

# State of the art

## *A plausible model of schizophrenia must incorporate psychological and social, as well as neurodevelopmental, risk factors*

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*Subtle alterations in brain development caused by genes or early environmental hazards, such as obstetric complications, play a role in projecting some individuals on a trajectory toward schizophrenia. High-risk and cohort studies demonstrate that children destined to develop schizophrenia tend to have delayed milestones and subtle neuromotor and cognitive impairments (particularly in coordination and language). These neurocognitive problems lead to difficulties in interpersonal relations, and their progressive alienation makes these at-risk children more likely to harbor odd or paranoid ideas. This cascade of increasingly deviant development may then be compounded by brain maturational changes during adolescence with a resultant lability of the dopaminergic response to stress. As a result, the individual is more susceptible to the effects of the abuse of dopamine-releasing drugs, and to other risk factors such as migration or stressful life events; social isolation may be a common pathway underlying several of the social risk factors.*

**Keywords:** genes; imaging; neurodevelopment; prenatal risk factor; relatives; risk factor; schizophrenia

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The idea that psychosis can have a developmental origin was common in the latter part of the 19th century,<sup>1</sup> but was subsequently displaced by Emil Kraepelin's view of "dementia praecox"<sup>2</sup> as a deteriorating illness. In the 1980s, a number of research groups began to speculate that schizophrenia might indeed have a significant developmental component.<sup>3-6</sup> In 1987, Murray and Lewis<sup>7</sup> summarized the evidence in an editorial in the *British Medical Journal* entitled "Is schizophrenia a neurodevelopmental disorder?" In the years since then, researchers have increasingly answered the question in the affirmative, but have also become aware that the simple "neurodevelopmental" hypothesis fails to explain all the available data. Therefore, in this paper, we consider how new information has caused the original "doomed from the womb" hypothesis to evolve. We begin by discussing the strongest evidence implicating a role for deviant development, ie, that concerning the characteristics of preschizophrenic children.

### **The antecedents of schizophrenia in childhood and adolescence**

#### **Neuropsychological development in childhood**

Children who go on to develop schizophrenia tend to display early neurological and cognitive problems. The early research focused on children with a family history of psychosis. Indeed, Fish<sup>8</sup> pointed out that the increased prevalence of neurological signs in multiple sensorimo-

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tor systems in the offspring of schizophrenics was consistent with an “inherited neurointegrative deficit.” High-risk studies concur showing that 25% to 50% of children born to mothers with schizophrenia have developmental abnormalities especially poor motor coordination in early childhood, and attention and information processing deficits later.<sup>9-11</sup> Walker<sup>12</sup> examined home movies of preschizophrenic children and noted more postural and upper limb movement abnormalities than in their well siblings. These abnormalities were most noticeable in the first 2 years of life, and ameliorated thereafter, raising the possibility of ongoing recovery from an early lesion.<sup>13</sup>

A series of large birth cohort studies were published through the 1990s. The 1946 British Birth Cohort Study followed up 4746 children for 43 years. The 30 children who were destined to develop schizophrenia, as a group, had delayed milestones (walking was delayed by 1.2 months), more speech problems, lower educational test scores, and a preference for solitary play.<sup>14</sup>

As part of the British National Child Development Study, Done et al<sup>15</sup> compared the childhood social adjustment of 40 patients with schizophrenia, 35 with affective psychoses, 79 with neurotic disorders, and 1914 controls. Those who later developed schizophrenia had significantly more neurocognitive problems and social maladjustment than controls at the age of 7 years, especially if they were male. Children who went on to develop affective psychoses did not differ from controls. Preneurotic children, especially if female, manifested poorer social adjustment than controls at age 11.

Cannon et al<sup>16</sup> compared elementary school records of 400 preschizophrenic children and 400 healthy controls born in Helsinki between 1951 and 1960. Poor performance in sports and handicrafts, which may indicate motor coordination deficits, were risk factors for schizophrenia. This finding is consistent with the high-risk and other birth cohort studies, and also the poor motor coordination seen on childhood videotapes.<sup>12,13</sup>

A prospective cohort study from Philadelphia compared 72 patients with schizophrenia, 62 of their unaffected relatives, and 7941 controls. Both the patients and their well relatives performed significantly worse than the nonpsychiatric controls (but did not differ from each other) on verbal and nonverbal cognitive tests at the ages of 4 and 7 years. Early social maladjustment, motor coordination deficits, and behavioral and language dysfunction (like echolalia, inappropriate laughter, or unin-

telligible speech) were significantly associated with both schizophrenia and sibling status. Hence, premorbid social, cognitive, and motor dysfunctions are significant indicators of vulnerability to schizophrenia, such vulnerability being the result of familial (genetic and shared environmental) factors.<sup>17-19</sup>

In the Dunedin (New Zealand) follow-up study, in which 761 children were regularly studied and followed up till the age of 26 years, the usual neurocognitive risk factors for schizophrenia were found. A child psychiatrist also interviewed the children at age 11 years, with a structured diagnostic interview searching for evidence of psychotic symptoms. Interestingly, those children who reported unusual quasi-psychotic experiences had a 16-fold increased risk for schizophreniform disorder at age 26 years. This study demonstrates a certain continuity of psychotic symptoms from childhood to adulthood and indicates that delusions often have their origins more than a decade before psychosis is formally diagnosed.<sup>20</sup> It is also interesting in that this and several of the other cohort studies point to receptive language deficits as being particularly noticeable in preschizophrenic individuals.<sup>14,15,18,21</sup> Much research indicates that auditory hallucinations are disorders of inner language.<sup>22,23</sup> Perhaps it is not surprising that children who have impaired language perception are more prone to misperceive their own inner speech as voices in adult life.

