

An Integrative Feedback Model of Schizophrenia

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Table of Contents

Abstract.....	3
Introduction.....	4
Schizophrenia- Research and Findings.....	6
General Overview of Schizophrenia as a Disease.....	6
Environmental, Social, and Interpersonal Factors.....	8
Genetics and Constitutional Factors.....	14
Central Nervous System	19
Existing Models.....	30
Critical Discussion of Existing Models.....	36
An Integrative Feedback Model of Schizophrenia.....	39
Clinical and Research Applications.....	44
Schematic of Integrative Feedback Model.....	45
References.....	46

Abstract

This paper presents a cross-disciplinary model, integrating the major findings of the past 40 years, to develop a more comprehensive view of the etiology and development of schizophrenia. A Literature Review is presented to expand on research covering each of the variables of the model, including genetic, neurological, and environmental. The model presented is a conceptual model intended to depict the relationship of various variables that place individuals at risk or protect them from developing schizophrenia. The model utilizes the concept of a feedback loop, which articulates the need to conceptualize the development of the disorder as being in a continuous state of interaction with all relevant variables. Consistent with this continuous interaction, this model assumes schizophrenia develops through multiple pathways. This is critical to an understanding of a disorder like schizophrenia that does not always have a pure genetic, neurological, or environmental source of causation. This model is intended as a conceptual tool to develop testable hypotheses for the purpose of developing potentially valuable solutions, such as early intervention programs.

Introduction

In the quest to understand the etiology and development of schizophrenia, many biological and environmental factors have been studied. The prevailing attitudes for the etiology and development of this disorder have differed across time and scientific discipline. In particular the latter shapes whether researchers emphasize biological bases versus environmental influences. Furthermore, our knowledge base regarding this disorder and the functioning of the human body has grown tremendously since the time of Kraepelin and Freud. Technology, such as neuroimaging, has allowed us to study and understand the human body in ways that have significantly altered the face of mental health sciences. Interpretation of raw data has greatly improved with the advent of new statistical models (McGuffin, 2003). These and other developments within science have contributed to the creation of many new fields of study. There has been an expansion of fields of study within the mental health sciences including neuropsychology, clinical psychology, molecular genetics, and so on. A consequence of the growing number of fields within science is that the developments within each framework often remain isolated from one another, despite having considerable implications for the understanding and treatment of mental disorders.

The etiology and development of schizophrenia remains elusive, in that no single field has been able to thoroughly explain the etiology and development of the disorder within its framework. Today, the fields of molecular genetics, neuropsychology, clinical psychology, epidemiology, social work, and others have contributed to the ongoing quest to understand this perplexing disorder. Numerous models have been proposed from the framework of each of these fields, yet in my extensive investigation of online databases, I

found no model integrating data into a comprehensive framework to elucidate the etiology and development of schizophrenia.

A central concept of the model that is presented in this paper is the relationship between brain plasticity and the development of schizophrenia. Generally, brain plasticity receives little or no attention in the literature on schizophrenia. Brain plasticity is important because it addresses the constant interface of neural structure with environmental and biological factors outside the central nervous system. Consequently, it impacts the entire system of the individual, psychologically and physiologically.

This thesis presents a cross-disciplinary model that integrates major findings of the past 40 years to develop a more comprehensive view of the etiology and development of schizophrenia. Because each discipline's contribution is essential to the understanding of schizophrenia as a whole, it is necessary to use a cross-disciplinary approach. There is a detailed explanation of how the findings from these different fields of study relate to one another and can be integrated as well as an explanation of the strengths and limitations of the model. Also discussed is how the model can function as a preventative tool for those at risk of developing schizophrenia.

