# CHAPTER 17

# The Fetal Origins of Adult Mental Illness

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*"I am a crooked, twisted piece of humanity. The sooner I die the better. God will relieve me from my sufferings, as I really cannot stand it."*
—Voices of the mad: Patients letters from the Royal Edinburgh Asylum 1873-1908. Allan Beveridge.[1]

## Abstract

This chapter critically examines the hypothesis that the origins of some adult mental illnesses such as schizophrenia, which is the focus of this review, derive from adverse events in utero, such as maternal nutrition deficiency, infection and hypoxia. The hypothesis was originally derived from neuropathological changes in patients with established schizophrenia that are highly suggestive of impaired neural development occurring around mid-gestation. Increasingly it appears that gestational timing and the severity of the insult, rather than type of insult, plays a critical role in subsequent behavioural outcome. Supporting the neurodevelopmental hypothesis, recent studies have demonstrated that serious mental illnesses such as schizophrenia and afferent disorders are associated firstly with behavioural abnormalities that are present from early childhood, and secondly with ongoing neural injury on serial magnetic resonance imaging through late childhood and adolescence. These data suggest that alterations in brain development during fetal life lead to an evolving damage over the course of childhood before finally being overtly expressed in early adulthood. Current data suggest that the initial loss of cells in utero leads to a long-term remodelling of the brain that is mediated by upregulation of physiological apoptosis. That such adult illnesses present with early behavioural and physiological clues, are progressive and not static in nature, and that the process is potentially governed by common mechanisms regardless of cause, offers significant new opportunities for intervention and treatment.

## Introduction

Schizophrenia is a surprisingly common disorder, with a lifetime incidence of around 1 in 100 people worldwide. It usually manifests its full form, with deterioration in personality, hallucinations and delusions, and cognitive impairment, in late adolescence and early adulthood.[1] It represents a major personal, social and medical burden, with costs in the billions of dollars per year. However, despite more than a hundred years of dedicated research, the aetiology of schizophrenia remains elusive. Certainly few subjects in neurobiology have generated as much fascination, controversy, and utter frustration as the hunt for the "cause" of schizophrenia—the Holy Grail of biological psychiatry.[2] Despite promising anatomical findings in the late nineteenth and early twentieth century, which suggested a neuropathological origin to the illness, subsequent research led to inconclusive and conflicting results. By the 1970s research

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on the neuropathology of the illness had come to a near standstill, with the general consensus on the subject succinctly summarised by Plum's now somewhat infamous dictum that schizophrenia is the *"graveyard of neuropathologists"*.[3]

This impasse reflected a number of factors, such as the relative crudeness of the methodology available, the belief that the neuropathology of schizophrenia was likely related to a chronic neurodegenerative process, and the inappropriate expectation of finding large abnormalities rather than smaller discrete ones.[4] Recent advances in imaging techniques, such as Magnetic Resonance Imaging (MRI) and Computerised Tomography scanning (CT), have allowed earlier detection and more precise investigations, which support a close association between schizophrenia and neuroanatomical abnormalities. This neuropathology literature has been extensively reviewed by others, and will only be discussed briefly in this chapter. Current data show that at the onset of schizophrenia, and thus independent of treatment effects, schizophrenic patients have enlarged cerebral ventricles with decreased volume of cortex (particularly in the prefrontal and temporal lobes) and of subcortical structures (particularly the hippocampus, amygdala, and dorsal thalamus). Further there is evidence of loss of neuropil (dendrites, spines and axons) and of extensive white matter changes which typically involves diffuse loss rather than active gliosis, as exemplified by the reduced size of the corpus callosum and prefrontal cortical white matter. There are alterations in normal cerebral asymmetries, and alterations in neuronal size, number, placement, orientation and clustering, with excessive cortical pruning, and consequent altered neurotransmitter function and aberrant functional connectivity of specific cerebral circuits.[2,4-10]

