Chapter 2
Causes

The exact nature of the etiological process of schizophrenia still remains elusive. Contemporary scholarship suggests that multiple factors contribute to the development of schizophrenia, including: (a) genes that cause structural brain deviations which make some individuals vulnerable to schizophrenia and (b) environmental factors such as negative prenatal and postnatal impacts and social stresses such as trauma and stigma. Furthermore, there may be an interaction or interplay between genetic vulnerability, neurobiological, and environmental factors that put a child or adolescent at the risk of developing schizophrenia.

Genetics

There is evidence that schizophrenia may be inheritable. Familial studies have indicated that parents of youth with EOS have higher rates of schizophrenia spectrum disorders than parents of patients with adult-onset illness and relatives of children and adolescents with ADHD (Margari et al., 2008; Nicolson et al., 2003). The risk of developing schizophrenia is about ten times higher if a first-degree relative has the illness. Among monozygotic (identical twins) twins of patients with schizophrenia, about 50% may develop the illness, and among dizygotic twins (fraternal twins) of patients with schizophrenia, about 10–15% have the illness. Also, 9% siblings of patients with schizophrenia may develop the illness, and 6% in half siblings. The approximate chance of developing schizophrenia in a child is 40% if both parents have the illness and 12% if one parent has it (Miller & Mason, 2002). In addition, when a biological child of individuals with schizophrenia is adopted, he or she has an elevated risk than the general population of developing schizophrenia, as expected for first degree relatives. Further, if one of the identical twins has schizophrenia, the children of both identical twins may have higher rates of schizophrenia (Fatemi & Folsom, 2009). Overall, the heritability estimates of schizophrenia are about 80–85% (Craddock, O’Donovan, & Owen, 2006).

Recent findings from behavioral genetic studies of schizophrenia indicate that the heritable vulnerability is unlikely to result from a single genetic locus or even a
small number of genes, rather resulting from multiple genes acting in concert or many single susceptibility genes acting independently (Walker, Kestler, Bollini, & Hochman, 2004). Researchers using molecular genetic techniques (such as candidate gene analyses, genome scans, and linkage studies) have identified several specific genes [e.g., serotonin type 2a receptor (5-HT2a) gene responsible for learning and memory and the dopamine D3 receptor gene for cognitive and emotional functions] as contributing to the development of schizophrenia (Badner & Gershon, 2002; Mowry & Nancarrow, 2001). More studies are needed to replicate such findings. Table 2.1 shows more risk genes for schizophrenia. In addition, many genetic alterations are proposed to be responsible for this illness. According to Lupski (2008), examples of such genetic alternations include “gain or loss of large chunks of DNA known as copy-number variations (CNVs). … DNA rearrangements involve duplications and deletions that can result in many characteristics, including inherited neurological diseases …” (p. 178). Walker et al. (2004) reported an association between the microdeletion on chromosome 22q11 deletion and schizophrenia. Such deletion occurs in about 0.025% of the general population, and it is often associated with structural abnormalities on the face, head, and heart. About 25% of individuals with 22q11 deletion meet the diagnostic criteria of schizophrenia, and the rate of this deletion appears to be higher in individuals with EOS or COS. More recently, researchers (e.g., Stefansson et al., 2008) found three genetic deletions located on chromosomal regions 1q21.1, 15q11.2, and 15q13.3 that are associated with schizophrenia and psychosis. A genome wide survey of rare CNVs in a large sample of patients (n = 3,391) and controls (n = 3,181) discovered deletions of 12p11.23 and 16p12.1–p12.2 in some patients. However, further studies are needed to replicate these findings. Furthermore, it is still unknown how often these gene alterations are inherited, how often they may lead to schizophrenia, and how often individuals who possess a genetic vulnerability for schizophrenia pass onto their offspring despite the fact that they have never been diagnosed with the illness.