Isohanni et al<sup>24</sup> studied over 12 000 subjects from the 1966 Finnish birth cohort at the time of their 31st birthday. Using a national hospital register, they identified 100 cases of schizophrenia, 55 other psychoses, and 315 nonpsychotic disorders. Data on the ages at which subjects learned to stand, walk, and control bowel and bladder functions were compared across the groups. Delayed milestones increased the risk for later psychosis in a linear fashion (so early milestones implied protection). There was no such association between milestones and nonpsychotic disorders. Apart from the interesting “dose–response effect” described, this study suggests that the childhood precursors may be specific to psychotic disorders as opposed to conveying risk for general psychopathology.

## Neuropsychological characteristics in late adolescent/early adult life

David et al<sup>25</sup> investigated the association between IQ and the later development of psychosis in a cohort study

of nearly 50 000 18-year-old males who were conscripted into the Swedish army in 1969 to 1970. By 1983, 195 subjects in the cohort had been admitted to hospital with schizophrenia and another 192 with nonschizophrenic psychosis. There was a highly significant association between low IQ scores and the subsequent development of schizophrenia. Indeed, the relationship between schizophrenia and IQ was linear, with risk gradually increasing as IQ fell at all levels of intellectual ability. The risk for nonschizophrenic psychoses was also higher in those with lower IQ, but the effect was less marked and non-linear. The effect size of the low IQ risk factor exceeded that of any other known environmental risk factors. The association between low IQ and schizophrenia could be directly causal with cognitive impairment leading to false beliefs and perceptions. Alternatively, the association could be indirect with factors such as abnormal brain development increasing the risk for schizophrenia, and incidentally causing the lower IQ.

Davidson et al<sup>26</sup> examined assessment scores for nearly 10 000 16- and 17-year-old boys entering the Israeli army. Deficits in social functioning, organizational ability, and intellectual functioning predicted later hospitalization with schizophrenia. There was a linear relationship between IQ and risk for schizophrenia, and the authors suggest that low IQ is itself a causal factor increasing the risk for schizophrenia; it could act independently or be one of the means by which other genetic or environmental influences exert their effect, or both. The authors suggest that low IQ could compromise information processing, leading eventually to the psychopathology of schizophrenia, or alternatively that high IQ may be protective.

### Risk factors in early life

#### Obstetric complications

Many small case-control studies reported an excess of obstetric complications (OCs) among patients with schizophrenia. Most of these early data have been summarized in two meta-analyses. Firstly, Geddes and Lawrie<sup>27</sup> confirmed an association between OCs and schizophrenia with an odds ratio of approximately 2. Secondly, Geddes et al<sup>28</sup> examined 11 studies, which used the Lewis and Murray scale<sup>29</sup> to interview mothers retrospectively about their offspring's gestation. Data were available for 700 patients with schizophrenia and 835 controls. Premature rupture of membranes, prematurity, and the use of resus-

citation or incubator emerged as significant risk factors for schizophrenia.

There were many methodological criticisms of this early work. However, in the last few years, a number of large register-based longitudinal studies (summarized in *Table I*<sup>30-43</sup>) have been published. Despite occasional inconsistencies, the new evidence overwhelmingly supports the notion that exposure to OCs is a risk factor for schizophrenia. Although the overall effect of OCs is modest, some studies suggest that the association may be stronger among male patients<sup>36,44</sup> and among cases with an early onset,<sup>37,38,45,46</sup> but not everyone believes this.<sup>43</sup>

The mechanism underlying the link between OCs and schizophrenia remains elusive, but recent long-term cohort studies with detailed obstetric information point to fetal/neonatal hypoxia.<sup>33,38,39</sup> According to Cannon et al,<sup>37</sup> the odds of schizophrenia increase linearly with an increasing number of hypoxic/ischemic complications. A plausible model is that those with a genetic liability to schizophrenia may be especially sensitive to the excitotoxic effects of hypoxia on the fetal/neonatal brain.<sup>37,47</sup>

#### Markers of prenatal deviant development

It is well established that the morphogeneses of the brain, the craniofacial region, and the epidermal ridges are intimately related. Minor physical anomalies (small alterations of ectodermal development, such as defects on the head, facial features, hands, and feet) are known to occur during the first and second trimesters of life.<sup>48</sup> An increase in minor physical anomalies is a consistent finding among patients with schizophrenia<sup>49-51</sup> and this has been interpreted as a marker of altered development.

