

# A Review of the Neurodevelopmental Hypothesis of Schizophrenia

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## INTRODUCTION

The complexity and heterogeneity of schizophrenia means that even its definition and diagnostic criteria are cause for debate, therefore the search for a satisfactory aetiological theory of this condition would always be challenging. This essay will introduce the neurodevelopmental theory in the context of other proposed aetiologies, presenting the evidence for neurodevelopmental abnormalities in schizophrenic populations and putative causes for these abnormalities. The models used to explain the development of symptoms will be described with an attempt to integrate other proposed aetiologies with the neurodevelopmental theory.

The genetic component of schizophrenia is undeniable given that having a schizophrenic relative is the biggest risk factor for schizophrenia. However, the fact that the monozygotic twin of a schizophrenic patient has only a 48 percent chance of developing the disease implies that other factors must be involved.<sup>1</sup> Biochemical theories focus on the possibility that localised excesses of one or more neurotransmitters, notably dopamine and serotonin, may account for the symptoms experienced in schizophrenia and the therapeutic effect of neuroleptics blocking these receptors reinforces this idea. Thinking has moved away from Lidz's 1949 'marital skew and schism' theory where the conflict resulting from 'schizophrenogenic' mothering alongside a submissive father-figure led to schizophrenia.<sup>2</sup> Social and familial factors such as low socioeconomic status and unstable parenting are still implicated as precipitants though not necessarily primary causes of the disorder. It seems likely that these influences are effecting change on an already vulnerable psychological makeup.

The neurodevelopmental hypothesis of schizophrenia states that a proportion of schizophrenia begins with impaired foetal or neonatal neurodevelopment rather than in young adulthood when psychotic symptoms first become manifest. The causes for this impairment are not specified but second trimester exposure to influenza, maternal stress and obstetric

complications have all been suggested based on epidemiological evidence. Murray and Lewis examined various schizophrenic epiphenomena suggesting that a neurodevelopmental model may serve to connect and elucidate them.<sup>3</sup>

The various neurodevelopmental hypotheses share three main assumptions:

- 1.The primary pathogenic defect is an early derangement of the orderly development of the central nervous system (CNS).
- 2.The period of active operation of the causative agent is of short duration, so the process is essentially static.
- 3.The behavioural consequences of this static process remain relatively latent until long after the primary pathogenetic process has run its course.<sup>4</sup>

There is no direct evidence of a pre- or peri-natal lesion associated with schizophrenia but indirect evidence of impaired development can be seen in macroscopic anatomical variations as well as microscopic immunohistochemical anomalies.

## **The Evidence**

Over the past decade, the most consistently demonstrated phenomenon on CT or MRI, is that schizophrenic patients have larger third and lateral ventricles than controls matched for age and sex, even in the case of monozygotic twins discordant for schizophrenia.<sup>5,6</sup> This phenomenon is not specific for schizophrenia, however, and is only identified in six to 40 percent of subjects.<sup>7</sup> Ventricular enlargement is presumed to take place at the expense of cerebral tissue and may be interpreted as indicating functional disorder in the adjacent brain substance. Widened third ventricles, in particular, may cause damage to diencephalic and limbic structures which are involved in excitatory autonomic functioning. This is evidenced by the relationship to premorbid reduction in electrodermal responses and heart rate in a study of high-risk individuals.<sup>8</sup> This is significant in light of evidence linking diminished autonomic responsiveness with negative symptoms of schizophrenia.

Ventricular enlargement is present at the onset of disease and has been found in most cases to be non-progressive, supporting a neuro-

developmental as opposed to a neurodegenerative aetiology.<sup>6</sup> One serial-MRI study, however, examined patients with schizophrenia, schizoaffective disorder and schizophreniform disorder and found a subgroup of patients whose ventricular expansion rate was significantly greater than that of the controls.<sup>12</sup> A recent investigation found no significant difference between patients and comparison subjects in rates of proportional grey matter reduction with age.<sup>11</sup> Further evidence against neurodegeneration is the lack of reactive gliosis, considered the hallmark of neuronal degeneration, in either immunohistochemical or Nissl stained post-mortem specimens of the brains of schizophrenic persons. This also casts doubt, however, on the possibility of perinatal damage since gliosis occurs in response to injury from the twentieth week of gestation.<sup>4</sup>

Cytoarchitectural abnormalities are also a feature in neuropathological reports on schizophrenic brains and suggest a defect in the formation of the cortical plate. One study used immunocytochemical staining of the frontal lobes of schizophrenic patients for the enzyme nicotinamide-adenine dinucleotide phosphate-diaphorase (NADPH-d). This enzyme is detectable only in a subset of neurons. Akbarian and colleagues found a significant decline in NADPH-d immunoreactive neurons in the cortical grey matter and the superficial white matter. However, rather than merely providing yet another sign of grey matter decay, the authors also documented a significant increase in the number of these neurons, with otherwise normal cellular characteristics in the white matter deeper than 3 mm below the cortical grey matter.<sup>13</sup> In the process of cortical development postmitotic neurons differentiate and migrate to their eventual locations within the grey matter. The cortical cellular lamination patterns emerge in an inside-out pattern; that is, cells destined for the deep layers of cortex emerge first from the ventricular zone, while cells destined for progressively more superficial locations emerge later and later.<sup>14</sup> The findings reported for the frontal cortex by Akbarian *et al.* thus take on added significance in that NADPH-d immunoreactive neurons are normally found in abundance in the early cortical plate. Given their ultimate postmigratory location among the upper cortical layers, they should be among the last cells to pass through the plate. The displacement of the NADPH-d immunoreactive neurons from the superficial cortical white matter to the deep subcortical white matter suggests either abnormal migratory behaviour of this class