Consistent with the well-known variability in the clinical presentation of the illness, the anatomical changes are also quite variable. However, the overall nature of these neuropathological changes is consistent with a significant prenatal impairment of development. As will be discussed below, it is now evident that while there appears to be a genetic component to schizophrenia and other mental illnesses, genetics does not fully account for their development. It remains controversial whether adverse environmental events act upon a preexisting genetic predisposition (similarly to e.g., insulin dependent diabetes mellitus),[11] or modify the epigenetic status of genes, or are simply coincidental.[12,13]

## The History of the Neurodevelopmental Hypothesis

The neurodevelopmental hypothesis proposes that adverse environmental events during fetal life impairs and subsequently alter neural development, leading to mental illness in adulthood.[10,14-19] Like all good theories, it has a long history. As early as 1891, the founding father of adolescent psychiatry, Scottish psychiatrist Thomas Storer Clouston, proposed that there was a developmental component to *"adolescent or developmental insanity"*.[20] He considered it a disorder of cortical development; *"the last cortical disease"*, and that the onset of psychotic symptoms was due to maturation during adolescence *"of certain parts of the brain which had lain dormant before"*.[20-23] This concept was subsequently superseded by the hypothesis proposed by Emil Kraeplin, much influenced by Alzheimer and his study of adult dementia, that the illness was a neurodegenerative organic brain disease;[24] a view Clouston *"strenuously"* objected to,[22] but one which held sway for a considerable number of years.[17,19,25] Even Kraeplin acknowledged, however, that there might be a developmental origin, at least in some cases where evidence of the illness existed in childhood,[23] as did Eugene Bleuler, who in 1911 coined the term schizophrenia; a term chosen to express the presence of schisms between thought, emotion and behaviour which characterises the "schizophrenias".[26] Bleuler reported that behavioural difficulties could be observed in childhood in more than half the patients who eventually developed schizophrenia.

This observation is fundamental, since it demonstrates that the underlying disorder that leads to schizophrenia evolves in some cases at least from early childhood if not before birth. In subsequent years these childhood clues about the potential developmental origins of schizophrenia were forgotten or dismissed, but subsequently rediscovered in the 1980's.[27,28] Prospective

follow-up studies of birth cohorts have confirmed that significant impairments in neuromotor, receptive language, and cognitive development are present among children later diagnosed as having schizophreniform disorder.[29-33] These premorbid behavioural changes can be seen as early as three years of age.[29] There is also an early childhood onset version of schizophrenia.[34] Thus, while schizophrenia typically manifests in its full form in adulthood, there is now good evidence to show that the illness is already in progress much earlier and is progressive in nature.

One key conceptual difficulty is reconciling the timing between origin and onset of the disorder: how can it be that an illness which manifests in adolescent or adult life could have its origins so long ago, in fetal life?[5,25] This apparent paradox may be resolved by understanding that neurodevelopment is a continuum started at conception, but not completed until adulthood. Disturbances in particular critical windows of maturation can thus have very long lasting effects.

## Neuropathological Evidence for Neural Injury before Birth in Schizophrenia

The key neuropathological data for an in utero origin to schizophrenia centre around neuronal migration, and, increasingly, glial proliferation. The presence of neuronal disarray, heterotopias and malpositioning are very suggestive since cytoarchitecture is largely determined during early fetal life, well before the last trimester.[5,35,36] Among the cellular findings are abnormal cytoarchitecture of the entorhinal cortex characterized by poorly formed layer II neuron clusters and laminar disorganization, a reduction and displacement of hippocampal and cortical pyramidal cells, and abnormal development of the subplate.[35,37-41] Such studies suggest disturbances of neuronal migration during the late first or early second trimester. An earlier time is excluded since gross abnormalities in the structure and cellular content of the cerebral cortex would be expected if neurogenesis were affected.[5]