Epidermal ridges appear on the hand between weeks 12 and 15 of life and after this period they remain unchanged.<sup>52</sup> Dermatoglyphic abnormalities are found in excess in schizophrenia.<sup>53-55</sup> Preliminary support for the idea they may be indirect indicators of aberrant brain development came from Van Os et al,<sup>56</sup> who reported an association between dermatoglyphic ridge counts and cerebral structural abnormalities measured by magnetic resonance imaging (MRI) in patients with schizophrenia. Similarly, compared with controls, patients with schizophrenia present a dermatoglyphic deviance (excessive fluctuating asymmetry of ridge counts), which correlates with their excessive mixed handedness. These can be interpreted as two related markers pointing toward greater developmental instability in schizophrenia.<sup>57</sup>

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Study	Sample and method	Main findings
Jones et al, <sup>31</sup> 1998	1966-born cohort with 11 017 Finnish subjects. Linked psychiatric and obstetric case registers. Follow-up at age 28 years	76 subjects had developed schizophrenia at age 28. Schizophrenic patients were significantly more likely than controls to have had perinatal brain damage or to be premature
Hultman et al, <sup>32</sup> 1999	Swedish population-based cohort study. Comparison of obstetric records for 167 patient/control pairs linked to psychiatric register	Schizophrenic patients were more likely than controls to have OCs, especially if male. Schizophrenia was associated with multiparity and maternal bleeding in pregnancy
Dalman et al, <sup>33</sup> 1999	Same cohort as Hultman et al. <sup>32</sup> Follow-up of 507 516 children born in the late 1970s	238 subjects developed schizophrenia during follow-up. Schizophrenia was associated with OCs. Preeclampsia was the strongest individual risk factor
Kendell et al, <sup>34</sup> 1996	115 case-control pairs from the Scottish population born in 1971 to 1974. Linked obstetric and psychiatric records	Schizophrenia was associated with a significant excess of OCs, especially preeclampsia and infants requiring hospital neonatal care
Kendell et al, <sup>35</sup> 2000	Reanalysis of same Scottish sample <sup>34</sup>	Selection bias was detected in the control group of the 1996 study. Reanalysis showed no significant association between OCs and schizophrenia
Byrne et al, <sup>36</sup> 2000	Compared obstetric records of 431 patient/control pairs. Linked with psychiatric case register	Global rate of OCs did not differ between patients and controls. Male patients with a young onset had significantly more OCs than controls
Cannon et al, <sup>37</sup> 2000	Prospective cohort study (NCP). Comparison of 72 patients, 63 unaffected siblings, and 7941 controls	The odds of schizophrenia increase linearly with increasing number of hypoxia-associated OCs
Rosso et al, <sup>38</sup> 2000	1955 Finnish birth cohort. 80 patients, 61 unaffected siblings, and 56 matched controls	Hypoxia-associated OCs significantly increase the odds of early-onset schizophrenia (but not of later-onset cases)
Zornberg et al, <sup>39</sup> 2000	Prospective cohort study (NCP). 603 individuals born between 1959 and 1966 were followed for 23 years after early childhood assessments	Hypoxic/ischemia-related fetal/neonatal OCs were associated with striking increase in risk for schizophrenia and other nonaffective psychoses (5.7% vs 0.4% for nonexposed)
Brown et al, <sup>40</sup> 2001	Comparison of 70 young adults from the rubella-exposed 1964 birth cohort, against 1510 unexposed controls from the ECA and the Albany/Saratoga studies	The subjects prenatally exposed to rubella had a substantially higher risk for nonaffective psychosis compared with unexposed controls (RR: 5.2)
Wahlbeck et al, <sup>41</sup> 2001	Cohort study of 7086 Finnish subjects. Linked obstetric and school health records with psychiatric register	Intrauterine and childhood malnutrition was associated with increased lifetime risk for schizophrenia
Dalman et al, <sup>42</sup> 2001	Case-control studies recruiting from the Stockholm psychiatric register: 524 patients with schizophrenia and 1043 controls matched by age, gender, hospital, and parish of birth. OC data were obtained from birth records	There was a strong association between signs of asphyxia at birth and schizophrenia with an odds ratio of 4.4 (95% CI: 1.9-10.3), after adjusting for other OCs, maternal history of psychosis, and social class
Thomas et al, <sup>43</sup> 2001		The increased risk of schizophrenia associated with OCs (asphyxia in particular) was not significantly modified by gender, maternal history of psychosis, or age of onset. Limited statistical power

**Table 1.** Register-based studies of obstetric complications (OCs) and schizophrenia. NCP, National Collaborative Perinatal Project; ECA, Epidemiologic Catchment Area; RR, relative risk; CI, confidence interval.<sup>30</sup>

### Are the brain deviances in schizophrenia developmental in origin?

The most consistent deviances described in schizophrenia are an increase in ventricular size and subtle global and regional cortical volume reductions.<sup>58-62</sup> Wright et al<sup>63</sup> carried out a meta-analysis of 58 MRI studies, which included 1588 patients with schizophrenia. The mean lateral ventricular volume was greater (126%) than that of controls and the mean cerebral volume was smaller (98%). Relative to the cerebral volume reductions, the regional volumes of the subjects with schizophrenia were 98% for the frontal lobes, 94% for the amygdala/hippocampus, and 96.5% for the thalamus. Recently, voxel-based methods of analyzing structural MRI images have enabled the whole brain to be examined, and implicated particularly the medial temporal region, insula, and anterior cingulate.<sup>64,65</sup>

Certainly, brain changes are present near to the onset of the frank psychosis. This is demonstrated by the numerous reports of ventricular enlargement and other deviations in first-onset cases of schizophrenia<sup>66-68</sup> and in early-onset cases too.<sup>69,70</sup> Furthermore, there is an excess of congenital lesions in patients with schizophrenia, such as aqueduct stenosis, arachnoid and septal cysts, and agenesis of the corpus callosum and cavum septum pellucidum.<sup>71,72</sup> However, such abnormalities are distinctly unusual and the findings are generally much more subtle. Indeed, it is an open question whether these differences in brain structure found between people with schizophrenia and normal subjects are “brain abnormalities,” which are an intrinsic part of the disease process itself. Alternatively, they might be regarded as deviations within the normal range, which increase the risk of developing schizophrenia.