Schizophrenia- Research and Findings

General Overview of Schizophrenia as a Disease

Kraepelin is often credited with being the first to describe schizophrenia in terms used by modern medicine (Hollis, 2000). Kraepelin viewed schizophrenia as an illness with a chronic progressive course and referred to the disease as dementia praecox (Mueser, 2004). Bleuler is credited with specifying the core symptoms of the disorder, specifically those impacting thinking, affect, goal-directed activity, and social interaction (Mueser, 2004). Currently, clinicians view schizophrenia as a spectrum disorder, in that variability among sets of core symptoms occurs among individuals (Liddle, 1987; Preston, 2004). These set traits include positive, negative and disorganized symptoms (Liddle, 1987; Preston, 2004). Identifying schizophrenia based on concrete and universally accepted criteria can often appear subjective (Mueser, 2004). Yet, the *Diagnostic and Statistical Manual (DSM)* and the *International Classification of Diseases (ICD)* are commonly referred to as the standards for criteria and have high levels of statistical reliability.

The *DSM-IV* describes schizophrenia as a disorder with a course of at least 6 months, and at least 1 month of either disorganized or positive symptoms. Positive symptoms involve delusions and/or hallucinations. Disorganized symptoms include those affecting thinking or behaviors. Thinking can be observed through the speech of a person, such as loose associations, or tangential thoughts. Disorganized behaviors may include contextually inappropriate responses (e.g., laughter at a funeral), inappropriate or odd dress, unpredictable and apparently spontaneous agitation, talking to oneself, catatonia and so on. The *DSM-IV* incorporates disorganized symptoms under the rubric

of positive symptoms and notes that it is often considered the most important differentiating factor when attempting to diagnose for schizophrenia. Negative symptoms are also considered when discussing the diagnosis of schizophrenia. Yet, negative symptoms do not differentiate between individuals with schizophrenia and those with other disorders (e.g., Depression). These symptoms include affective flattening (restricted range and intensity of emotion), avolition (lack of goal-directed activity), and/or alogia (paucity of speech). In addition, the person shows significant deficits in a variety of areas of life functioning, including occupational, educational, social, financial, and daily living skills.

Schizophrenia is often a debilitating mental illness for those affected and ranks among the top 10 leading causes of long-term disability in the world (Mueser, 2004). In the United States, the yearly incidence of schizophrenia ranges between 0.5 to 5.0 per 10000 persons, with a lifetime prevalence of about 0.5% to 1.5% (*DSM-IV*, 2000). The World Health Organization finds similar rates of incidence across world populations (Mueser, 2004). In general, age of onset tends to occur in late adolescence through the early 30s (*DSM-IV*, 2000). Schizophrenia has been observed across the spectrum of ages, with earliest reported onset being 5 years of age (*DSM-IV*, 2000). Other trends indicate that women tend to have a later age of onset than men do (Mueser, 2004). From data gathered in the U.S. and Great Britain, over-diagnosis occurs more frequently among minority patients. In the U.S., over-diagnosis occurs most frequently among African-Americans and Asian-Americans.

The course of the disorder varies across the population; in some people, it is abrupt whereas others experience a more gradual course leading to positive symptoms

(*DSM-IV*, 2000). Specifically, women tend to have a more benign course of illness, including fewer hospitalizations and better social functioning (Mueser, 2004). Most individuals present with prodromal symptoms (i.e., social withdrawal, unusual behaviors, etc...) with a gradual exacerbation of these symptoms. Others observe that the initial phase includes symptoms more consistent with depression (Mueser, 2004). Research also indicates that individuals presenting with positive symptoms earlier in their illness tend to have a poorer long-term prognosis (*DSM-IV*, 2000). Once positive symptoms manifest, the progression of the disorder varies substantially by individual (*DSM-IV*, 2000). Some individuals show no remission of positive symptoms, others show partial remission, whereas others appear to have a full remission with a return to premorbid functioning (*DSM-IV*, 2000). Factors that are commonly understood to impact the persistence of the disorder include, poor premorbid functioning, being male, poor insight, neurological abnormalities, early age of onset, delay in receiving treatment, poor treatment compliance, poor neurological functioning, and family history of schizophrenia (*DSM-IV*, 2000).