However, these data are not conclusive, since some studies have not found evidence for abnormal migration in schizophrenia,[42-44] and other, more consistent findings such as alterations to neuronal size and synaptic and dendritic organisation may occur later in life, well after birth.[5,35] The differences between studies may reflect the methodological difficulties and subtle nature of the cytoarchitectural changes.[35] Alternatively, it could mean that in many cases the putative in utero insult may occur after mid-gestation, when migration is largely complete.[45,46] At this stage there is a marked increase in glial proliferation and if correct this would suggest that we should expect to see a consistent reduction in the amount of white matter.[45,46]

Imaging data suggests that this is indeed the case, but it has not been fully appreciated until recently because of technical difficulties,[47] although the consistent presence of ventriculomegaly in patients strongly suggests diffuse white matter atrophy.[48] Instead the focus has been on whether "lesions" exist. Traditionally, the absence of "gliosis" (i.e., astrocytic activation or scarring) in histopathological and imaging studies of patients with schizophrenia has been taken to mean two things: (1) that this must be a neurodevelopmental process and not a neurodegenerative one (which would leave tell-tale scars), and/or (2) that any changes must have taken place before the third trimester, based on the study by Friede, which supposedly showed that gliosis cannot occur until after the end of the second trimester.[5] In fact both conclusions are highly likely to be erroneous. There is evidence that that astrocytic activation can occur as early as 20 weeks of gestation,[49] and in any case a few studies have found periventricular white matter lesions in region of patients.[50,51]

Critically, modern imaging data has confirmed that the most common pathological feature of both schizophrenia and affective disorders is diffuse loss of white matter.[10,48,52-58] This loss appears to be region specific. There is, for example, loss of oligodendrocytes (the myelinating cells of the central nervous system) and astrocytes and altered oligodendrocyte ultrastructure in specific layers of the prefrontal cortex.[52,58] Consistent with these findings, there is evidence of impaired and reduced myelination in schizophrenia,[59,60] and altered expression of myelination related genes.[61] Thus there is impairment of the normal age-related development of the frontal and temporal lobes in adulthood.[62]

Loss of the supporting glia likely contributes to the atrophy of neurons that has been described in the prefrontal cortex.[52] Layers III and V of the dorsolateral prefrontal cortex, which give rise to glutamatergic projections to neostriatum, demonstrate the most structural pathology. The fundamental pathophysiology of schizophrenia remains unclear, but evidence suggests that there is excessive stimulation of striatal dopamine D2 receptors, deficient stimulation of prefrontal dopamine D1 receptors, and alterations in prefrontal connectivity involving glutamate transmission at the NMDA subtype of receptor.[63]

## How Good Is the Evidence for Underlying in Utero Events?

A variety of prenatal events can adversely affect neuronal development including hypoxia, maternal undernutrition, exposure to viruses and infection, maternal stress and maternal lifestyle and other health problems (key factors are discussed below).[16,64-67] Meta-analysis suggests that schizophrenics are twice as likely to have been exposed to obstetric complications as controls.[67,68] However, most babies with obstetric complications do not develop schizophrenia and most patients with schizophrenia do not have an apparent history of these complications.[69]

The significance of these findings is highly debated. They might reflect a genetic predisposition,[6,18,70,71] which might be to obstetric complications rather than directly with mental illness.[72] For example, poor pregnancy outcomes occur more frequently among women with schizophrenia and they are at greater risk for increased interventions.[73-77] Obstetric complications do not seem to be particularly specific to schizophrenia since there now appears to be an association with affective disorders as well.[78,79] These epidemiological data are, of course, limited by lack of detail particularly with respect to gestational timing, and by an inappropriate focus on peripartum events.[80,81] It is likely significant that schizophrenia, for example, appears to be mainly related to events which occur in the first or second trimester.[5]

Since numerous adverse events are apparently equally associated with different types of mental illness, it maybe speculated that it is not the type of insult (i.e., infection versus hypoxia) which is important to outcome, but rather the gestational timing of the initial insult. Insult severity, duration, and the additive effects of interactions between insults are also likely to be key factors. The similarity in neuropathology between many illnesses is consistent with the shared symptomology of these illnesses, which often makes diagnosis difficult. It is also consistent with the increasingly accepted concept that affective disorders and schizophrenia, at least, are not distinct illnesses per se, as Kraeplin first proposed, but rather represent a psychiatric continuum ranging from unipolar to bipolar disorder to schizoaffective psychosis all the way to schizophrenia.[82] Neural impairment and injury, like psychiatric disorders, may be viewed as a continuum, with timing and severity of an insult critical factors in outcome.[83]