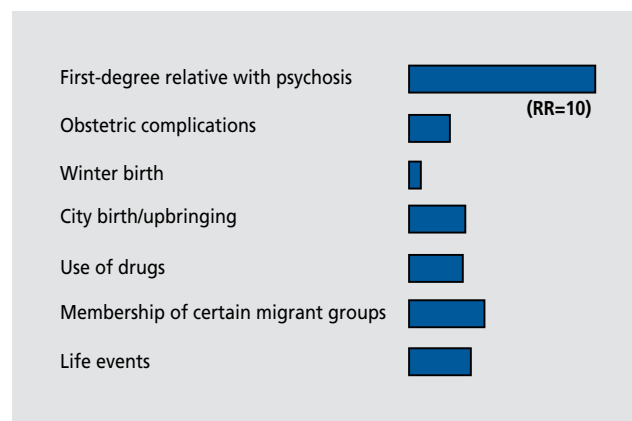
One piece of evidence does, however, point to fetal life. The normal brain is typically asymmetrical, and the development of brain asymmetry is usually complete by the middle of the third trimester of gestation. A number of studies revealed a reduced asymmetry in several brain areas in schizophrenia.<sup>73-75</sup> A recent meta-analysis, reviewing handedness, language, and anatomical studies, confirms the decreased anatomical and functional cerebral lateralization in schizophrenia.<sup>76</sup> This reduced asymmetry found in several brain structures in schizophrenia is likely therefore to originate during fetal life. Neuropathological studies have largely confirmed the neuroimaging data concerning gross anatomy,<sup>77</sup> but there

has been much less consistency concerning histopathological findings. Three influential papers reported cytoarchitectonic findings suggestive of altered neuronal migration during fetal life.<sup>78-82</sup> Unfortunately, none of these initial reports has been fully replicated.<sup>83-87</sup> The other histopathological evidence frequently cited in support of a fetal origin of schizophrenia is the absence of gliosis in postmortem schizophrenic brain.<sup>88-90</sup> Certainly, the absence of fibrillary gliosis strongly argues against an adult-onset degenerative process; however, it does not prove a developmental one.<sup>91</sup> Thus, we can conclude that there are currently no replicated histopathological findings that unequivocally implicate aberrant neurodevelopmental in fetal life.

### The causes of structural brain deviances in schizophrenia: nature or nurture?

The environmental factors that we discussed earlier have only a modest risk-increasing effect, and generally operate in the context of genetic risk (*Figure 1*).<sup>92</sup> The genetic predisposition to schizophrenia has been well established and, recently, two large twin studies have confirmed that a high proportion of the variance in liability to schizophrenia is due to additive genetic effects.<sup>93-95</sup>

A number of investigators have asked whether the first-degree relatives of people with schizophrenia show any of the same brain structural deviations as their schizophrenic kin. The Maudsley Family Study<sup>96</sup> examined



**Figure 1.** Individual risk factors and their effect sizes. RR, relative risk. Modified from reference 92: Van Os J, Jones P, Sham P, Bebbington P, Murray RM. Psychosis as a continuum of variation in dimensions of psychopathology. In: Haffner H, Gratz W, eds. *Search for the Causes of Schizophrenia*. Vol 4. Berlin, Germany: Springer; 1999:59-80. Copyright © 1999, Springer.

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patients and well relatives in families with several schizophrenic members, ie, families assumed to transmit a high genetic load. Sharma et al<sup>96</sup> carried out MRI scans in patients, well relatives, and controls. They further divided the relatives into standard relatives and presumed “obligate carriers” (relatives who, although well themselves, have psychotic offspring and psychotic siblings or parents and therefore appear to be transmitting genetic risk). The so-called obligate carriers showed a similar increase in lateral ventricular volume to the patients themselves; other relatives were midway between patients and controls, as one might expect from a group in which some, but not all, carry susceptibility genes.<sup>97,98</sup> Stefanis et al<sup>99</sup> used the Maudsley Family Study samples to show that this is not the whole story. They compared hippocampal volumes in (i) people with familial schizophrenia, but no pregnancy or birth complications (OCs); (ii) people with schizophrenia with no family history but severe OCs; and (iii) controls. Reduction in the left hippocampal volume was associated with the diagnosis of schizophrenia, but this was accounted for by the patients with a history of severe OCs. Patients from the familial group did not differ from controls. This study confirms the work of McNeil et al<sup>100</sup> showing that decreased hippocampal volume in schizophrenia is in part a consequence of early environmental damage and points toward one causal mechanism, ie, severe OCs lead to hypoxia, which causes left hippocampal (and other cerebral) damage. This work contrasts with other studies that found that the unaffected relatives of people with schizophrenia have decreased hippocampal volume.<sup>101-103</sup> It may be that the discrepancy lies in whether or not it was just the hippocampus or the hippocampal-amygdal complex that was measured.