of neurons or an abnormal degree of survival within their layer of proliferation beyond their normal life cycle in the developing cortex.<sup>15</sup> Based on the timing of this neuronal migration the disturbance of normal development would be expected to occur in the mid to late second trimester.<sup>14</sup> This is in concordance with the proposition that exposure to influenza in the second trimester may play a part in the development of schizophrenia.

Craniofacial dysmorphism may provide another clue to the neurodevelopmental processes in schizophrenia since cerebral morphogenesis is very closely related to craniofacial morphogenesis. Minor physical anomalies (MPAs) may constitute biological markers of first and early second trimester dysgenesis and have been found to occur in excess in patients with schizophrenia. These MPAs are mainly due to an overall narrowing and elongation of the mid and lower anterior face region and include heightening of the palate and narrowing of the mouth.<sup>16</sup> In schizophrenic subjects there is a correspondence between MPAs and increased third ventricle size. At a symptomatic level, prominence of MPAs has been associated with more severe negative, but not positive, symptoms and with lower premorbid, but not current, intellectual function. Embryological considerations implicate the operation in schizophrenia of dysmorphogenic events over a time frame that may have limits of six to 17 weeks, but more likely encompasses nine to 16 weeks of gestation; over this interval, neurogenesis, migration from the ventricular zone, early programmed cell death and early myelination are interacting in the development of brain structure and function.<sup>17</sup>

'Neurological soft signs' (NSS) are present in excess in patients with schizophrenia. These are minor neurological abnormalities in sensory and motor performance identified by clinical examination and are thought to reflect a failure in the integration within, or between, sensory and motor systems. A systematic review by Dazzan and Murray concluded that an excess of NSS is already evident in patients suffering their first episode of psychosis and also in high-risk subjects without psychosis.<sup>18</sup> There was also a particular excess of NSS in those subjects exhibiting mixed-handedness. Crow has suggested that schizophrenia may be attributable to an abnormality in cerebral lateralisation, possibly involving abnormal expression of a cerebral dominance gene on the X chromosome.<sup>20</sup> Another

hypothesis is that the variability observed in schizophrenic patients could be due to some attentional deficit that interferes with a consistent unilateral mode of responding.<sup>21</sup>

One final contributor to the neurodevelopmental theory is the presence of abnormality in the premorbid period. These abnormalities take the form of childhood psychosocial abnormalities<sup>30</sup>, for example, aloof social habits, avoidance of social interaction and delay in reaching early developmental milestones.<sup>16</sup> One longitudinal birth cohort study found significant impairments in neuromotor, receptive language and cognitive development only among children later diagnosed as having schizophreniform disorder, as opposed to other psychiatric disorders. These impairments were independent of the effects of socioeconomic, maternal and obstetric factors, providing evidence for an early-childhood pan-developmental impairment that is specifically associated with schizophreniform disorder.<sup>19</sup>

### **Causative Agents**

Aetiological agents for neurodevelopmental abnormalities have been implicated on the basis of epidemiological studies. It is probable that these agents exert influence over a developing CNS that is vulnerable through genetic preloading. There is consistent evidence of a small excess of births of people with schizophrenia in the cold winter months, pointing to some associated environmental factor causing neural damage in the foetus or neonate. Maternal exposure to an infectious agent is a likely candidate and the damage may be immune-mediated rather than a direct consequence of infection. Several studies have suggested that a foetus in its second trimester during an influenza epidemic is at increased risk.<sup>22</sup> A Japanese study reported greater than twice the risk of developing schizophrenia in females exposed to flu epidemic in 1957, while they were at five months gestation.<sup>23</sup> This early damage would correlate with the absence of gliosis on neuropathological examination and would be just inside the timeframe proposed for the action of an agent affecting neuronal migration and formation of the cortical plate.