## Hypoxia

It is increasingly clear that hypoxia can occur in the preterm fetus.[83,84] Experimentally, we now understand that despite its immaturity the preterm fetus is physiologically resilient and has a mature response to severe hypoxia.[85-89] Paradoxically, however, the capacity to survive prolonged asphyxia can place the preterm fetus at greater risk of surviving with injury than is the case later in gestation.[90] Prenatal injury, as shown by severe placental pathology such as infarction, can occur without detectable clinical signs in infants who go on to develop cerebral palsy later in childhood.[91] Studies in rodents and fetal sheep show that chronic sub-lethal hypoxia started in mid-gestation is associated with smaller brains, reduced white and grey matter volumes, ventriculomegaly and disordered neuronal migration and dendritic development.[92-96] Further, acute white matter loss after perinatal hypoxia-ischaemia leads to long-term reductions in myelination post-natally.[97] In preliminary work from our laboratory in the fetal sheep, we have observed that a sufficiently severe, but acute period of asphyxia in mid-gestation that causes subcortical injury leads to chronically evolving diffuse white matter loss, (but no cystic lesions), ventriculomegaly, and long-term, impairment of cortical development.[98] These findings were related to reduced glial proliferation and upregulation of programmed cell death.

Importantly, white matter injury, while a dominant cause of neural injury in the preterm infant, also occurs later in gestation after severe hypoxia-ischaemia.[99-101]

Clinical data, particularly studies of multiple births, are consistent with these data and suggest that exposure to hypoxia-ischaemia is a common cause of neurodevelopmental injury.[67,81,102-104] The high concordance reported in monozygotic (MZ) twins is often cited as irrefutable evidence for the etiological influence of genetics: MZ twins share 100% of their genes, and mental illness still develops if the twins are adopted. However, it is striking that far from showing 100% concordance for schizophrenia, MZ twins have reported rates between 26 and 47%, and rates as low as 6% for dizygotic (DZ) twins.[105] For schizophrenia, MZ concordance rates are significantly lower when samples are selected from a twin register as opposed to a psychiatric facility,[106] but twin registries typically record zygosity by sex rather than by explicit genotyping, and thus the real association may be even lower than reported.[107,108] The emphasis on genetics has obscured the fact that twins share a lot more than their genes, they share an in utero environment where impaired nutrition and oxygenation are common. Thus, the increased concordance of twins for mental illness might relate to their increased rate of neural injury as discussed below. Seminal imaging work by Suddath and colleagues supports this hypothesis. They demonstrated that there were significant neuroanatomical differences, including smaller anterior hippocampi and enlarged lateral and third ventricles, between twins discordant for schizophrenia and concluded that the cause of schizophrenia in those cases was at least in part not genetic.[109]

Infants born as part of multiple births have very high rates of brain injury and neurodevelopmental handicap compared to singletons.[110-112] Cerebral palsy (CP) is, for example, 5-10% more frequent in twins than singletons (1-2%), while triplets have a 47 fold higher risk.[113] The loss of a co-twin in utero is associated with a 13-15 fold higher risk for CP compared to live-born twins,[110,111,114] with an absolute risk of later neurodevelopmental impairment reaching 60%.[112] The higher relative risk is not solely due to higher rates of low-birthweight and prematurity (both of which are predictive for schizophrenia),[115] as normal birthweight twins also show increased risk of neural injury compared to singletons.[116,117]