## Other early environmental effects

A slight increase in risk for schizophrenia exists among individuals born in late winter/early spring.<sup>104,105</sup> These results point towards an etiological agent acting during gestation, birth, or early childhood rather than around the time of onset. While some studies suggested this seasonal effect could be secondary to exposure to influenza in the uterus during winter,<sup>45,106,107</sup> other research failed to find such a link.<sup>108</sup> Intrauterine rubella infection has also been put forward as a potential risk factor for schizophrenia.<sup>40,109</sup> Buka et al<sup>110</sup> studied blood samples of mothers of 27 cases with psychosis and 54 matched controls as

part of the Providence Collaborative Perinatal Project. Maternal blood samples collected during pregnancies in the early sixties were retrieved and analyzed for evidence of perinatal pathogens capable of affecting brain development. The offspring of mothers who had elevated levels of IgG and IgM immunoglobulins and antibodies to herpes simplex type 2 during pregnancy were at increased risk of developing schizophrenia and other psychotic illnesses in adulthood.

Other potential early hazards described are maternal malnutrition,<sup>111</sup> maternal diabetes mellitus,<sup>112</sup> and maternal stress.<sup>113,114</sup> Finally, Rantakallio et al<sup>115</sup> and Westergaard et al<sup>108</sup> demonstrated that the window of opportunity for risk-increasing insults is wider than was previously thought, as those exposed to childhood viral central nervous system (CNS) infections were five times more likely to develop schizophrenia than those not exposed. There is also some evidence that brain injury in childhood may increase the risk of developing schizophrenia.<sup>116</sup>

## What the simple neurodevelopmental model fails to explain

### Why does damage occurring in early life cause symptoms only decades later?

Brain maturation is a prolonged process that continues until well after adolescence, so one possible explanation for the late onset of symptoms is that lesions could lie silent until maturation affects the neuronal circuits that were deviant, but normally not functional, in childhood.<sup>117-121</sup> Animal models have given some support to this view; Lipska et al<sup>120</sup> reported that hippocampal lesions made to newborn rats remained relatively silent until adult life.

However, an alternative model suggests that at least some of the crucial developmental events occur in adolescence. Recent neuropathological studies report a decrease in the volume of the cortex, an increase in neuronal density, and also loss of synaptic markers, findings compatible with synaptic loss.<sup>122-124</sup> Keshavan and colleagues<sup>125</sup> have used magnetic resonance spectroscopy (MRS) to show that schizophrenics show a phosphomonoesterase pattern suggestive of failure of new synapse production and excessive synaptic reduction. They suggest that the ventricular enlargement and cortical volume decrement may arise in part from an excess of the

normal cortical pruning that occurs in normal adolescence.<sup>126</sup> This has been christened the “late” (as opposed to “early”) neurodevelopmental model.<sup>127</sup>

This model could perhaps explain the seemingly contradictory findings concerning whether brain deviance in schizophrenia occurs prior to illness onset or is progressive.<sup>128,129</sup> The initial evidence suggested the former, but in recent years there have been suggestions that some cerebral ventricular enlargement and volumetric reductions in the temporal lobes in schizophrenia may have a progressive course,<sup>130,131</sup> which is possibly limited in time.<sup>132</sup> Lieberman et al<sup>133</sup> examined 107 first-onset cases, of which 51 were followed over 1 to 6 years. They confirmed the presence of ventricular enlargement and hippocampal volume reductions at the time of the first episode. In addition, they reported a progressive increase in ventricular volume in those patients with poor outcome only, but found no further reductions in cortical or hippocampal volumes on follow-up. Another longitudinal study focusing on childhood-onset schizophrenia reported that brain abnormalities were progressing during adolescence, but became stable in early adulthood.<sup>134</sup> Further work from the same group using high-resolution MRI scans showed that, compared with 12 matched controls, 12 adolescent early-onset patients had accelerated gray matter loss over a 5-year follow-up period. The authors interpret the dynamics of their anatomical findings in the light of family and twin imaging studies. They conclude that early neurodevelopmental deviances and later gray-matter loss are probably related and influenced by common genes, while they also support the notion that nongenetic triggers contribute to the onset and initial progression of the illness.<sup>135</sup> Possibly, first-onset patients presenting in childhood or adolescence may show the brain structural consequences of synaptic pruning, but those samples that comprise adult patients may show little change. This is an interesting view, but the supporting evidence so far is sparse. Allin and Murray<sup>136</sup> point out that many questions remain on the progression of brain morphology deviances in schizophrenia. Finding answers will require larger samples, controlling for the interactions of clinical outcome and medication, and longer follow-up periods.

