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# Neurodevelopmental Theories of Schizophrenia: Application to Late-Onset Schizophrenia

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## ABSTRACT

*A review of literature on the neurodevelopmental origins of schizophrenia is presented, with particular attention to neurodevelopmental processes in late-onset schizophrenia. Definitions of the term "neurodevelopmental" as used in schizophrenia literature are first provided. Next, evidence for the developmental origins of the neuropathology in schizophrenia is reviewed. This evidence includes studies of the associations between schizophrenia and neurodevelopmental brain aberrations, minor physical anomalies, obstetric complications, prenatal viral exposure, childhood neuromotor abnormalities, and pandysmaturation. A brief discussion of the predominant theories about the neurodevelopmental origins of schizophrenia is then provided. The concept and nature of "late-onset schizophrenia" is next defined and discussed. Finally, the neurodevelopmental literature is discussed in relation to the phenomenon of late-onset schizophrenia. Based on this review, we conclude that there exists a strong likelihood that late-onset schizophrenia involves neurodevelopmental processes.*

*Keywords: Psychosis, neurodegeneration, dementia, cognition, aging, developmental disabilities.*

## INTRODUCTION

While neurodevelopmental theories of schizophrenia have been increasingly popular over the past decade (Feinberg, 1983; Mednick, Cannon, 1991; Murray et al. 1992b; Weinberger, 1987), their potential application to late-onset schizophrenia (LOS) has generally been ignored or discounted (Murray et al. 1992b). Late-onset schizophrenia has been viewed as a neurodegenerative disorder involving unknown cerebral pathology which emerges late in life close to the time of onset of symptoms (Murray et al. 1992b). Recent research, however, suggests that many LOS patients have subtle but life-long premorbid abnormalities, e.g., childhood maladjustment, and presence of premorbid paranoid or schizoid personality traits (Jeste et al. 1995b). Although the severity of these premorbid aberrations is typically less than that observed among patients with early-onset schizophrenia (EOS), their early presence suggests that many LOS patients, similar to those with EOS, may have a neurodevelopmental component.

The following brief review discusses evidence rel-

evant to neurodevelopmental origin of schizophrenia in general, some of the predominant theoretical descriptions or speculations, as well as some summary comments toward integrating the neurodevelopmental perspective into an understanding of the emergency of schizophrenia in later life. A key component to this integration is the recognition that maturation (including changes in the brain) does not cease in early life, but rather continues throughout the lifespan. Greater appreciation of maturational changes occurring in later life permitting manifestation of LOS may also provide insight into the clinical expression and neuropathology of schizophrenia in general.

## Defining Neurodevelopmental Origins of Schizophrenia

Although not necessarily discounting the potential influence of psychosocial factors, neurodevelopmental models rest on the assumption that schizophrenia is primarily a disorder of the brain. The "developmental" part of the term neurodevelopmental has been used with at least

two different connotations in the literature. In most cases the term expresses the notion that the neuropathology underlying schizophrenia originated early in the development of the central nervous system (CNS), i.e., during the pre- or perinatal period (Murry et al. 1992b; Mednick, Cannon, 1991; Weinberger, 1995). In some cases, however, the emphasis is not placed in the early origins of the pathology, but rather on the importance of the maturational context in the unfolding or expression of the underlying pathology (Feinberg, 1983; Walker, 1994; Weinberger, 1987). These two meanings of the term neurodevelopmental are by no means mutually exclusive. The former may be important in understanding premorbid abnormalities, and the latter in understanding the delay of full clinical onset until later in life.

#### **EVIDENCE FOR DEVELOPMENTALLY BASED NEUROPATHOLOGY IN SCHIZOPHRENIA**

There are several lines of evidence suggesting that the neuropathology underlying schizophrenia often originates in early CNS development. In general, this literature has not addressed the potential effects of aging or late age of onset. Nonetheless, there are several areas worthy of investigation with older schizophrenia patients.