It is likely that it is not zygosity which underlies this risk, but chorionicity; that is whether the fetuses shared a placenta.[118,119] MZ twins share the same chorion in most cases (monochorionic, MC), whereas DZ and around a third of MZ twins are of the dichorionic type (DC).[108] Fetal mortality is significantly higher and neurologic morbidity is up to 7-fold higher in MC than DC twins.[112,120] Monochorionic multiple gestations are frequently complicated by antenatal necrosis of the cerebral white matter,[121] and by abnormal cortical plate development shown by polymicrogyria or microgyric-like pattern, and heterotopias.[122] Discordant growth, the death of a twin in utero, and twin-twin transfusion are key associations.[112,121,122]

The apparent damage is typically present by 22 and 32 weeks gestation, in a pattern which is consistent with that reported in schizophrenia.[122] MZ twin pairs concordant for schizophrenia are more likely to have been monochorionic. Pairwise concordances for MZ twins without monochorionic markers averaged 10.7%, whereas concordance for MZ twins with one or more monochorionic markers was 60%.[123] These data again strongly suggest that it was sharing a placenta rather than genes which was most important. A relationship between chorion type and concordance of abnormal behaviour between MZ and DZ pairs has also been supported by several other studies,[124,125] but not all.[126]

## Nutrition

Pasamanick first suggested that maternal malnutrition may lead to behavioural abnormalities in childhood.[127] Nutrition and oxygen delivery are often inextricably interlinked and impaired fetal and placental growth in both singletons and twins discordant for schizophrenia may be a function of both factors.[51,115,128] Nutritional inadequacy in one form or another is one of the largest single nongenetic contributors to mental retardation and aberrant neural development.[129] As discussed elsewhere in this book, the relative imbalance of the current

western diet may well lead to persistent metabolic and cardiovascular derangements.[130] The modern desire to be thin, which affects as many as 1% of pregnancies through inappropriate maternal dieting,[131] may also play a contributory role. Reduced caloric intake, nutritional imbalance (e.g., increased carbohydrate and reduced protein intake) and micronutrient deficiencies such as folate, homocystein and vitamin D may all impair fetal brain development, reduce glial proliferation, increase apoptosis, and lead to glutamate, serotonin and GABA neurotransmitter abnormalities.[129,132-137] In MC twins, there is a reduction of some essential and nonessential amino acids in the growth-restricted twin compared to their co-twins, including glycine.[138] Altered glycine metabolism may be important because of the glycine modulatory site on the NMDA receptor, which inhibits glutamate function. There is evidence that reduced glutaminergic activity contributes to the symptoms of schizophrenia.[139]

The effects of nutritional deprivation before birth persist well into adulthood and are associated with behavioural changes,[132,140,141] such as alterations in sleep-wake cycles and arousal.[142] Similar disturbances in sleep continuity, and in the balance of slow-wave and rapid eye movement sleep are a consistent feature of schizophrenia.[143] Recent data show that indicators of intrauterine and childhood undernutrition have a complex association with increased risk of later schizophrenia,[128] but that it is prenatal not childhood growth which is most important.[144] For example, there is a reverse J-shaped association between adjusted birth weight and schizophrenia, with mean hazard ratio of 7.0 for males of low birth weight (<2.5 kg) and 3.4 for those of high birth weight (>4.0 kg). The Dutch Winter Famine studies have demonstrated a strong link between malnutrition in mid-gestation and later schizophrenia (around a 2 fold increase), whereas late-gestation undernutrition was associated with affective disorder, with exposure in the third trimester having a greater effect than exposure in the second trimester.[64,65,104,145-147] Taken with the data on injury in twins, these data further suggest that gestational timing rather than the nature of the event is more important to later behavioural outcomes.