### Later-onset schizophrenia

As noted earlier, a key difficulty for the “early” neurodevelopmental model is why the onset of frank psy-

chosis does not occur until several decades after the supposed developmental lesion(s). The “late” developmental model attempts to explain the onset in the second decade of life by invoking brain maturational events in adolescence, but, of course, cases with such an onset remain a minority. People develop schizophrenia throughout adult life into old age, and late-onset patients show relatively normal premorbid adjustment.<sup>137</sup> Furthermore, according to Howard et al,<sup>138</sup> the relatives of late-onset psychosis cases seem to carry less genetic loading for schizophrenia and are at higher risk for affective disorders. A potential explanation is that patients with late-onset schizophrenia may in fact have a different illness, possibly with etiological factors in common with affective psychosis; a second possibility is that the symptoms may arise from brain degeneration.<sup>139</sup>

What factors influence the age of onset of psychosis? Onset is generally earlier in males than in females.<sup>137,140</sup> Furthermore, those patients with a family history of schizophrenia tend to have an earlier age of onset than cases with less genetic risk,<sup>141,142</sup> regardless of their gender.<sup>143</sup> As noted earlier, OCs may also be associated with early onset,<sup>36,45,144</sup> as are other indicators of aberrant neurodevelopment, such as premorbid cognitive and behavioral deficits, minor physical anomalies, smaller brains, and larger cerebral ventricles.<sup>145,146</sup>

One may conclude that the role of neurodevelopmental impairment is most marked in early-onset schizophrenia, but it becomes progressively less obvious in patients with increasing age of onset. In other words, only a proportion of the variance in liability to schizophrenia can be attributed to impaired brain development.

## Is schizophrenia more than a brain disorder? The role of social risk factors

The view that schizophrenia is simply a brain disorder remained unchallenged from the late 1970s to the late 1990s. Thus, the simple neurodevelopmental model implied that schizophrenic symptoms are simply a consequence of the development of aberrant neural networks.<sup>147</sup> However, there is increasingly robust evidence that social risk factors play a crucial role in the development of schizophrenia (*Figure 2*).<sup>30</sup> However, for most social risk factors, while there is a clear association with schizophrenia, the direction of causality has not been demonstrated.

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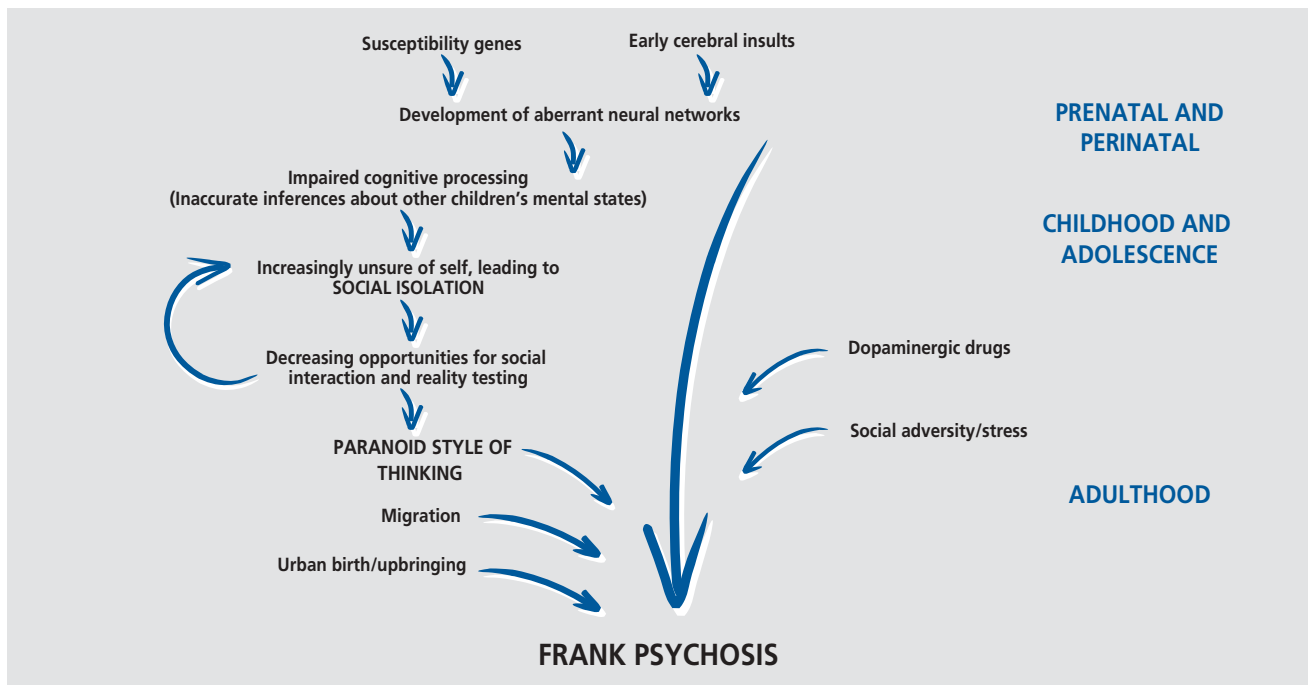
## Could an adverse upbringing convey higher risk for schizophrenia?

In the British 1946 Birth Cohort, those 4-year-old children rated as having a poor mother–child relationship had a 6-fold increase in risk for schizophrenia later in life. Of course, this does not tell us whether poor mothering was a causal risk factor, or whether the preschizophrenic child was so deviant as to be unable to form a close bond with the mother.<sup>14</sup> However, children of schizophrenic mothers who were adopted away and then reared in adverse circumstances have a higher risk than those brought up in loving homes by stable adoptive parents.<sup>148</sup> Furthermore, Mirsky et al<sup>149</sup> noted that children with known genetic risk for schizophrenia were more likely to develop the disorder if they lived on a kibbutz, rather than in a family home. Overall, kibbutz children did not have a higher risk, suggesting that high-risk children carry a genetic vulnerability to the social environment.