##### Brains of Patients With Schizophrenia

Many studies of the brains of patients with schizophrenia (either in vivo via neuroimaging, or Post-mortem) suggest that structural abnormalities associated with schizophrenia are often non-progressive and of early origin. For example, while many schizophrenia patients appear to have a slight enlargement of the lateral and third ventricles (Suddath et al. 1990; Schulz et al. 1983), these enlargements are not associated with duration of illness (Nasrallah et al. 1986; Weinberger et al. 1987), nor do they appear to change over long-term follow-up (Pillowsky et al. 1988). Similarly, several studies have shown that the brains of schizophrenia patients tend to have slightly less volume and weight than healthy normal subjects (Nasrallah, 1993), but post-mortem studies suggest that these structural changes can occur in the absence of significant gliosis (Bogerts,

1993; Bruton et al. 1990; Roberts et al. 1986). Since gliosis is associated with neurodegenerative processes, its absence would suggest that structural abnormalities originated during early developmental period. Perhaps the most interesting data, however, come from reports of abnormalities in the cytoarchitecture in certain regions in the brains of schizophrenia patients, suggesting a disruption in neuronal migration during the early brain development (Jakob, Beckmann, 1986; Kovelman, Scheibel, 1984). Thus, in at least some cases, it appears that there are abnormalities in the brains of schizophrenia patients that were present very early in development.

##### Minor Physical Anomalies

Minor physical anomalies (MPAs) are mild congenital abnormalities, such as high palate, "electric hair", adherent ear lobes, and the like (Waldrop et al. 1968). Since MPAs and the CNS both derive from the ectodermal layer, MPAs are thought to reflect aberrations in the CNS development during the first or second trimester (Green et al. 1994; Dykes et al. 1991).

There have been several reports of an increased frequency of MPAs among schizophrenia patients (Green et al. 1994; Gualtieri et al. 1982; Guy et al. 1983; Lohr, Flynn, 1993). For example, Green et al. (1994) found that inpatients with schizophrenia had significantly more MPAs than several comparison groups including patients' psychiatrically healthy siblings, a group of inpatients that schizophrenia patients with higher numbers of MPAs tend to have worse premorbid functioning (Guy et al. 1983). Overall, findings from studies of MPAs among schizophrenia patients are consistent with a neurodevelopmental model, although there have been a few reports failing to find a strong association between schizophrenia and MPAs (Alexander et al. 1994; Cantor-Graae et al. 1994b).

##### Obstetric Complications

Evidence of a link between obstetric complications and schizophrenia was reported as early as 1939 (Mednick, Cannon, 1991). Unfortunately, this literature is marked by inconsistencies. For example, some authors have suggested that the

association between obstetric complications and schizophrenia is strongest among patients lacking a strong genetic predisposition to the disorder (Cantor-Graae et al. 1994; Heyman, Murray, 1992; O'Callaghan et al. 1990), while others have concluded that obstetric complications are most strongly associated with schizophrenia in genetically high-risk patients (Mednick, Cannon, 1991). The specific nature of relevant complications and their etiological role also remain points of controversy. Nonetheless, the weight of evidence suggests a slightly higher incidence of obstetric complications among subjects who later develop schizophrenia. Thus, it is possible that some neurodevelopmental lesions originate or are at least exacerbated by obstetric complications (for more extensive reviews see (Dykes et al. 1991; McNeil, 1988; Weinberger, 1995).

#### Increased Risk Associated with Prenatal Viral Exposure

Mednick et al. (1988) found a significant elevation in the incidence of schizophrenia among Helsinki residents whose mothers had been in their second trimester of gestation during a 1957 influenza epidemic. Replication attempts have been mixed, with some investigators reporting positive results (Adams et al. 1993; Kunugi et al. 1995; O'Callaghan et al. 1991) while others found no such association (Crow, Done, 1992; Susser et al. 1994).