Maternal dietary insufficiency has also been shown to increase risk. Birth cohorts exposed to early prenatal nutritional deficiency during the Dutch Hunger Winter of 1944/1945 were compared with those unexposed, with regard to the risk of hospitalization for schizophrenia in

adulthood. Toward the end of World War II, a Nazi blockade precipitated a severe famine in western Netherlands. The Dutch Hunger Winter was unique in that a famine of brief and clearly defined duration afflicted a population that maintained excellent records on food rations and on health outcomes during the famine and in subsequent decades. The exposed birth cohort had a significant two-fold increase in the risk for schizophrenia.<sup>24</sup>

Considerable evidence shows that schizophrenic patients are more likely than controls to have a history of obstetric complications of any type. A Scottish case control study found that there were highly significant differences between cases and controls for complications of pregnancy and complications of delivery.<sup>25</sup> In this study, pre-eclampsia was the only individual complication of pregnancy for which the case/control difference was significant. Non-spontaneous delivery, Caesarean section, forceps or manipulation, were the only complications of delivery for which the case/control difference was significant. One longitudinal cohort study examined various complications including extreme prematurity and foetal hypoxia and found that pre-eclampsia was the strongest individual risk factor for schizophrenia when the authors controlled for potential confounding factors.<sup>26</sup>

There are difficulties in acknowledging obstetric complication as an aetiological agent for schizophrenia. Firstly, it would be logical to assume that with improved antenatal and obstetric care, the incidence of schizophrenia would drop and that there would be regional variation in schizophrenia rates that could be correlated with the standard of maternity care. There is no evidence of such a relationship. Secondly, the absence of gliosis on post-mortem neuropathological examination of schizophrenic brains and the putative critical time period for derailment of cortical development, nine to 16 weeks gestation, do not support the role of obstetric complications in neural damage. Finally, while there is a definite association between schizophrenia and obstetric complications, they may just share a common aetiological agent, for example, maternal infection in the second trimester.

### **Neurodevelopmental Models**

The problem with the neurodevelopmental hypothesis of schizophrenia is how to explain the long lag between prenatal damage to the foetal

brain and the onset of psychotic symptoms in adolescence and early adulthood.

Two models have been proposed to explain this latent period:

**1. The early neurodevelopmental model.**

This is based on the view that a fixed lesion from early life interacts with normal neurodevelopment occurring later, lying dormant until the brain matures sufficiently to call into operation the damaged systems.<sup>3</sup> One problem with this analogy is that the onset of schizophrenia is heralded by an absolute deterioration from previous levels of functioning, not just a failure to keep pace with peers.<sup>4</sup> In addition, this theory is not completely consistent with the results of neuroimaging studies. The ventricles may enlarge with both early and late tissue volume loss but volume measurements that include extracerebral CSF volumes can determine whether or not there has been late volume loss.<sup>4</sup> MRI allows the most reliable measurement of intracranial volume and specific components, extracerebral CSF as well as ventricular CSF. Several studies have demonstrated a significant overall loss of brain tissue with an increase in extracerebral, sulcal, CSF space.<sup>9,10</sup> Only a diffuse lesion resulting in a loss of brain tissue volume, *after* maximum brain volume expansion has already taken place, will result in an equivalent increase in total CSF space, (extracerebral and ventricular) with no change in intraventricular volume. This is because intracranial cavity expansion is driven by brain growth and is irreversible after the skull sutures fuse. Diffuse loss of tissue limited to the pre- or peri-natal time period will result in a smaller intracranial cavity and persistent enlargement of the lateral ventricles but *not* in an increase in the extracerebral CSF space.<sup>4</sup>

**2. The late neurodevelopmental model.**

Based on data that indicate substantial changes in brain biology during adolescence, this model proposes that schizophrenia may result from an abnormality in periadolescent synaptic pruning.<sup>27</sup> Synapse density appears to show a rapid rise following birth until a peak at about two years. This is followed by a decline until a plateau is reached during the late teens. The age at which this plateau is reached is close to the greatest

acceleration in onset of schizophrenia.<sup>28</sup> A minimum threshold of use exists below which a synapse is pruned.

Genetic predisposition may produce an inappropriately high 'synapse use threshold' and lead to excessive pruning.<sup>28</sup> Also, early developmental injury could cause 'dyspruning' in some areas, for example, in the prefrontal cortex, leading to reduced connectivity and negative symptoms. Compensatory retention or proliferation of some other connections that would normally have been pruned out may also occur. The anomalous persistence of these circuits could lead to 'parasitic foci' that become autonomous, causing positive symptoms.<sup>29</sup>

**CONCLUSIONS**

It seems that the neurodevelopmental theory, occurring on a background of genetic vulnerability, allows the maximal integration of the epiphenomena and epidemiological evidence associated with schizophrenia. The late developmental model offers a realistic explanation of the timing of onset of the clinical manifestations of the disorder. It seems likely the genes involved in the regulation of pruning are under some element of hormonal control and this may have an influence on the gender difference in age of onset of symptoms. Alterations in fundamental circuitry, especially the anomalous persistence of neurons that would normally be pruned could explain the background of neurotransmitter excess in the dopamine and serotonin theories of schizophrenia. The early developmental model may well characterise a separate subtype of schizophrenia where psychosocial stresses or other environmental factors serve to unmask a deficiency in the neural circuitry, resulting in decompensation.

The heterogeneity of the illness may be evidence of aetiological heterogeneity, however, and the neurodevelopmental theory may only hold true for a subtype of schizophrenia. There is definitely value in clarifying even a small subtype of a disorder that will affect one percent of people in their lifetime, if that in turn elucidates a method of prevention.

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