Table 2.1 Etiological Factors of Schizophrenia

<table>
<thead>
<tr>
<th>Risk Genes</th>
<th>Early Insults: Prenatal, Perinatal, and Postnatal Risks</th>
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<tbody>
<tr>
<td>Neuregulin, Dysbindin, D-amino acid oxidase, Catechol-O-methyltransferase, Proline  dehydrogenase, Reelin, serotonin type 2a receptor, dopamine D3 receptor</td>
<td>Viral Infections: herpes simplex, influenza, rubella</td>
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<td>Toxins: Lead, alpha-aminolevulinic acid</td>
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<td></td>
<td>Obstetric complications: Mother hypertention, loss of husband while being pregnant, malnutrition, delivery complications</td>
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<td></td>
<td>Other Environmental Factors: Vitamin D deficiency, winter birth, high latitude, inner city residence, drug use, natural disasters</td>
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<td>Brain Abnormality: Reduction in whole brain and hippocampal volume, low volume of total cortical gray matter, high volumes of white matter, ventricular, and basal ganglia; larger superior temporal gyri relative to brain size; lack of normal right-greater-than left hippocampal asymmetry; larger ventricles, smaller temporal lobes, reduced metabolism in frontal lobe, significant reduction of mid sagittal thalamus</td>
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Despite encouraging findings linking risk genes to schizophrenia, molecular genetic studies also reveal that there is significant overlap in the genes that contribute to schizophrenia and other psychiatric disorders like schizoaffective disorder, and the manic syndromes associated with Type I Bipolar Disorder, which also present psychotic symptoms (Cardno, Rijsdijk, Sham, Murray, & McGuffin, 2002; Potash, Willour, Chiu, Simpson, & Mackinnon, 2001). This indicates that “there are genetic vulnerabilities to psychosis in general, and that the expression of these vulnerabilities can take the form of schizophrenia or an affective psychosis, depending on other inherited and acquired risk factors” (Walker et al., 2004, p. 409).

**Concluding Comments Regarding the Role of Genetics**

The available data suggest that multiple genetic factors account many cases of schizophrenia (Nicolson et al., 2003). The genetic explanations of schizophrenia either take the additive format or interactive format, with the former indicating that a certain number of factors/genes work together to reach a critical threshold for schizophrenia to develop and the latter as multiple predisposing genes interacting with each other to cause schizophrenia (e.g., Tsuang, Stone, & Faraone, 2001). However, still yet to be identified are potential environmental and biological risk factors that may interact with genetic predispositions and lead to symptoms characteristic of schizophrenia.

**Environment**

As indicated in the previous section, the etiology of schizophrenia appears to involve genetic factors. Nevertheless, about 60% of all individuals with schizophrenia do not have a first or second degree relative with this disorder or known as having the illness. Further, the degree of concordance for schizophrenia among identical twins is only about 50%, indicating that risk factors in the environment may play a role in the development of schizophrenia. In fact, Tsuang et al. (2001) found that the nonshared environment of twins accounted for almost all of the liability for schizophrenia. Identified environmental factors that put an individual at risk of developing severe mental illnesses like schizophrenia include prenatal, perinatal, and postnatal factors and social stresses like trauma and stigma.

**Prenatal Risks**

Over the last two decades, researchers have theorized that toxic exposures and infections during prenatal phase may elevate the risk of later developing schizophrenia. For example, a growing body of literature supports the hypothesis that lead
exposure that damages or disrupts the developing central nervous system is associated with schizophrenia. Opler et al. (2008) reported that elevated prenatal levels of alpha-aminolevulinic acid (alpha-ALA), a proxy for prenatal lead exposure (Pb), is associated with almost a twofold increase in risk for schizophrenia spectrum disorders later in life. Further, there was a 10–20-fold risk of developing schizophrenia following prenatal exposure to rubella (Brown, 2006; Brown et al., 2004; Brown et al., 2001). In addition, prenatal virus exposure in genetically high-risk individuals may increase the likelihood of an individual’s developing schizophrenia. In addition, in a study examining the interaction between gene and environment, Carter found that 21% of schizophrenia candidate genes interact with influenza virus, 22% with herpes simplex virus1, and 13% with rubella. However, conclusive evidence of an in utero infectious etiology of schizophrenia remains elusive (Lewis & Levitt, 2002).

Research findings also suggest people who develop schizophrenia are more likely to be born in the winter and early spring or in higher latitudes when compared with the general population (Kinney et al., 2009; Torrey, Miller, Rawings, & Yolken, 1997). Two hypotheses have been put forth to explain these observations. One is associated with increased influenza infection of pregnant mothers in cold temperature and the other is related to possible Vitamin D deficiency due to lengthened time indoors and shortened exposure to sunlight in cold weather. Both prenatal exposure to influenza and Vitamin D deficiency have been found to be associated with the development of schizophrenia (McGrath, 1999; Torrey et al., 1997). However, people with other psychiatric illnesses like depression and bipolar were also likely born in winter (Lewis & Levitt, 2002). Therefore, more research is warranted to delineate factors that may contribute more to the development of schizophrenia.