The factors mediating these inconsistent findings are unclear at this time, but may partially relate to differences in sampling techniques, rigidity of diagnostic criteria, or the nature of the viral infection itself. The precise mechanism by which viral infections might increase the risk for schizophrenia is also unclear, although current hypotheses tend to focus on the effects on neuronal development. For example, Murray and his colleagues (Murray et al. 1992a) have suggested that the genetic vulnerability for schizophrenia may involve a predisposition to react adversely to maternal influenza virus such that the activated immunological processes lead to disorganized development of the fetal brain. A more specific model was proposed by Conrad and Scheibel (1987). They speculated that neuraminidase, an enzyme associated with certain

viruses, alters sialic acid concentration, in turn changing the binding properties of the cell adhesion molecules involved in normal neuronal migration and alignment. Thus, the neuronal misalignment observed in some areas of schizophrenia patients' brains (Jakob, Beckmann, 1986; Kovelman, Scheibel, 1984) may be at least partially attributable to prenatal viral exposure. Further research on these lines is warranted.

#### Childhood Neuromotor Abnormalities and Pandysmaturation

Walker and colleagues have conducted a series of studies in which they assessed the motor functioning of children who later developed schizophrenia as adults (Walker, Lewine, 1989; Walker et al. 1994). These assessments were made by observing old home movies made of the schizophrenia patients and comparison subjects when they were children. In their initial study the investigators found that raters blind to diagnosis were able to distinguish pre-schizophrenia children younger than 8 years old from their healthy siblings at above chance levels (Walker, Lewine, 1989). Furthermore, the pre-schizophrenia children were apparently identifiable by simple gross observation, since raters had been given no specific criteria on which to make their judgments. In a subsequent study, Walker and colleagues found that the pre-schizophrenia children had higher rates of neuromotor abnormalities, and worse motor skills when compared to either their healthy siblings or to a group of children who later developed mood disorders (Walker et al. 1994).

A related line of evidence has been reported in a series of longitudinal reports by Fish and her colleagues (Fish, 1987; Fish et al. 1992). They followed a cohort of infants of mothers with schizophrenia since the 1950's, and assessed them when infants for a condition labeled "pandysmaturation". According to Fish, Pandysmaturation is a marker for an inherited neurointegrative defect, and is characterized by a transient retardation of gross motor or visual-motor development (followed by a return to normal levels), which is accompanied by a parallel transient

retardation in skeletal growth. Fish's results suggest that infants exhibiting pandysmaturation are at a higher risk for "schizophrenia spectrum" disorders in adolescence or adulthood, such as, schizophrenia, or schizotypal or paranoid personality.

### Conclusions

While controversies remain, the weight of evidence from the above reports suggests that the underlying neuropathology associated with schizophrenia can long pre-date the onset of clinical symptoms. Nonetheless, several questions remain unanswered. For example what is the precise nature of the neurodevelopmental lesion(s)? Are all the cases of schizophrenia neurodevelopmental? How might neurodevelopmental and neurodegenerative processes interact? Some of the prominent theories of speculations on such issues are reviewed in the next section.

## **THEORIES AND MUSINGS ABOUT NEURODEVELOPMENTAL ORIGINS OF SCHIZOPHRENIA**

### 'Synaptic Pruning'

One of the first neurodevelopmental theories of schizophrenia was proposed by Feinberg (Feinberg, 1983). Feinberg's theory was based on the observation that the clinical symptoms of schizophrenia most frequently emerged in late adolescence or early adulthood. He presented evidence that there was a major rearrangement of brain structures and function during adolescence, and that a part of this reorganization involved a programmed reduction in synaptic density ("synaptic pruning"). Based on these data, he proposed that the appearance of schizophrenic symptoms might reflect a defect in the synaptic pruning process involving elimination of either too many, too few, or the wrong synapses during adolescence. Although this theory may be viewed as being somewhat speculative, animal model studies have tended to support Feinberg's general assertions regarding adolescent brain reorganization and synaptic pruning (Keshavan et al. 1994).