## Infection

Fetal infection has been suggested to be a possible etiologic factor based on epidemiological findings that individuals with schizophrenia and affective disorders tend to be born in winter/spring when compared to the general population and that there is a strong association between maternal influenza and mental illness in offspring.[64,148] Although schizophrenia has been linked with multiple infectious agents that differ in their antigenicity, modes of transmission, and teratogenic potential, it is likely that they share some pathogenic mechanisms.[149] Experimentally, potential mechanisms of action include induction of pro-inflammatory cytokines,[149,150] endotoxin-induced fever,[151-153] and hypotension and cerebral hypoperfusion/hypoxia.[154,155] Infection may also sensitise the brain to subsequent hypoxic injury.[156] In twin studies, there is evidence that a shared placenta and amniotic sac increases the risk of both fetuses being exposed to infection (chorioamnionitis),[64,157] whereas a dichorionic placenta helps to limit the spread of infection.[158]

## Clues from the Preterm Infant

Schizophrenia shows a typically remitting and relapsing course.[5] If the neurodevelopmental hypothesis is correct, then why should a neurological injury sustained in utero lead to such variable symptoms in adulthood?

One possible link is that glia continue to be produced and myelination continues to develop well into middle age in key corticolimbic relay areas.[159-161] Glia are not simply an important but passive matrix for the brain. In addition to their traditional roles in neuronal migration and inflammatory processes, glia are now known to provide trophic support to neurons, to regulate local neuronal metabolism and neurotransmission, and the formation of synapses (including pruning).[162,163] The early appearance of ventriculomegaly suggests that there has been a profound loss of glia in prenatal life, as is seen on in utero imaging,[164] such that there may be an inadequate number in adulthood to consistently support neuronal function. The loss of glia

in patients suffering from schizophrenia and affective disorders is further evidence for pathological events in mid-gestation as this is the maximal time of increased glial proliferation and differentiation.[165] The impact of prenatal loss of glia is perhaps best illustrated by the neurodevelopmental delay, behavioural abnormalities and increased rate of mental illness in children who are born prematurely,[166-168] Pathologically, such infants demonstrate highly selective early white matter damage, which leads to long-term reductions in grey matter volume and complexity of neuronal structures.[167,169,170] The neurological sequelae of preterm birth (including epilepsy, cerebral palsy and attention deficit) associated with these perinatal white matter lesions seem to be a consequence of the post-injury grey matter transformations.[171,172] This sequence of events is strikingly similar to those in patients with schizophrenia. Disturbingly, there is now evidence to show that preterms are also at greater risk of developing mental illnesses such as schizophrenia in adulthood.[173]

Importantly, however, infants do not necessarily deliver even after a major insult in utero. There is now increasing evidence to show that neurodevelopmental delay in term babies is also associated with white matter loss and subsequently impaired neuronal development which apparently had its origins much earlier in fetal life.[174-176]

## Other Neuropathological Features

There are a number of other features of the neuropathology of schizophrenia, which suggest a fetal insult around mid-gestation. For example, it is known that normal human brain symmetry is determined early in development, during the early second trimester of gestation. Studies have suggested that the left side of the brain is generally more severely affected in schizophrenia than the right,[177] and thus that some event occurred during this stage. Similarly, gyrification occurs largely between weeks 16 and 19 weeks of gestation, and sulcal-gyral abnormalities have been found in imaging MRI studies of schizophrenic patients.[178,179] Finally, as Clouston himself observed, schizophrenia is associated with an increased risk for other congenital and physical abnormalities, such as cranio-facial abnormalites like cleft palate, which have their origins in mid-gestation.[180-183]

## Cerebral Housekeeping or Implementing "Plan B"

The development of the brain is a highly complex coordinated process that can be roughly divided into neurogenesis, neuronal migration, glial proliferation, and neuronal differentiation. These events occur as part of a specific timetable in discrete critical windows of time, which is presumed to be largely under genetic control.[168] This unfolding maturational program can be derailed by environmental events; cell proliferation, differentiation, and migration can be slowed or inhibited or cells killed outright. Importantly, because many events only occur at a particular "critical window of time",[132,184] even if the event causing this impairment is acute (transient hypoxia due to placental infarction for example), the impairment is irreparable and this has consequences for subsequent neural development. The architectural plan for brain development started in utero does not, of course, reach completion until early adulthood, when final connections are made in the prefrontal and temporal lobes, and corticolimbic pathways. These are all key regions where aberrant neuronal development may contribute to the behavioural dysfunction of schizophrenia.

