be turned off or on depending on the cellular milieu. When this occurs, the RNA message encoded by the genes is altered but there is no change in the DNA. A discussion of the complexities of this process is beyond the scope of this paper. Nonetheless, the field of epigenetics is revolutionizing our view of the origins of vulnerability for schizophrenia and other diseases. Recent molecular genetic studies have shown that the profiles of gene expression patterns differ in members of monozygotic twin pairs who are discordant for schizophrenia (Tsang, Huang, Holmes, & Bahn, 2006). Thus the member of the twin pair that is affected by psychosis shows a different pattern of gene expression than does his or her healthy twin.

Scientists are only beginning to understand the nature, breadth, and determinants of epigenetic effects (Akbarian & Huang, 2009). It is known, however, that a host of prenatal factors, including maternal exposure to stress, can influence patterns of gene expression in offspring. Thus fetal development is assumed to be a period characterized by a high rate of epigenetic processes. Further, as described later, adolescence may be another critical period for changes in gene expression that trigger the onset of mental illness.

Prenatal complications

As noted previously, mounting evidence of a relation between prenatal complications and risk for schizophrenia was partially responsible for interest in neurodevelopmental models of schizophrenia. This now-vast literature has linked a range of prenatal factors with heightened risk. Included among these are prenatal exposure to maternal viral infection, nutritional deficiency, psychosocial stress, blood type incompatibility, and a host of complications that can lead to the fetus receiving insufficient oxygen (hypoxia; Clarke et al., 2006). All of these factors are known to have the potential to alter fetal brain development.

Brain structural abnormalities

Early studies of brain abnormalities in patients with schizophrenia revealed that such patients have enlarged ventricles, the areas of the brain that contain cerebrospinal fluid. Numerous subsequent investigations have shown reductions in the volumes of several other brain regions, most notably the temporal lobes, and particularly the hippocampus (located within the temporal lobe), a key region for memory functions. At the cellular level, postmortem studies have revealed abnormalities in the structure and placement of neurons, irregularities that typically arise during the formation of the fetal brain (Connor, Guo, & Akbarian, 2009). Taken together, these findings lend additional support to the notion that schizophrenia is a brain disorder and that at least some of the brain abnormalities originate during fetal development.

Neurodevelopmental Mechanisms in the Onset of Schizophrenia: Adolescence/Early Adulthood

The prodrome

Among the most well-established aspects of schizophrenia is its modal age of onset, usually the early 20s. Yet, prior to the onset of clinical symptoms of psychosis, there is a period of functional decline and gradual emergence of more subtle symptoms, a period now referred to as the *prodrome* (Addington et al., 2007). Lasting from months to several years, the prodrome is characterized by a range of signs, including depression, anxiety, and a decrease in social interaction. But the key factors defining the prodrome are attenuated psychotic symptoms—namely, perceptual abnormalities, unusual ideations, disturbances in thought, and suspiciousness. Perceptual abnormalities entail sensory experiences that are perplexing or disturbing but that do not constitute clinical hallucinations because the individual doubts that they are real (e g., "I seem to keep hearing my mother calling my name before I fall asleep, even when I know she isn't home. It is strange. I guess I must be hearing the TV in the next apartment."). Unusual ideations entail ideas that are unlikely to be based in reality but do not meet criteria for delusions because, again, the individual is not convinced of them (e.g., "Every time I turn on the radio the first song I hear is always about a guy who is leaving home, and I keep thinking that the DJ is playing those songs to give me the message that I should leave home. But that could not be true, right?").

The prodrome usually has its onset during adolescence, leading investigators to conclude that neurodevelopmental processes during this period are playing some role in triggering the expression of latent vulnerability for psychosis. Developmental neuroscientists have documented a host of brain maturational processes that occur in adolescents, and several of these have been implicated in theories about the neural mechanisms underlying the onset of psychosis.

Adolescent brain development

Scientific data on postnatal brain development, especially from studies using MRI, burgeoned in the past decade, and the findings clearly indicate that maturational changes in the brain extend through adolescence and into early adulthood (Walker, 2002). In particular, it has been discovered that normal neurodevelopmental processes during adolescence are both regressive and progressive. Regressive processes include reductions in gray matter volume and the pruning (reduction) of synapses. Progressive processes include increases in white matter and in volume of the amygdala and hippocampus. Some of these processes continue into at least the early 20s, and all are assumed to enhance brain function and to subserve the acquisition of adult cognitive abilities.

