

FEATURE REVIEW

The neurodevelopmental model of schizophrenia: update 2005

JL Rapoport¹, AM Addington¹, S Frangou² and MRC Psych²¹Child Psychiatry Branch, NIMH, NIH, Bethesda, MD, USA; ²Section of Neurobiology of Psychosis, Institute of Psychiatry, Kings College London, London, UK

Neurodevelopmental models of schizophrenia that identify longitudinal precursors of illness have been of great heuristic importance focusing most etiologic research over the past two decades. These models have varied considerably with respect to specificity and timing of hypothesized genetic and environmental 'hits', but have largely focused on insults to prenatal brain development. With heritability around 80%, nongenetic factors impairing development must also be part of the model, and any model must also account for the wide range of age of onset. In recent years, longitudinal brain imaging studies of both early and adult (to distinguish from late ie elderly) onset populations indicate that progressive brain changes are more dynamic than previously thought, with gray matter volume loss particularly striking in adolescence and appearing to be an exaggeration of the normal developmental pattern. This supports an extended time period of abnormal neurodevelopment in schizophrenia in addition to earlier 'lesions'. Many subtle cognitive, motor, and behavioral deviations are seen years before illness onset, and these are more prominent in early onset cases. Moreover, schizophrenia susceptibility genes and chromosomal abnormalities, particularly as examined for early onset populations (ie *GAD7*, 22q11DS), are associated with premorbid neurodevelopmental abnormalities. Several candidate genes for schizophrenia (eg dysbindin) are associated with lower cognitive abilities in both schizophrenic and other pediatric populations more generally. Postmortem human brain and developmental animal studies document multiple and diverse effects of developmental genes (including schizophrenia susceptibility genes), at sequential stages of brain development. These may underlie the broad array of premorbid cognitive and behavioral abnormalities seen in schizophrenia, and neurodevelopmental disorders more generally. Increased specificity for the most relevant environmental risk factors such as exposure to prenatal infection, and their interaction with susceptibility genes and/or action through phase-specific altered gene expression now both strengthen and modify the neurodevelopmental theory of schizophrenia.

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Schizophrenia is a complex and severe brain disorder with poorly defined etiology and pathophysiology. For more than two decades, the 'neurodevelopmental' model has been the prevailing explanatory theory. In its simplest form this model posits that schizophrenia is the behavioral outcome of an aberration in neurodevelopmental processes that begins long before the onset of clinical symptoms and is caused by a combination of environmental and genetic factors.^{1,2}

Evidence for this broad neurodevelopmental model is overwhelming and comes from many diverse lines of research. As reviewed below, individuals who later develop schizophrenia are more likely than healthy

comparison subjects to have experienced pre- or perinatal adverse events or to have been exposed to potentially harmful stressors. Preschizophrenic individuals also exhibit increased rates of minor physical anomalies, which are subtle indicators of disturbed prenatal development of the ectoderm,³ as well as minor deviations in motor, cognitive, and social development. These observations strongly suggest that abnormalities in brain function are present very early in life in individuals who later develop schizophrenia.

Attempts to provide a more specific conceptualization of the neurodevelopmental hypothesis led to tension between those favoring an early (pre- or perinatal), 'static' brain lesion model^{4,5} and those advocating a late adolescent disturbance in brain maturation.^{6,7} Initial postmortem studies appeared to support the early neurodevelopmental model as they reported abnormalities in neuronal migration and organization, considered fetal in origin.^{8,9} Subsequent

Correspondence: Dr JL Rapoport, Building 10, Room 3N202, 10 Center Drive, MSC 1600, Bethesda, MD 20892-1600, USA.

E-mail: rapoport@helix.nih.gov

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and more reproducible observations of reduced neuronal size and arborization,¹⁰ which could have developed later in life, indicated that the pathophysiological processes involved in schizophrenia need not be restricted to the pre- or perinatal period. This is in agreement with brain imaging studies that reveal a pattern of progressive changes both for early onset as well as chronic adult patients. Candidate genes for schizophrenia and genes involved in development generally are typically expressed across developmental periods, often in different brain regions. These provide a probable basis for the widespread brain and behavioral precursors to schizophrenia. The heterogeneity of these genes and the 'noise' inherent in development² could further contribute to the variable developmental course.

This highly selective review covers recent work in the areas of prenatal risk/development, premorbid risk, brain imaging, and genetics as they relate to the neurodevelopmental model of schizophrenia. These new data provide an increasingly specific formulation of the nature and timing of insults to neurodevelopmental processes at least for some patients.¹¹

As variability in age of onset is a factor that all models must take into account, particular attention is placed on results from studies of patients with very early age of onset. These studies are fueled by the assumption that some particularly salient risk factors account for the greater severity and very early onset. New data continue to support the basic tenet of the neurodevelopmental origins of schizophrenia.

Pre- and perinatal risk

A large number of studies find some relationship between obstetric complications (OCs) and later onset of schizophrenia. The two main reasons for the interest in OCs are the availability of relevant data from objective and contemporaneous medical records and the specificity of the nature and timing of such events.