**Perinatal Risks**

Several perinatal factors have been identified to be associated with increased risk for schizophrenia. General nutritional deprivation and lack of specific micronutrients during pregnancy have been implicated as risk factors for schizophrenia (Opler & Susser, 2005). Susser et al. (1996) found that the rates of schizophrenia almost doubled for individuals conceived under conditions of nutrient deprivation during early gestation. Body mass index or low birth weight is also found to be associated with schizophrenia. Low maternal BMI was significantly associated with schizophrenia in the adult offspring. This finding was independent of maternal age, race, education, or cigarette smoking during pregnancy.

In addition, Sørensen and colleagues proposed that maternal hypertension during pregnancy and its treatment with diuretics in the third trimester of pregnancy were independently related to the development of schizophrenia in the offspring, and the association remained significant after controlling from maternal diagnosis of schizophrenia (Sørensen, Mortensen, Reinisch, & Mednick, 2003). There was also
a sevenfold risk of developing schizophrenia following exposure to influenza in the first trimester (Brown, 2008).

A meta-analysis of the effect of exposure to obstetrical complications on the development of schizophrenia shows that those with obstetrical complications are twice as likely to develop schizophrenia (Geddes & Lawrie, 1995). Obstetrical complications refer to a broad class of negative events and child development during pregnancy, labor-delivery, and early neonatal period (McNeil, 1988). Furthermore, labor-delivery complications (LDCs) were associated with an increased risk of EOS (Verdoux et al., 1997). Those who developed schizophrenia by age 22 were 2.7 times more likely to have abnormal presentation at birth and 10 times more likely to have a complicated Caesarean section. In twin studies, LDCs, rather than negative pregnancy events, identify monozygotic twins of which one or both developed schizophrenia, but not twins who were not affected. Specifically, in instances where one twin has schizophrenia and the other does not and when one twin was affected with schizophrenia and was born second, there were high rates of prolonged labor and lower rates of complications during pregnancy. Nevertheless, if the twin affected with schizophrenia was born first, the rate of prolonged labor was low and the rate of complications during pregnancy was high (Verdoux et al.). However, it should be noted that 97% of those with labor-delivery complications in population-based studies do not develop schizophrenia, which indicates that LDCs have low predictive value for the appearance of schizophrenia (Lewis & Levitt, 2002). Based on the gene and environment interaction model, “the offspring born with LDCs of individuals with schizophrenia may be more likely to develop schizophrenia than the offspring born without LDCs, whereas the same degree of LDCs does not increase risk of schizophrenia in the offspring of control subjects” (Lewis & Levitt, p. 416).

Postnatal Risks

Among the few studies examining the relationship between infection during childhood and the risk of subsequent schizophrenia, Dalman et al. (2008), in their cohort study of more than one million Swedish participants, found a weak association between viral central nerve system infections during childhood and the later development of schizophrenia spectrum disorders. Among the different viral infections, only mumps and cytomegalovirus infections were found to be associated with increased risk for psychosis.

Trauma

Trauma is another environmental factor that may operate independently or interact with genetic vulnerability to trigger psychotic symptoms of schizophrenia (Morgan & Fisher, 2007). For instance, research findings indicate 35% of patients
diagnosed as schizophrenia as adults had been removed from home due to neglect, doubling the rate of other psychiatric diagnosis (e.g., Robins, 1996). In the study of over 100 children with schizophrenia spectrum disorders, “13% had a history of physical abuse, 10% sexual abuse, 14% neglect, and 20% witnessed trauma in the past” (Frazier et al., 2007, p. 982).

Read and colleagues indicate that ‘child abuse is a causal factor for psychosis and ‘schizophrenia’ and, more specifically for hallucination, particularly voices commenting and command hallucinations” (Read, van Os, Morrison, & Ross, 2005, p. 330). Child abuse is also related to early age of onset and more positive symptoms. In the Finnish Adoptive Family Study of Schizophrenia, the risk elevated significantly if the adoptees were raised in families with unfavorable atmosphere, while the risk of schizophrenia of those with genetic vulnerability did not differ from those adoptees with no genetic risks if they were raised in families with a favorable atmosphere (Tienari et al., 1994). These findings support the role of negative life events in the development of schizophrenia.