Environment, Social, and Interpersonal Influences

As is discussed in later sections, genetic mutations and neurological insults are implicated in the etiology and development of schizophrenia. It has been observed that these genetic and neurological impairments only manifest themselves as schizophrenia under the impact of environmental stressors (Berner, 2002). Many researchers argue that genetic and neurological influences create a predisposition or vulnerability for the disorder, whereas environmental factors are likely required for an individual to develop schizophrenia (Beebe, 2003; Gourion, 2004; Green, 1998; Read, 2001). The following

sections will introduce many of the environmental stressors implicated in the development and etiology of schizophrenia. Many of these studies are based on findings from several High-Risk Longitudinal Studies that involved access to large sets of data.

Early separation and institutionalization. The role of early separation of a child from his or her biological parents has been of particular interest within the field of psychology. Separation can involve the loss of a parent through death or through the institutionalization of the parent (e.g., hospital) or child (e.g., orphanage, foster care). This particular environmental stress has been associated with the development of psychopathology both from theoretical and data based publications. Agid (1999) showed that 29.1% of patients with major depression, 17.7% of those with bipolar disorder and 22.4% of schizophrenia patients had experienced a loss of a parent before the age of 17 years, compared to 7.6-7.9% of control subjects. Patients in the study were matched to control subjects on a number of variables to assure that findings would not be a consequence of different base risks for early parental loss (Agid, 1999). Based on studies of children reared in Romanian orphanages, data indicates that institutionalization affects all aspects of a child's development, but does not necessarily always lead to psychopathology (MacLean, 2003). MacLean (2003) offered that the contribution of negative post-institutional environments increases the risk of psychopathology.

On the basis of the 1962 Copenhagen High-Risk Study, researchers concluded that individuals who experienced both maternal absence and institutionalization (orphanage) showed the greatest risk for developing the disorder; this was true particularly in males (Walker, 1981). The same researchers did not find paternal and maternal separation as predictors of later schizophrenia when the child was placed in

foster care or with relatives (Walker, 1981). From these results, it appears that separation not involving institutionalization of the child in state-run facilities may be a protective factor. Protective factors are those environmental effects that appear to prevent the expression of this disorder. This will be a component of the model presented later in this paper.

Additionally, Higgins (1997) studied differences in the adult expression of schizophrenia among children raised by parents with schizophrenia and those who were separated. The outcome of this study showed that a slightly higher rate of psychopathology was observed among those raised apart from their mothers (Higgins, 1997). The severity of the illness among these mothers was suggested to be a key factor influencing the development of schizophrenia among their children (Higgins, 1997). Higgins (1997) noted that children were probably more likely to be given up or removed by child services when the parents were more psychotically disturbed, as evidenced by earlier age of hospitalization and possibly onset. In turn, this suggested to Higgins (1997) the possibility of a greater genetic predisposition for the illness among these children (Higgins, 1997). Yet the quality of the placement was not described in Higgin's study. This is important because research by Olin (1996) offers that the risk factor of a child who is genetically vulnerable for the development of schizophrenia can be reduced through placement with a positive foster family.

In light of the studies associating parental separation with the increased risk of developing schizophrenia, others have attempted to identify how different kinds of parental loss are associated with the symptom picture expressed in persons with schizophrenia. Furukawa et al. (1998) found differences across persons with

schizophrenia who had experienced a parental loss. Men who lost their father displayed fewer negative symptoms (Furukawa, 1998). Panic attacks were common among schizophrenic men who experienced separation from their mothers (Furukawa, 1998). Hallucinations were most common in schizophrenic women who experienced the loss of a father (Furukawa, 1998). Furukawa (1998) observed that due to the differences of symptom pictures manifested by individuals with schizophrenia who experienced a parental loss, there appears to be a pathoplastic effect occurring rather than a pathogenic process.