### Genetic, Teratogenic, and Psychosocial Interactions

Mednick, et al (1991) proposed a "two-hit

hypothesis" of schizophrenia genetic, incorporating teratogenic, and psychosocial variables. According to Mednick and his colleagues, the first necessary "hit" for schizophrenia is a disruption in neural development during the second gestational trimester. According to these authors, the disruption in neural developmental may be largely under genetic control, but may also be mimicked or exacerbated by a viral infection, toxins, or other teratogenic exposure during the second trimester. By itself this first hit does not lead to full schizophrenia, although such an individual may develop "schizophrenia spectrum traits", such as a schizoid or schizotypal personality disorder.

According to Mednick et al (1991), development of full schizophrenia requires a "second hit" which may come in either of two forms: (a) obstetric complications, or (b) disruptions in the early social environment. The form of this second hit may determine the extent to which negative versus positive symptoms predominate in the patient's early symptom profile. For example, these authors argue that delivery complications are associated with a widening of the third and lateral ventricles, and that damage to the periventricular tissue of the third ventricle leads to a reduction in autonomic responsiveness, which is associated with negative symptoms of schizophrenia. In contrast, Mednick et al. (1991) assert that a stressful early family rearing environment can lead to autonomic hyperresponsiveness, and this "second hit" may lead to a predominance of positive symptoms.

### Maturation and Prior Lesions

Weinberger (1987) proposed an interaction between pre-existing neurodevelopmental aberrations and normal maturation. According to this model, a lesion in the afferent dopaminergic projections to the prefrontal cortex leads to dopaminergic underactivity in the prefrontal cortex. Underactivity of the prefrontal cortical neurons exerting inhibitory control over mesolimbic further suggested that negative symptoms were related to the dopamine underactivity in the dorsolateral prefrontal cortex, while positive symptoms were a function of the

overactivity of the mesolimbic dopamine neurons.

Weinberger (1987) suggested several examples of ways in which maturational changes might interact with an underlying lesion to yield different symptom presentations. For example, he noted that the dorsolateral prefrontal cortex did not reach full maturity until late adolescence or early adulthood. Therefore, a prefrontal lesion origination early in neurodevelopment might not become fully apparent until this area normally reaches relative maturity. Furthermore, the period between adolescence and early adulthood is typically one of heightened psychosocial stress, and is the time when brain dopamine activity reached its peak. If, as Weinberger suggests, this mesolimbic-prefrontal circuit is involved in adaptation and response to stress, then a lesion causing prefrontal dopamine underactivity may hinder physiological and behavioral adaptation, which might lead to a chain reaction culmination in schizophrenic decompensation. Furthermore, the waning of positive symptoms, and increase in prominence of negative symptoms often observed among older schizophrenia patients may both reflect declines in dopamine activity associated with normal aging.

#### Conclusions

The above theories illustrate some of the possible means by which developmental/maturational processes may interact with genetic, environmental, and psychosocial factors. Feinberg's and Weinberger's theories attempt to explain the delay of the onset of schizophrenia until adolescence or early adulthood. It is possible that similar process might explain the phenomenon of late onset schizophrenia.

#### WHAT IS "LATE-ONSET SCHIZOPHRENIA"?

The concept of LOS has had a long and controversial history. Although both Kraepelin and Bleuler recognized that schizophrenic symptoms did not appear in some patients until older adulthood, LOS has historically been an underrecognized entity (Jeste et al 1995a; Jeste et al. 1995c). For example, the DSM III-R (American Psychiatric Association, 1980) restricted the diagnosis of schizophrenia to patients with onset of illness before age 45 years. This age restriction was dropped

in the DSM-III-R (American Psychiatric Association, 1987), and a specifier "late-onset" was added for patients in whom clinical symptoms first appeared after age 45. The DSM - IV also has no upper age restriction in the diagnosis of schizophrenia, although the specifier "late-onset" has been eliminated (American Psychiatric Association, 1994). Despite the recent formal recognition of LOS, schizophrenia with onset in later life remains an understudied phenomenon.