Adolescence is, of course, also characterized by dramatic changes in hormonal levels and activity. Sex hormones, particularly testosterone and estrogen, rise precipitously around puberty due to activation of the hypothalamic-pituitary-gonadal (HPG) axis. Recently, research has shown that adrenal hormones, in particular hormones involved in the biological response to stress, also increase during the course of adolescence. Notable among these are the hormones governed by the hypothalamic-pituitary-adrenal (HPA) axis, including cortisol (Walker at al., 2008). These findings and others have contributed to the growing view that adolescence is associated with heightened sensitivity to stress. Consistent with long-standing vulnerability–stress models, specifically the notion that stress plays a role in triggering the expression of vulnerability, this further implicates the adolescent stage as a critical period.

Because neurons have receptors for hormones, changes in hormone levels have implications for brain function and development. In binding to receptors on neurons, hormones can affect neurotransmitter function and can trigger changes in the expression of genes in the nuclei of neurons. Recent findings indicate that these hormonal effects may be driving normal developmental changes in brain structure.

Although much is still unknown about neurotransmitter changes in the developing brain, there is evidence of increasing activity in dopamine systems following the onset of puberty (Walker et al., 2008). This is relevant to theories about the etiology of schizophrenia, because dopamine continues to be the major neurotransmitter implicated in psychotic disorders. It has been hypothesized that abnormal activity of subcortical (below the cortex) brain regions involving dopamine may underlie the onset of psychotic episodes. It should be noted, however, that cortical dopamine activity appears to be reduced in schizophrenia. Further, other neurotransmitters, including glutamate and gamma-Aminobutyric acid, have also been hypothesized to be part of the pathophysiology of schizophrenia.

The Broad Neurodevelopmental View

Contemporary models of schizophrenia now incorporate changes in brain structure and function that span from the fetal period through young adulthood. Of course, these models are largely based on inferences from research findings, as well as on speculation. Nonetheless, a picture is beginning to emerge. Figure 1 is intended to illustrate the key elements in the neurodevelopmental process.

We begin with the origins of vulnerability at the left of the figure. We know that genetic factors, both heritable and acquired (e.g., mutations), are linked with risk for schizophrenia. In addition, exposure to prenatal complications enhances risk. The adverse effects of prenatal complications may be restricted to fetuses characterized by certain genetic risk factors, or they may contribute independently to risk for schizophrenia. This is one of many questions that remain to be answered.

Moving to the right in Figure 1, it is generally assumed that genetic factors and prenatal events confer vulnerability for schizophrenia. In other words, vulnerability is typically congenital (i.e., present at birth) and may entail abnormalities in brain regions where dopamine plays a critical role in