Rearing experiences. As noted above, negative rearing experiences either with a parent or in foster care appear to increase the risk of developing schizophrenia in children with a genetic risk for the disorder (Olin, 1996). Olin (1996) presented a number of studies that show a relationship between poor parenting and later psychopathology. Types of poor parenting involved inconsistent parenting, over-involvement, and hostility toward the child (Olin, 1996). Hamilton (1999) found that parents of children with schizophrenia were more likely to be verbally critical than were parents of depressed children or normal controls. Similarly, the Copenhagen 1962 High-Risk Project found persons with schizophrenia report less satisfactory relationships with their mothers and fathers than others (Olin, 1996). Additionally, the UCLA Family Project found that persons who later developed schizophrenia experienced parents who were unable to create and maintain a shared focus with the teenager (Olin, 1996). This project also found that these same children experienced higher rates of negative, critical, intrusive, and guilt inducing experiences from their parents (Olin, 1996). These experiences within the family were found to occur at higher rates among individuals with schizophrenia

spectrum disorders than in normal controls (Olin, 1996). Additionally, Olin (1996) and Bensten (1998) reported that a number of studies have consistently replicated findings showing that relapse is higher in individuals whose families are negative, critical, intrusive, and guilt inducing.

The findings presented above present some conceptual difficulties. Do negative family interactions promote the development of schizophrenia or is this a relational style pulled for as a consequence of the developing disorder? In regards to the majority of findings, it appears that people at risk of developing schizophrenia and raised in positive family environments, specifically those with positive expressions of affect, may be protected from the expression of this disorder (Isley, 1999; Olin, 1996; Schiffman, 2002). Furthermore, the evidence regarding relapse rates associated with poor caretaker-child relationships (Olin, 1996) suggests that family interactions play a direct role in the development and expression of the disorder.

Advanced pre-morbid symptoms preceding the onset of schizophrenia. Earlier investigations have shown that approximately one-third of schizophrenic patients exhibited obvious premorbid behavioral abnormalities (Cannon, 1997). Cannon (1997), in his study of patients with schizophrenia, found that those who later are affected with schizophrenia are impaired socially from a young age, with a noticeable deterioration during adolescence, and they show poor school adjustment, even when differences between groups in premorbid IQ are taken into account. Cannon et al. (1997) proposed that poor social adjustment in adolescence is an early manifestation of vulnerability to adult psychotic illness. A possible explanation is that pathogenic processes, possibly of neurodevelopmental origin, leading to psychosis in adulthood, can also predispose a

person to attentional difficulties, distorted perceptions, unusual thought processes, and decreased empathic ability, thus compromising social functioning.

Several studies on children with schizophrenia have found a mean IQ of between 80 and 85, with about one-third of cases having an IQ below 70 (Gilvarry, 1997). This represents a mean IQ score about 10 points lower than those reported in studies of adult schizophrenia (Gilvarry, 1997). Kremen et al. (1998) found that there is an increased risk of developing psychotic symptoms in adulthood for a subgroup of individuals with substantially greater than expected IQ declines during childhood. Other researchers have found that patients with schizophrenia and unaffected siblings, without other spectrum disorders, shared a neuropsychological deficit in verbal fluency (Hughes, 2005).

Hollis (2000) presented research suggesting that adolescents affected with schizophrenia have difficulties with cognitive tasks, especially those that make demands on short-term memory, working memory, processing speed, and selective and continuous attention. On the other hand, subjects did not display deficits in skills that were well-established prior to onset of the disorder (Hollis, 2000). Hollis (2000) observed that there seems to be a good correlation between negative symptoms and the above deficits, which affect frontal and executive functions. Yet, these deficits do not appear to be particular to the disorder of schizophrenia (Hollis, 2000). A similar correlation appears to be present with those affected with attention-deficit hyperactivity disorder (Hollis, 2000).

Summary of environmental risk factors. Erlenmeyer-Kimling (1993) attempted to identify early behaviors and emotional predictors of developing schizophrenia. These researchers found that attentional dysfunction, social isolation, and psychosis were all more common among subjects at risk for schizophrenia (Erlenmeyer-Kimling, 1993).

Likewise, Freedman et al. (1998) found difficulties with attention and physical anhedonia to be most highly associated with risk of developing this disorder. Risk factors were also identified by Olin (1996) as involving parent deviant communication, balanced warm family interactions, chronicity and severity of parent pathology, and socioeconomic status. Miller et al. (2002) studied adolescents and attempted to show certain behavioral abnormalities are related to mild psychotic symptoms and possibly the development of schizophrenia in adulthood. In Miller's (2002) study, the researchers found that children engaging in withdrawal and/or delinquent-aggressive behaviors were at increased risk of developing the disorder. Miller (2002) added that the most predictive symptom is isolated psychotic symptoms in those who are most likely to develop schizophrenia later in life.