As discussed in relation to premature birth, cell loss may continue long after the acute injury has finished. Cells, be they neurons or glia, require other glia and neurons to provide the necessary support and signals cues to survive.[185-187] This balance is exquisitely fine. During normal development substantial numbers of initially generated cells do not form appropriate connections or are in excess of requirements. These cell are removed by physiological apoptosis.[188] Critically, however, programmed cell death is also triggered when cells lose essential input from other cells, for example due to injury elsewhere in the brain. In such a pathological situation, upregulation of apoptosis is a normal part of the complex 'social' controls that ensure that individual cells behave for the good of the whole.[185] The brain will thus develop according to

an alternate architectural plan—Plan B. Inevitably this leads to a smaller, less complex brain, but a functional one; in as much as function is defined by the ultimate human prime directive: the ability to reproduce.

A critical part of this process may not be simply abnormal neuronal connections, but loss of white matter cells, consistent with the association of mild ventriculomegaly with later impaired grey matter development and neurodevelopmental delay and behavioural difficulties. The hypothesis that loss of glial support is a major contributor to long-term outcome is consistent with the pathological profile of patients with schizophrenia of variable neuronal loss, but a consistent reduction in soma size and abnormal synaptic connections. Oligodenrocytes enhance the number of functional synapses that form between neurons, and regulate neuronal activity. Glia are also a primary source for the growth factors necessary to inhibit apoptosis.[189] Insulin-like growth factor (IGF-I) is a key mediator of normal brain development; regulating neural stem cell proliferation, differentiation, and maturation, as well as promoting myelination, neurite outgrowth and synaptogenesis.[190] In recent years it has been proposed that a derangement of the IGF axis may be involved in the aetiology of schizophrenia,[191] and that the excessive synaptic pruning which is a feature of the schizophrenic brain, is a function not of late (post-natal) neurodevelopmental events, but rather occur secondary to diminished trophic cues.

Is there clinical evidence for such increased, on-going apoptosis? Recent imaging data shows that children who go onto develop schizophrenia have accelerated loss of cortical grey matter compared to controls during adolescence.[192] This deficit enveloped increasing amounts of cortex throughout adolescence, starting in parietal regions, and then swept forward into sensory and motor regions. By 18 years of age this process had moved into the critical areas of the brain known to be key to schizophrenia; the dorsolateral prefrontal and temporal cortices - areas which initially were not affected. This aberrant development is also seen in MZ twins discordant for schizophrenia.[193] It is likely that this is an upregulation of the normal remodelling of the brain is in part mediated by an upregulation of physiological apoptosis.[186] Consistent with this there is some evidence that apoptotic processes are upregulated in the brain of schizophrenic patients at postmortem,[194] and that alterations in glutamate receptor activity seem to be important.[195]

## Perspective

This chapter has examined the hypothesis that schizophrenia and other mental illnesses may have at least in part their origin in preceding fetal neurodevelopmental injury. Although the combined epidemiological, neuroanatomical, behavioural, and imaging evidence is highly suggestive, the data cannot yet definitively distinguish the roles of inherited predisposition and environmental triggers. Considerable work remains to properly understand the impact of timing and the nature of different adverse events in utero on the brain, and how these relate to the post-natal development of disease. Such knowledge would offer at the very least, improved detection of children at risk of later mental illness and thus the potential for earlier intervention. Regardless of the precise origins of the disease, there is now inconvertible proof that schizophrenia is an evolving disease that involves both significant premorbid developmental problems and progressive anatomical and cellular deterioration during childhood and adolescence well before the 'mental illness' appears fully in adulthood. Current data strongly suggest that the most likely mechanisms involve upregulation of physiological programmed cell death and a pathological imbalance in excitatory neurotransmission. This very long-term evolution offers the tantalising possibility that some intervention, whether pharmacological or behavioural might be able to arrest the progression of the disease before the florid symptoms appear, or even to favourably remodel the brain.

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