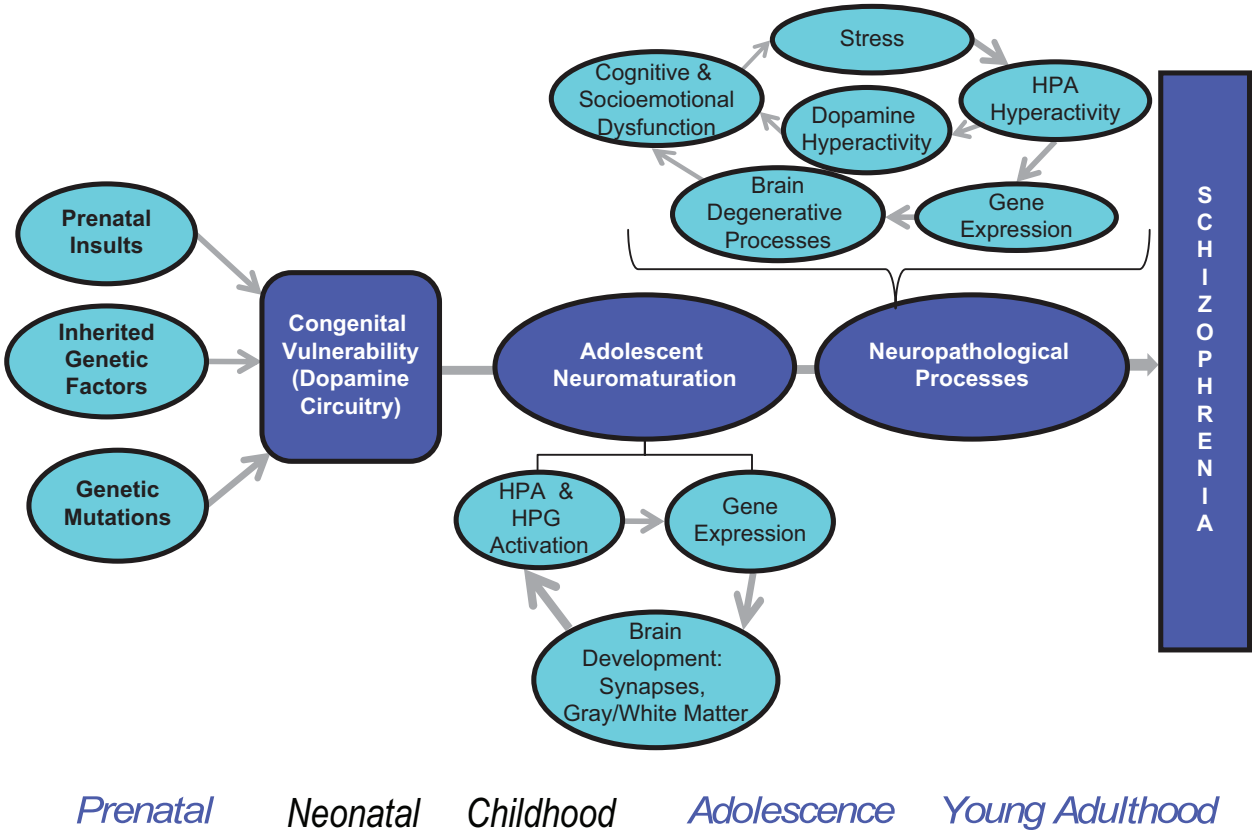

Fig. 1. Neurodevelopmental pathogenesis of schizophrenia. Stress-induced and developmental increases in cortisol can augment brain dopamine activity and changes in gene expression. The latter can lead to neurodegenerative brain changes that give rise to impaired cognition and social and emotional functioning. These impairments can increase stress, thereby exacerbating the neuropathological process.

neurotransmission. The striatum, a subcortical region that is part of many important circuits connecting various brain regions, is currently assumed to be a likely candidate.

Continuing to the right in Figure 1, it is not until later in life, following the onset of adolescent maturation, that vulnerability begins to be manifested in the prodromal signs of psychosis. As described earlier, during this age period, the adolescent brain is undergoing normal maturational changes that affect synapses as well as gray and white matter volumes. There is a gradually building consensus around the hypothesis that abnormal neurodevelopmental processes during adolescence give rise to the brain dysfunction that leads to schizophrenia. More specifically, there is evidence that the decrease in gray matter (suggesting reduced neuronal interconnections rather than loss of cell bodies) and heightened dopamine activity in the striatum are more marked in at-risk youth who subsequently manifest psychotic disorders. There is also evidence that those who develop psychosis manifest a decline in volume of the hippocampus. These abnormal changes may contribute to abnormalities in connectivity among neurons, thereby interfering with brain function.

As illustrated in Figure 1, this neuropathological process may entail a feedback loop. It has been demonstrated that both stress exposure and increases in cortisol secretion can augment brain dopamine activity. Thus, the normative increase in HPA activity during adolescence may be a contributing factor in the emergence of prodromal symptoms during this period. The hypothetical model proposes that HPA activity and concomitant cortisol secretion trigger both dopamine activity and gene expression changes that, in turn, contribute to neurodegenerative changes, such as exaggerated gray matter decline, volume reduction in the hippocampus, and reduced connectivity. At the behavioral level, the result is increasing impairment in the domains of cognition and social and emotional functioning. These impairments can contribute to stress that further exacerbates the neuropathological process. The final outcome of these converging events is the first episode of psychosis.

Conclusions

It is important to emphasize that the neurodevelopmental model depicted in Figure 1 is speculative. It reflects a combination of empirical research findings and hypotheses about causal processes. Other elements and mechanisms are likely involved. Further, schizophrenia is varied in its clinical

presentation, and it is generally assumed that there is variability in how it originates. As noted, genetic research indicates that many genes and genetic mechanisms are involved as are many prenatal complications. Finally, recent findings from genetic studies indicate that schizophrenia shares genetic risk factors with other forms of psychosis, such as bipolar disorder with psychotic features. In sum, the model depicted in Figure 1 is assumed to be highly oversimplified and unlikely to account for all cases. It does, however, incorporate many current views and can serve as a point of departure for future models. For example, future research is likely to reveal that interactions between genetic and environmental factors and dynamic epigenetic processes are key pieces of the puzzle, and these will certainly be elements in future neurodevelopmental models.

We clearly have a long way to go in unraveling the complex etiological pathways to schizophrenia. But there has been significant progress. In part, our progress is our acceptance of two facts about the etiological process: (a) that it is extremely complicated, and (b) that it interacts with the development of the brain at critical periods.

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Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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