Genetics and Constitutional Factors

Basics of genetics. One must understand genetics to comprehend and utilize the information contributed by this area of study. DNA is made up of two strands, one strand from each parent. These strands of DNA come together to form 46 different chromosomes (23 pairs). Approximately 3 billion base pairs of DNA (A-T, C-G) make up the different chromosomes (base pairs are like steps on a long ladder - the chromosome). Additionally, these base pairs form almost 40,000 different protein-coding genes. These proteins are essential in the formation of the thousands of different structures within the human organism, from insulin, connective tissue, neural structure, and so on. Interestingly, these protein-coding regions make up about 5% of the genome. The function of the rest of the genome is not completely understood, but it is thought to be generally directed toward regulation of transcription, translation, and replication of

genetic coding. As our understanding of genetics grows, it is likely that new information will increase and/or alter our current understanding of human function and disease processes.

Stretches of the chromosome that are responsible to produce one specific protein are called genes. When a mutation occurs on a gene, disease may manifest itself.

Therefore, it is logical that somewhere among the different pairs of chromosomes, a link to the possible cause of schizophrenia can be found. Whether it is a single gene or more likely the interaction of a number of different genes (McGuffin, 2003), researchers have begun to identify genes that may be implicated in the development of schizophrenia.

Genotype and phenotype are also important concepts that influence how we understand the development of disease. The genotype of an organism is the actual physical material made up of DNA that was passed to the organism by its parents at the organism's conception. Phenotype is the result of the interaction of genotype (a single gene or a number of interacting genes) and the environment. In other words, genetic codes passed to a child by its parents will change with the child's interaction with its environment. Moreover, even cloned individuals or identical twins, although identical in genotype, will differ from each other in phenotype because of variations in their developmental environments (McGuffin, 1995). Therefore no two people will be identical in appearance or traits, even if they share identical genotypes. The implication of this in schizophrenia research is significant, because multiple interacting forces are involved in the possible development of the disorder. Researchers have emphasized the focus of research on two broad areas, heredity and mutations resulting from factors in the environment.

Heredity. The genetic influences in the etiology and development of schizophrenia have been implicated for well over a hundred years (McGuffin, 1995). The first serious attempts to explore the genetic influences of schizophrenia began in the 1920s with Luxenberger and Rudin in Germany (McGuffin, 1995). Since these earlier years, it has been known that schizophrenia is more common within families than what is found in the general population (McGuffin, 1995). In the general population, the lifetime risk of developing schizophrenia is about 1% (McGuffin, 1995). Gottesman (1991) found that schizophrenia was 10 times higher in the siblings or offspring of schizophrenics. Gottesman's (1991) results are based on a consolidation of numerous European studies published between 1921 and 1987. The risk of developing schizophrenia within families increases with the number of first-degree family members affected. McGuffin (1995) noted that the risk of developing schizophrenia increases from about 10% to 16% when both a sibling and parent already have the disorder. This risk increases further when both parents have the disorder to about 46% (McGuffin, 1995). Olin and Mednick (1996) cited research that used broader inclusion criteria, which included a diagnosis of schizotypal personality. These findings indicate that when a broader inclusion criteria were used, risk of developing schizophrenia spectrum disorder increases across the board (Olin & Mednick, 1996).

Molden (1998) summarized findings from twin studies conducted across a similar period as Gottesman's research. Molden (1998) found a concordance rate of about 46% for monozygotic twins and a 16% concordance rate among fraternal twins. Although one might expect the concordance rates among monozygotic (identical) twins to be 100%, one must remember that genotypes are altered as they interact with the environment. In

the years to come, researchers may better understand what environmental factors increase the risk or help prevent the expression of the schizophrenia.