Few authors have discussed the relevance of neurodevelopmental theories to LOS. An exception is Murray and his colleagues (1992b) who suggested that LOS often represents an underlying degenerative cerebral pathology. They stated that "Such patients, usually present after the age of 60 and have good premorbid functioning in the intellectual and occupational spheres. It is implausible, therefore, that they suffer from a neurodevelopmental disorder" (p.366). Based on preliminary research comparing the clinical and neuropsychological characteristics of EOS and LOS patients (Jeste et al. 1995b), however, we believe that it is premature to discount the plausibility of neurodevelopmental process in LOS.

Jeste et al. (1995b) compared the clinical and neuropsychological characteristics of patients with DSM - III - R diagnoses of LOS or EOS, as well as a group of normal comparison subjects, all over the age of 45 years. Patients with LOS were more likely than those with EOS, to be female, to manifest paranoid subtype, and to have had better premorbid functioning in the adolescence and early adulthood. Nonetheless, patients with LOS and EOS had similar ratings of childhood maladjustment, and rates of family history of schizophrenia. They were also similar to each other, and different from the normal comparison subjects, in terms of psychopathology ratings and overall pattern of neuropsychological impairment. The premorbid personality of the LOS patients sometimes had schizoid or paranoid traits, although not meeting the DSM - III - R criteria for personality disorders. The similarities in childhood maladjustment, family history, and neuropsychological

impairment suggest that LOS might have neurodevelopmental origins similar to EOS (Jeste et al. 1995a; Jeste et al 1995c).

### DISCUSSION

Any attempt to develop a comprehensive model of schizophrenia is hindered by the heterogeneous nature of this disorder. Patients with schizophrenia differ in clinical presentation (American Psychiatric Association, 1994), age of onset (Jeste et al. 1995c), and outcome (Marinow, 1986). Therefore, it is doubtful that a single etiological model can explain all the cases currently subsumed under the label "schizophrenia". Perhaps a more realistic approach is to attempt to identify factors underlying the variability among a sizable proportion of schizophrenia patients. We believe that an appreciation of both neurodevelopmental and neurodegenerative factors would be helpful in regard to the latter goal, particularly in the case of LOS.

A strict dichotomy between neurodevelopmental and neurodegenerative processes is probably faulty (Bilder et al. 1995). Rather, one might ask for each patient: How much of the observed dysfunction is attributable to neurodevelopmental factors, and how much is neurodegenerative in origin? One route to answering this question may be an examination of the lifetime course of cognitive decline. For example, Bilder and his colleagues have reported studies employing archival documents, such as childhood school records, which suggest that many schizophrenia patients evidence early mild premorbid impairment in cognitive abilities (Bilder et al, 1992, Bilder et al. 1995, Reiter et al. 1995). This lower functioning is present in many schizophrenia children as early as the first grade, strongly suggesting a neurodevelopmental origin (Reiter et al. 1995). In addition to early subtle premorbid cognitive impairment, there is often a phase of a second cognitive decline associated with the first 5 to 10 years after the onset of active schizophrenia (Bilder et al. 1992; Schwartzman, Douglas, 1962). This additional decline may reflect the onset of a neurodegenerative process, or transient illness-related neurobiological changes.

Among a minority of schizophrenia patients there is a continued deterioration in functioning once schizophrenic symptoms have manifested, as per Kraepelinian notion of "dementia praecox". Chronically hospitalized patients with unremitting clinical symptoms appear to be the most likely ones to show this pattern of progressive decline cognitive decline (Bilder et al. 1992; Davidson, Haroutunian, 1995; Heaton, Drexler, 1987). This continued decline could reflect a progressive neuropathologic process, or as some have suggested (Davidson, Haroutunian, 1995), the progressive cognitive decline might simply reflect an interaction between a static preexisting lesion and normal aging. In any case, the presence of progressive dementia in no way precludes a neurodevelopmental component. There are many neurodevelopmental disorders, such as Down's syndrome, which place patients at significant risk for subsequent neurodegenerative dementias, e.g., Alzheimer's disease.