Several models are used to explain the association between trauma and the development of schizophrenia (Read et al., 2005; Walker & Diforio, 1997). First, early traumatic experiences may predispose persons to be more psychologically and cognitively sensitive to emotional distress which may trigger psychotic symptoms. Specifically, negative beliefs about self (helpless, vulnerable), world, and others (dangerous, suspicious) are found to be associated with psychosis (e.g., Morrison, 2001), and so are positive beliefs about psychotic experiences (such as paranoid as a survival strategy). According to Read et al. (2005), the second model implicates faulty source monitoring. Hallucinations are strongly related to childhood abuse and they are often, however, memories of the traumatic experience indicative of PTSD rather than psychotic symptoms of schizophrenia. However, when individuals with abuse history confuse between inner experience (memory of the past) and outer experience (external event happening in the present) and when they contribute such internal event to an external event (which is called faculty source monitoring), they start to experience heightened level of distress and develop delusional explanations of the experience. Henquet, Krabbendam, Dautzenberg, Jolles, and Merckelbach (2005) proposed that source monitoring difficulties are a “prominent feature of schizophrenia” (p. 57). Furthermore, faulty source monitoring is more related to visual, tactile, and olfactory hallucinations than to auditory ones. Third, Walker and Diforio (1997) proposed a traumagenic neurodevelopmental (TN) model in understanding the relationship between trauma and the development of schizophrenia. This TN model integrates social, psychological, and biological factors, and it proposes that one’s brain is affected by environment throughout his or her life. They reported neurological abnormalities evidenced in schizophrenia patients in the brains of traumatized children. Such abnormalities include hippocampal damage, cerebral atrophy (loss of brain cells), ventricular enlargement, and reversed cerebral asymmetry, which were related to cognitive deficits such as memory and attention. Lastly, Walker and Diforio proposed the model of stress cascade and psychosis in
Neurobiology

schizophrenia that life stressors may trigger or exacerbate psychotic symptoms as they increase dopamine activity, particularly in the subcortical region of the limbic circuitry. It is important to note that not all individuals who have been diagnosed with schizophrenia have experienced trauma, thus, implicating other etiological influences.

**Stigma**

Stigma, as a structural discrimination and social adversity, not only starts after a person is diagnosed as schizophrenia, but may serve as a causal factor of schizophrenia in response to the behavioral expression of genetic risk. van Zelst (2009) hypothesized that individuals at the prodromal stage may manifest early signs of psychosis, such as paranoid reactions or odd speech. These behaviors may lead to negative social interactions and stigma which increase the risk of these individuals’ transitioning to psychotic disorder in general and schizophrenia in particular.

**Concluding Comments Regarding the Role of the Environment**

Different environmental factors may play a role in the development of schizophrenia. However, currently, there is little evidence supporting any one environmental factor as playing a primary role in the development of schizophrenia. In many cases, it appears that environmental factors interact with genetic vulnerability to influence the development of schizophrenia.

**Neurobiology**

No single pathology has been found to account for all the cases of schizophrenia, including EOS, rather, several different etiological models have been proposed. The following addresses neurobiological basis of schizophrenia.

**Brain Structure**

Lab studies show abnormal brain structures among individuals of EOS (e.g., Lawrie, McIntosh, Hall, Owens, & Johnstone, 2008). Brain structural studies show that superior parietal lobe pathology, particularly on the right, was progressively more pronounced in COS cases. Positive association between age of onset
of psychosis and right parietal gray matter volume in EOS were also reported. Parietal cortices regulate spatial representation and motor planning and goal directed attention set shifting. Deficits in these regions may be related to motor abnormalities, and they are more prominent in EOS (Burke, Androutsos, Jogia, Byrne, & Frangou, 2008).

In addition, the longitudinal assessment of EOS cases from the NIMH cohort found gray matter loss that appeared first in parietal regions and then spread to the prefrontal cortex (Vidal et al., 2006). Burke et al. (2008) investigated the effect of age of onset on front-parietal gray matter among adolescents with schizophrenia and found the earlier the onset of schizophrenia the less the gray matter volume in the right parietal lobe, and the longer the duration of the illness. The parietal cortices are associated with such cognitive functions as spatial representation, coordination, self monitored motor function, motor imagery, abstract motor planning, and goal directed attention shifting. Parietal abnormalities may also be associated with the inability to differentiate between self-produced and externally generated behavior, which is the hallmark of psychosis. Wood et al. (2003) postulate that reduced gray matter density may be responsible for cognitive impairments in spatial working memory and rapid information processing (tasks like story recall). In fact they suggest that the prefrontal cortex seems the most promising region in terms of prediction of later psychosis.