Unlike Huntington's disease, cystic fibrosis, and other diseases, the risk of developing schizophrenia does not follow a Mendelian pattern of transmission (McGuffin, 1995). Some families have many affected members with schizophrenia, but according to McGuffin (1995), this is the exception rather than the rule. Additionally, many individuals affected with schizophrenia have no history of the illness in either first or second-degree relatives (McGuffin, 1995). One study has shown this number to be as high as 60% of individuals diagnosed with schizophrenia (McGuffin, 1995). This presents many challenges in understanding the role genetics play in the etiology and development of schizophrenia. If schizophrenia behaved similarly to Huntington's disease, then a gene with its protein-encoded functions would likely lead to the development of schizophrenia and create the kind of cerebral alterations observed in many persons with schizophrenia. However, researchers working within this framework have not been successful to date in identifying the exact location of a single gene or the interaction of multiple genes responsible for the development of the disorder (McGuffin, 1995). Others have suggested the concept of incomplete penetrance can be used to explain the trend of not following a Mendelian pattern of transmission (McGuffin, 1995). These authors endorse the possibility of locating a single gene responsible at the genotypic level (McGuffin, 1995). Other researchers posit that genes present a vulnerability to the development of the disorder but require a set of environmental effects (McGuffin, 1995) for schizophrenic symptomatology to manifest.

Gene linkage studies. Gene linkage studies is part of a research method called positional cloning. This method is used to identify regions on a chromosome that contains a susceptibility gene for the disorder (McGuffin, 2003). Various methods are utilized to narrow down regions until a specific gene is identified (McGuffin, 2003). Many researchers have identified numerous genes, but no linkage study has consistently been replicable across other studies (DeLisi, 2002; Jordan, 1998). Regardless, DeLisi (2002) suggested that the positive findings on chromosomes 2, 10, and 22 should be pursued. In particular, on chromosome 22 is the protein-encoded gene COMT that is involved in the functioning of dopamine, epinephrine, and norepinephrine (Shifman, 2002). This gene has been implicated in part due to what is known about the functioning of anti-psychotic medications. Shifman (2002) researched a large sample of relatively homogenous probands of Ashkenazi Jews and he found significant associations between this gene and schizophrenia. McGuffin (2003) suggested that evidence of susceptibility genes located on chromosomes 8, 13, and 22 are convincing. The National Center for Biotechnology Information has compiled a list of possible schizophrenia susceptibility loci from a large number of studies (www.ncbi.nlm.nih.gov). The list is extensive, representing more than just the chromosomes noted by DeLisi (2002) and McGuffin (2003). Despite the large number of possible schizophrenia susceptibility loci, gene linkage studies may be narrowing the search.

Researchers have also performed linkage studies comparing schizophrenic families (probands) with controls (McGuffin, 2003). Interestingly, the protein generating genes identified through these studies have all been involved in glutamatergic transmission in the brain (McGuffin, 2003). When the process of glutamatergic

neurotransmission is intensified or excessive, synaptic and neuronal degeneration may occur; in other words, cell death occurs in the brain (Bahr, 2002). This suggests support for the results of various neuroimaging studies and post-mortem studies, which have observed atrophy of the cortex (Beebe, 2003; Read, 2001) and cell pruning (Siekmeier, 2002). As can be seen, a plethora of information is emerging through gene linkage studies. According to McGuffin (2003), the direction of existing research suggests that genes do not play an exclusive role in the development of schizophrenia. The impact of environment must also be examined (McGuffin, 2003).

Central Nervous System

The central nervous system, in particular the brain, acts as the middleman between environmental and genetic influences. As noted at the end of the last segment, genes may play a significant role in the etiology and development of schizophrenia. For example, the mutations of the COMT gene on chromosome 22 would be consistent with neurological evidence found in studies comparing persons with schizophrenia with controls (Shifman, 2002). In addition, a great deal of neurological research has focused on the impact of environmental effects that have an impact on neural structures.