## The effect of being born or brought up in a city

Several studies in the 1990s indicated that being born or brought up in a city increases the risk for schizophre-

nia.<sup>150</sup> In one of the most impressive, Mortensen et al<sup>151</sup> examined a Danish national sample and showed that the relative risk for schizophrenia associated with urban birth was 2.4 and that there was a dose–response relationship (the larger the town of birth, the greater the risk) suggesting a causal effect. Mortensen and colleagues pointed out that because so many people are born and live in cities, a relatively small increase in risk would cause a large increase in the numbers of people with the disease. Indeed, they calculated that the population-attributable risk (PAF) for urban birth was 34.6%, compared with 9% or 7% for having a mother or father with schizophrenia, respectively. The estimate of PAF appears robust, as a similar PAF has previously been reported in data from another country,<sup>152</sup> where, in addition, it was shown that the effect of urban birth/upbringing is not confounded by urban residence in adult life.<sup>153</sup> Finally, in a further analysis of the above Danish study, Pedersen and Mortensen<sup>154</sup> have shown that the association between urbanization and schizophrenia is based on continuous or repeated exposures during upbringing (not just urban birth), and that there is indeed a dose–response relationship between urban upbringing and risk for schizophrenia.



**Figure 2.** The cascade of increasingly abnormal function that culminates in the onset of full-blown psychosis, including the main risk factors for psychosis over life.<sup>30</sup>



### The risk associated with isolation

The Swedish conscript study discussed above also looked at the interaction of premorbid personality and social isolation. Young men who felt they were more sensitive than their peers, had fewer than two close friends, and did not have a girlfriend had an increased risk of later developing the disorder.<sup>155</sup> Once again this raises the question of whether these characteristics are an expression of a schizoid or schizotypal personality or whether they are in themselves independent risk factors. Until proven otherwise, it is wise to consider that both may be true, ie, individuals with a schizoid or schizotypal personality may be less able to make social relationships, and then the social isolation itself may cause them to become increasingly deviant. Van Os et al<sup>156</sup> found that people who were single had a slightly higher risk of developing psychosis if they lived in a neighborhood with fewer single people, compared with a neighborhood with many other single people. The authors suggested that single status might give rise to perceived (or actual) social isolation if most other people are living with a partner. The question of whether social isolation may increase the risk for schizophrenia (or rather whether a close relationship may be protective) is also raised by Jablensky et al,<sup>157</sup> who showed that marriage had a protective effect for males, and that this was not simply a consequence of better-adjusted males being able to marry.

### The migration effect

As far back as the 1930s, Odegaard<sup>158</sup> noted that Norwegian migrants to the USA were at increased risk for schizophrenia, while as recently as 1999, Mortensen et al<sup>151</sup> reported that children born in Greenland to Danish mothers had a relative risk of 3.7 for schizophrenia. However, the most striking findings have come from the UK, where numerous studies have reported an increased incidence of schizophrenia among African-Caribbean people.<sup>159</sup> Misdiagnosis,<sup>160</sup> drug abuse,<sup>161</sup> and increased neurodevelopmental insult<sup>162-164</sup> have been largely ruled out as possible explanations. A high genetic predisposition seems unlikely, since the increased risk is not shared by those living in the Caribbean.<sup>165</sup> Indeed, Hutchinson et al<sup>166</sup> found that morbid risks for schizophrenia were similar for parents and siblings of white and first-generation African-Caribbean patients. However, morbid risk

for siblings of second-generation African-Caribbean psychotic probands was approximately 7 times higher than that for their white counterparts. This study, which almost exactly replicates the work of Sugarman and Craufurd,<sup>167</sup> suggests the operation of an environmental agent that is operating on this population in the UK, but not in the Caribbean; social isolation and alienation are plausible candidates. Finally, Boydell et al<sup>168</sup> noted that the incidence of schizophrenia in migrants is greatest when they live in areas with few other migrants; again one possible explanation is relative isolation and lack of social support.

### Stressful life events

Three prospective studies have found an association between life events and onset of psychosis.<sup>169-171</sup> Stressful life events in the 3 weeks preceding onset or relapse seemed important, although the effect size was greater in affective psychosis than in schizophrenia. However, it is difficult to exclude the possibility that some of these events may have been caused by the patient, and thus reflect his/her inherited personality characteristics.