Furthermore, increased gray matter loss in EOS could be genetically influenced and a trait marker of individuals with EOS. Gogtay et al. (2003) found using NIMH COS data that significant gray matter reduction in younger healthy full siblings of COS in left prefrontal and bilateral temporal cortices relative to healthy controls. However, such cortical deficits in siblings disappeared by age 20, which suggests a “plastic or restitutive brain response in these nonpsychotic, nonspectrum siblings” (Gogtay, 2008, p. 33). Yoshihara et al. (2008) also found in a study of patients with EOS that the positive symptom score of Positive and Negative Symptom Scale (PANSS) (higher values indicating more severe symptom) is negatively correlated with gray matter volume in the right thalamus, and the positive symptom score of PANSS was positively related to cerebella white matter.

Several meta-analysis studies report bilateral reduced volume in hippocampus,indicative of potential markers of psychosis (Lawrie & Abukmeil, 1998; Wright et al., 2000). Structural imaging studies indicate that reductions in hippocampal volume occur during the transition from the premorbid to prodromal to the overtly psychotic phases of the illness (Matsumoto et al., 2001). However, the smaller hippocampal volume may not predict later psychosis but instead be a result of environmental insults such as obstetric complications.

Other brain regions have been examined as potential markers of later showing positive symptoms. Enlarged lateral ventricles were the first and most consistently reported brain abnormality in schizophrenia research. Sowell et al. (2000) also found symmetry ventricles in participants with EOS, whereas a larger ventricle in the left hemisphere was found in control participants. “It is probable that neuroanatomical cerebral abnormalities present prior to disease onset play an etiopathogenic role in the development of schizophrenia” (Mehler & Warnke, 2002).
**Brain Chemistry**

Researchers in the field of schizophrenia have been exploring neurochemistry bases for schizophrenia. Over the past four decades, dopamine and dopaminergic mechanisms have been a central hypothesis of the development of schizophrenia and the findings over the years have been reframing the theoretical explanations of such neural circuitry models of schizophrenia (Howes & Kapur, 2009). The dopamine hypothesis started in 1970s when it was believed that psychosis was caused by excessive transmission at dopamine receptor and antipsychotic drugs were invented to block these receptors to treat psychosis. However, this hypothesis did not delineate the relationship between the role of dopamine receptor and positive and negative symptoms, nor did it specify the link between genetics and neurodevelopmental deficits and specify the abnormal brain regions.

Latest findings from the past decade have modified the domapine hypothesis. Many recent findings link dopamine hyperfunction most closely to psychosis (positive symptoms), a hallmark of schizophrenia (Howes & Kapur, 2009). The latest dopamine hypothesis was enriched with findings from gene variants and environment risk factors that influence dopaminergic functions. Two major components of the current dopamine hypothesis are: (a) multiple hits – different gene variants, neural transmitters such as serotonin, norepinephrine, glutamate or y-aminobutyric acid (GABA), and environmental factors such as trauma and prenatal, perinatal, and postnatal factors, interact to result in dopamine dysfunction (Meyer & Feldon, 2009). (b) Dopamine regulation is linked to “psychosis” rather than schizophrenia. The exact diagnosis, therefore, “reflects the nature of the hits coupled with sociocultural factors and not the dopamine dysfunction per se” (Howes & Kapur, p. 555).

**Concluding Comments Regarding the Role of Neurobiology**

Neurobiological research findings indicate that the neuropathologies associated with schizophrenia are related to abnormalities in different localities of the brain. These abnormalities involve different brain structures, neurotransmitters, genetic variants, all of which may interact with environment factors to lead to symptoms associated with schizophrenia. Table 2.1 summarizes neurobiological findings of schizophrenia.

**Concluding Comments**

This chapter has presented the complicated etiology of schizophrenia in general and EOS in several sections. Despite the multitude of research exploring its causes, definitive causes of schizophrenia and EOS in particular remain elusive. As individuals with schizophrenia present a variety of symptoms at different stages of life under different
circumstances, it is unlikely to find a single cause for schizophrenia, including EOS. This observation is consistent with the hypothesis that “schizophrenia is probably neither a single disease entity and nor is it a circumscribed syndrome – it is likely to be a conglomeration of phenotypically similar disease entities and syndromes” (Tandon, Nasrallah, & Keshavan, 2009, p. 1). Researchers generally agree on a multifaceted etiological model of schizophrenia, including genetic, neurobiological, neuroanatomical mechanisms, and environmental factors. Future studies are needed to clarify and specify the nature of the complex interplay among the different factors and their unique contribution to the development of schizophrenia in general and EOS in particular.
Identifying, Assessing, and Treating Early Onset Schizophrenia at School
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