Traumatic brain injuries. Although much remains unknown regarding the etiological time line of schizophrenia, neurological deficits resulting from a number of pathways have direct correlation with psychosis. This damage may result from either genetic or environmental etiologies. A number of studies within the fields of neuropsychology, psychology, and neurology have identified various conditions that may cause schizophrenic-like psychosis: myelination as in multiple sclerosis (Grossman, 2003; Prigatano, 1992), hyponatremia – iron deficiency (Nadler, 1984), epilepsy (Adachi,

2002), Huntington's Disease (Prigatano, 1992), and traumatic brain injury (Fujii 2002; Sachdev, 2001).

Traumatic brain injuries (TBI), which have been linked to schizophrenic-like psychosis (SLP), are correlated well with many cognitive, emotional, and behavioral deficits (Newburn, 1998). TBI refers to damage to the brain resulting from an external force (Prigatano, 1992). Specifically, injuries that result in damage to the left temporal, right parietal, and frontal lobes are linked in studies to the development of schizophrenic-like psychosis (Fujii, 2002; Prigatano, 1992; Sachdev, 2001). Schizophrenics with TBI present with a distinct symptom picture when they are compared with non-TBI schizophrenics (Fujii, 2002; Sachdev, 2001). Patients with SLP display predominantly auditory hallucinations and paranoid delusions (Fujii, 2002; Sachdev, 2001), whereas negative symptoms, such as tangential thought, derailment of thought, blunted affect, and/or catatonia is mild or not present (Sachdev, 2001). Sachdev (2001) also found via regression analysis that a positive family history of psychosis and duration of loss of consciousness are the best predictors of SLP.

Individuals with SLP, resulting from TBI, have a mean age of onset of 26.3 years, a mean latency of 54.7 months after head injury, and usually a gradual onset with a subacute or chronic course (Sachdev, 2001). Fujii (2002) found on average that most individuals with SLP have a 1- to 2-year latency following head injury before schizophrenic-like psychosis develops. The delay of onset of psychosis observed by both Sachdev (2001) and Fujii (2002) has some important implications. Even with a direct and immediate insult to the cortex, symptoms of psychosis do not manifest immediately. Even in more traditional forms of schizophrenia, symptoms of psychosis usually do not

present in early childhood. Instead, a variety of prodromal symptoms, including behavioral, cognitive, and emotional characteristics, develop that predate the onset of psychosis. Prodromal symptoms are important because they suggest the presence of neurological deficiencies and alteration. The possible role of prodromal symptoms and latency of psychosis will be considered within the context of brain plasticity later in the paper.

Brain injury in general offers researchers with valuable information, which obviously would be completely unethical to gather with non-TBI subjects. TBI research gives us clues, if not direct evidence, of the particular regions of the brain responsible for the symptoms observed in those affected with schizophrenia. If TBI can replicate the symptoms of this disorder, then it is also logical to implicate other forms of brain injury, especially those that occur pre- and post-natally. Furthermore, TBI offers evidence that schizophrenia's etiology and development may evolve from multiple pathways, in addition to the influences of genetics.

Other neurological insults: Pre-natal. A variety of pre-natal complications have been studied for their possible role in the etiology and development of schizophrenia. In the Copenhagen 1962 High Risk Project, Mednick (1987) observed that individuals studied who later developed schizophrenia experienced significantly more complications in the period around the time of birth. Additionally, those who had a family history of schizophrenia and experienced periventricular damage increased their risk of developing schizophrenia later in life (Mednick, 1987). Periventricular damage usually occurs as a result of hypoxia or ischemia, which refers to the constriction of blood vessels in the brain causing the reduction of oxygen to the brain. Others, including Jones (1998) and

Cannon (2002), replicated these findings. Jones (1998) found that individuals who are affected with schizophrenia were generally born earlier and had lower birth weights. Cannon et al. (2002) completed a meta-analysis of existing studies on obstetric complications and its relationship to the development of schizophrenia. The authors of this study found significant differences between schizophrenic subjects and normal comparison groups (Cannon, 2002). The births of people with schizophrenia often involved diabetes in pregnancy, low birth weight, emergency cesarean section, congenital malformations, uterine atony, rhesus variables (comprising rhesus incompatibility, rhesus-negative mother, rhesus antibodies), asphyxia, bleeding in pregnancy, and pre-eclampsia (Cannon, 2002). It is possible that a genetic factor predisposes these individuals to develop neural and ventricle deficits that make them more sensitive to the stress of delivery (Olin, 1996).