### Further environmental risks: the impact of drugs

It is well known that abuse of dopamine-releasing drugs such as amphetamines and cocaine can precipitate psychosis; cannabis appears to have similar risk-increasing effects, though over a longer period of time. Again, there is the question of whether individuals with certain genotypes may selectively expose themselves to drugs to whose psychotogenic effects they are particularly vulnerable. For example, in the Swedish conscript study discussed above, Andreasson et al<sup>172</sup> found that heavy cannabis consumption at the age of 18 was associated with a 6-fold increased risk of developing schizophrenia over the next 13 years. The dose-response relationship suggested causality. But might the 18-year-olds have been taking cannabis because they were already disturbed? Over half of those who admitted to heavy cannabis use at age 18 already had a psychiatric diagnosis. However, even when these individuals were excluded, cannabis consumption remained a risk factor for later psychosis. This finding has recently been replicated in a cohort of children followed up in Dunedin

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(New Zealand). Cannabis consumption at age 15 years was associated with a significantly increased risk for later schizophreniform disorder. Again there was an interaction with psychiatric symptoms, so that those who had shown mild but quasi-psychotic ideas at age 11 years were especially vulnerable to the risk-increasing effects of cannabis. As in the Swedish study, the effect of cannabis consumption remained significant when this was taken into account.<sup>173</sup>

McGuire<sup>161</sup> et al showed that the relatives of patients with cannabis-associated psychosis had an increased morbid risk themselves. Chen<sup>174</sup> noted similar findings for methamphetamine use in a large Taiwanese sample. Those methamphetamine abusers who developed a psychosis were distinguished from those who did not by a greater frequency of schizoid and schizotypal traits in childhood and by having more relatives affected with schizophrenia. Thus, it may be that some individuals abuse drugs because they already have psychiatric problems and, among them, it is those who have a genetic predisposition to psychosis who are particularly likely to develop a schizophreniform psychosis.

## Conclusion

Genetic epidemiological and molecular studies both imply that liability to schizophrenia is inherited not through a single major gene, but through a number of

genes of small effect. Some of those genes are likely to be involved in the control of neurodevelopment<sup>175</sup> and some are probably shared with other psychotic conditions such as bipolar disorder.<sup>94</sup> Studies of the relatives of patients with schizophrenia indicate that families transmit minor developmental deviations, which are relatively innocent in themselves; for example, slight alterations in brain structure,<sup>96</sup> in neurophysiology,<sup>176</sup> or in neurocognition.<sup>97</sup> However, when a child is unlucky enough to inherit several of these traits, and is also exposed to environmental insults to the developing brain, such as OCs, then their cumulative effect puts that individual on a trajectory of increasing deviance. Well-designed, whole-population-based studies have confirmed that children destined to develop schizophrenia show an excess of minor emotional, neuromotor, and cognitive difficulties, and that these lead them to become increasingly isolated from their peers and to harbor odd ideas. There are some interesting but as yet unconfirmed claims that this early developmental deviance may then be compounded by maturational brain changes during adolescence, which result in a lability of the dopaminergic response to stress. The developmentally compromised individual is then especially vulnerable to (and indeed may selectively expose him/herself to) certain stresses during adolescent or adult life, such as abuse of drugs and social adversity, especially isolation. □

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### **Un modelo convincente de esquizofrenia debe incorporar factores de riesgo psicológicos y sociales, así como del neurodesarrollo**

*Alteraciones sutiles del desarrollo cerebral, causadas por genes y daños ambientales tempranos (como por ejemplo complicaciones obstétricas), parecen jugar un papel clave en proyectar ciertos individuos hacia el desarrollo de esquizofrenia. Estudios de cohortes y de sujetos con alto riesgo demuestran que aquellos niños destinados a sufrir esquizofrenia tienen retrasos del desarrollo y sutiles déficits motores y cognitivos (especialmente en coordinación y lenguaje). Estos problemas neurocognitivos causan dificultades en interacciones sociales y el aislamiento progresivo que estos niños experimentan aumenta sus probabilidades de generar ideas paranoides o extrañas. Esta cascada de desarrollo anómalo progresivo probablemente se complementa con alteraciones de la maduración cerebral durante la adolescencia, resultando en una mayor labilidad de los sistemas dopaminérgicos de respuesta al estrés. En consecuencia, estos jóvenes son más vulnerables al abuso de drogas liberadoras de dopamina, así como a otros factores de riesgo como la migración o los acontecimientos vitales estresantes. El aislamiento social podría ser una vía común para diversos factores de riesgo socioambientales.*

### **Un modèle plausible de la schizophrénie doit intégrer les facteurs de risque psychologiques, sociaux et neurodéveloppementaux**

*Des altérations discrètes du développement cérébral d'origine génétique ou liées à des facteurs de risque environnementaux précoces, tels que les complications obstétricales, interviennent en propulsant certains sujets sur la trajectoire menant vers la schizophrénie. Des études de cohorte et portant sur les risques élevés montrent que les enfants prédestinés à la schizophrénie ont tendance à présenter un retard touchant les grandes étapes du développement psychomoteur ainsi que des altérations neuromotrices et cognitives discrètes (touchant en particulier la coordination et le langage). Ces désordres entraînent des difficultés dans leurs relations interpersonnelles et leur aliénation mentale progressive fait que ces enfants à risque sont plus enclins à exprimer des idées bizarres ou paranoides. Cet enchaînement de développements déviants croissants pourrait alors être aggravé par des modifications de la maturation cérébrale au cours de l'adolescence entraînant une instabilité de la réponse dopaminergique au stress. De ce fait, le sujet est plus sensible aux effets de l'emploi excessif de médicaments libérant de la dopamine et aux autres facteurs de risque tels que la migration ou les événements de vie stressants ; l'isolement social pourrait être une voie commune sous-jacente à plusieurs facteurs de risque sociaux.*

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