In the majority of patients with schizophrenia, however, cognitive impairment appears to level off after the first few years of illness, with some patients even showing partial recovery of abilities (Heaton, Drexler, 1987; Heaton et al. 1994; Hoff et al. 1991; Sweeney et al 1991). Thus in general, schizophrenia does not appear to be best characterized as a progressive neurodegenerative disorder (Goldberg et al. 1993; Hyde et al 1994). Furthermore, as the prior research discussed above attests, it appears likely that neurodevelopmental process are usually involved at least to some degree in most patients with schizophrenia. Given its neurodevelopmental origins, the delay and variability in age of onset require explanation.

### Moderators of Onset Variability

It is conceivable that early and late-onset schizophrenia are distinct; however, the similarities in the family history, clinical features, and neuropsychological functioning between EOS and LOS patients suggest that this is not the case (Jeste et al. 1995b). There has been little research on neurodevelopmental processes in LOS. Nonetheless, to the degree that LOS does involve neurodevelopmental lesions, how could the delay of

onset until later life be understood?

Analogous to the maturational factors discussed by Feinberg (1983) and Weinberger (1987) which may explain the delay of onset until adolescence, there are other age related changes occurring later in life which may explain the emergence of late-onset psychosis in vulnerable individuals (i.e., those with the neurodevelopmental lesions) One route to understanding such later life maturational changes may be exploring the tendency for schizophrenia to have a later age of onset among women compared to men (Harris, Jeste, 1988). In part, the delay of onset in women may relate to a premenopausal protection provided by estrogen (Harris et al.1995). In addition, some authors have suggested an interaction between gender and decreased in dopamine receptor density with aging. Specifically, men appear to lose D2 receptors faster than women, leaving women with a relative excess in older age. Interested readers are referred to Harris et al. (1995) for a detailed review of gender influences in schizophrenia.

Another factor which may be involved in the delay of the clinical onset of schizophrenia may be patients' premorbid brain reserve capacity (Satz, 1993). It is possible that early lesions are silent in patients until they have passed some threshold of neuropathological loss. Normal aging, and/ or the onset of a secondary neurodegenerative disorder, could deplete the reserve that was protective for some patients in earlier life. For example, in a recent neuroimaging study, Corey-Bloom and her colleagues (Corey-Bloom et al. 1995) found that LOS patients had significantly larger thalamic volumes compared to the EOS patients. The implications of these preliminary findings are not fully clear at present, but it is possible the larger thalamus in some way relates to premorbid reserve. "Brain reserve" is admittedly a difficult construct to measure, but further indirect assessment of the brain reserve hypothesis could be conducted through examination of the relationships between age of onset of illness and familial/ parental functioning through studies of monozygotic twins.

### CONCLUSIONS

Based on the above literature, it appears that

LOS, similar to EOS, is likely to have neurodevelopmental origins. Empirical research is needed to clearly document the neurodevelopmental origins of LOS, but the premorbid and familial similarities between the EOS and LOS patients speak to common origins. Better understanding of the reasons why some patients do not manifest schizophrenia until late in life may prove important in understanding and treating schizophrenia in general.

There are clearly a number of issues needing further research. When the apparent protective role of estrogen is better understood, prophylactic treatments for high-risk individuals may become more feasible. Similarly, appreciation of the distinction between neurodevelopmental and neurodegenerative cognitive declines, could be helpful in influencing the functional outcome of schizophrenia. For example, it is possible that those experiencing an acute decline associated with the onset of clinical symptoms may benefit from cognitive rehabilitation techniques similar to those employed with head injury patients. In contrast, identification of premorbid deficits in high-risk individuals may allow early intervention. Further studies of these issues promise many potential benefits.

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