Another possible obstetric complication that may be implicated in the development of schizophrenia is a mother's exposure to influenza during pregnancy. Contraction of influenza during the second trimester of pregnancy has been linked to the increased risk of developing schizophrenia (Olin, 1996). These results have been replicated in at least three other studies (Olin, 1996). Other researchers found a connection between influenza exposure, but their results indicate that future risk of developing schizophrenia was significant only for the first trimester (Brown, 2004). Brown's (2004) analysis revealed that the risk of developing schizophrenia is seven times higher for those born to mothers exposed to the influenza virus in the later part of the first trimester and earlier part of the second trimester. Inconsistent results in these and other studies raise questions regarding the validity of the findings. Yet, Green (1998)

emphasized that most of the research does suggest that infant exposure to a virus is correlated and therefore should be considered. Green (1998) hypothesized that hemolytic disease and brain damage may result in the infant of an infected mother due to the autoantibody production of the mother or the effects of Rhesus incompatibility between mother and fetus. This hypothesis is supported by data gathered through a perinatal project in Denmark (Green, 1998).

The brains of schizophrenic patients: Post-mortem and neuroimaging studies.

A number of studies have provided support for differences in the cortical structures of people with schizophrenia versus people without schizophrenia. Post-mortem studies of the brains of people with schizophrenia have indicated a couple of important findings. Green (1998) presented several studies showing that the brains of people with schizophrenia have abnormal cell orientation in both hemispheres. The brain cells in people not affected with schizophrenia were neatly aligned in rows (Green, 1998). On the other hand, the brain cells in those with schizophrenia showed significant disarray (Green, 1998). In other studies, researchers found that there may be a problem of cell migration, especially in the temporal and prefrontal regions of the brain, in persons with schizophrenia (Green, 1998). These studies show that cell distribution in the cortex of schizophrenics is denser in the deeper layers than it is in normal controls (Green, 1998). Green (1998) noted that because the brain develops from the inside out, these studies support the hypothesis that neurons failed to migrate as far as would be expected (Green 1998). The failure of cell migration inhibits the creation of optimal neural connections (Green, 1998). The result is an exacerbation of synaptic pruning, leading to even denser packing of cells deep within the cortex (Green, 1998). Synaptic pruning is the process

whereby a neuron selectively loses synaptic connections by withdrawing its dendritic branches (Green, 1998). The process of synaptic pruning results in less than optimal processing of a person's brain (Green, 1998). Green (1998) argued that failure for cells to migrate is most likely to have occurred during the second trimester of fetal development, rather than the result of institutionalization or medications. Rapoport (1999) offered additional data regarding the observed cortical atrophy in those affected with schizophrenia from early childhood. Specifically, Rapoport (1999) found that subjects with early-onset schizophrenia displayed a decrease in cortical gray matter volume during adolescence four times higher than normal subjects. Additionally, this atrophy reflected a disease process, in that it was a progressive deterioration of cortical tissue (Rapoport, 1999).

The various structural neuroimaging techniques, such as MRI, fMRI, rCBF (cerebral blood flow), CT, and PET have identified differences in the structure and functioning of the brain of those with schizophrenia. Neurological abnormalities observed in schizophrenics, include over-reactivity of the hypothalamic-pituitary-adrenal (HPA) axis; dopamine, norepinephrine, and serotonin abnormalities; and structural changes to the brain such as hippocampal damage, cerebral atrophy, ventricular enlargement, and reversed cerebral asymmetry (Beebe, 2003; Green, 1998; Read, 2001). Regarding most of the above findings, researchers have yet clearly identified if these are the cause or the consequence of schizophrenia (Grossman, 2003). Additionally, these findings are not consistent across the board; that is, the presence of these abnormalities differ across those affected with schizophrenia.