A meta-analysis of population-based data¹² found significant estimates for three main categories of OCs: (1) complications of pregnancy (bleeding, pre-eclampsia, diabetes, and rhesus incompatibility), (2) abnormal fetal growth and development (low birth weight, congenital malformations, and small head circumference), and (3) complications of delivery (asphyxia, uterine atony, and emergency Cesarean section). Although a number of methodological issues pertaining to sampling biases and accuracy of information may raise skepticism about the contribution of individual obstetric events, the increase in overall risk for schizophrenia conferred by such events seems genuine but small. Based on meta-analytic studies, the pooled odds ratio of the effect of exposure to OCs on the subsequent development of schizophrenia has been estimated to be about 2.0 (95% confidence interval 1.6–2.4).^{13,14}

Several studies suggest that the impact of obstetric complications may be higher for individuals with

greater impairment, and with an early age of onset (usually defined as onset before 18 years of age).^{15–19} This raised the possibility that childhood onset cases would reflect an even stronger association with obstetrical adversity. However, findings from the National Institute of Mental Health (NIMH) study on childhood onset schizophrenia (COS; onset before age 13 years), which included 60 COS patients, and from the Maudsley Early Onset Schizophrenia (EOS; onset before age 17 years) Study, which included 70 patients with late childhood and adolescent onset, do not indicate increased overall rate of OCs with the exception of excessive vomiting in first trimester relative to 53 healthy siblings^{20,21} and higher frequencies of fetal distress and forceps delivery¹⁸ compared to tightly matched healthy children. In sum, while sample sizes were moderate, we can say that any strong effects or pre- or perinatal adversity (eg odds ratios of 3 or greater) do not appear to precipitate a particularly early onset of schizophrenia.

Obstetrical events in schizophrenia are often considered as having a direct causative effect but none of the available data can refute the hypothesis that they are merely markers of some other causal process, particularly since OCs are themselves multifactorial in origin. For example, low birth weight and small head circumference reflect fetal growth retardation but almost *any factor* affecting the fetus adversely will retard its growth. Conversely, exposure to OCs in the prenatal period is associated with a number of unfavorable outcomes, many of which are unrelated to schizophrenia or even brain development in general. For example, intrauterine malnutrition is associated with increased risk for schizophrenia²² but also for other psychiatric²³ and nonpsychiatric disorders such as cardiovascular disease.²⁴

Some OCs involve specific biological mechanisms that may be more relevant to the pathogenesis of schizophrenia. Bleeding in pregnancy, pre-eclampsia, and delivery complications are thought to reflect chronic hypoxia or acute asphyxia.¹² The association between schizophrenia and serologically confirmed *in utero* influenza,^{25,26} rubella, and respiratory infections²⁵ may reflect abnormal maternal immune response. Elevation of proinflammatory cytokine levels is a key component of the response to pathogens. Compared to pregnancies leading to healthy offspring, maternal second trimester levels of interleukin-8 (IL-8) are significantly elevated in pregnancies of schizophrenic offspring,²⁶ while maternal levels of another cytokine, tumor necrosis factor alpha (TNF-alpha) were increased in late gestation in pregnancies giving rise to cases of psychosis including schizophrenia.²⁷

It is still not clear how hypoxic-ischemic damage or increased maternal cytokine levels contribute to the schizophrenia phenotype. Cannon and co-workers¹⁶ argue that ischemic damage leads to neuronal loss in temporal brain regions such as the hippocampus, which are known to be involved in schizophrenia (see premorbid risk below) and are sensitive to anoxic

insults.²⁸ In late adolescence, synaptic pruning may exacerbate the deficits of the reduced neuronal reserve leading to psychosis. Gilmore *et al*²⁹ reported inhibition of neuronal dendritic growth in rat neuronal cultures exposed to cytokines and argue for a similar effect in the developing brain of individuals that later present with schizophrenia. Further Watanabe *et al*³⁰ assessed the effects of newborn rats treated with leukemia inhibitory factor (LIF) and found that LIF-treated rats displayed decreased motor activity during juvenile stages, and developed abnormal prepulse inhibition during and after adolescence indicating a discrete impact on neurobehavioral development. Tohmi *et al*³¹ similarly found that cytokine-treated neonatal rats produced neurobehavioral deficits in adulthood. Both theories suffer from lack of direct supporting evidence but provide a useful heuristic function.

It is increasingly apparent that environmental factors (such as obstetric complications) interact with genetic factors. For example, fetal hypoxia predicts reduced gray matter (GM) and increased cerebrospinal fluid (CSF) volume bilaterally throughout the cortex in schizophrenic patients and their siblings, but not in comparison subjects at low genetic risk for schizophrenia.³² Similarly, while maternal infection is a clear risk factor for neonatal stroke, inflammation usually acts in synergy with other risk factors including thrombophilias to increase this form of cerebral palsy.³³

Future studies will rely on large prospective populations and archived biological material (eg infant newborn blood spots, maternal blood samples) to better address these questions. With the widespread use of prenatal ultrasound scans, it is possible that fetal measures will also enhance the power to detect early insults.³⁴ This approach has yielded interesting results. Ultrasound imaging studies of fetal brain development show predictive value of fetal ventriculography for neurodevelopmental disorders and potentially for schizophrenia.²⁹

Premorbid risk

Follow-back, cohort, and special population studies show that the premorbid history of patients with adult onset schizophrenia is replete with a variety of subtle neurodevelopmental abnormalities in multiple domains beginning in childhood.³⁵ These are of relevance, as they are believed to reflect abnormalities in early brain development in regions underlying motor, cognitive, and social/emotional functioning.

Early developmental delays/abnormalities

There are numerous reports of developmental delays in preschizophrenic children. In a classic study, preschizophrenic children were found to have abnormal upper limb movements in home movies.³⁶ Two major British cohort studies, the National Survey of Health and Development and the National Child Development study, found delays in the speech and

motor development of British children born during specified periods in 1946 and 1958, respectively.^{37,38} Such abnormalities were most obvious before the age of 2 years for motor milestones and between the ages of 2 and 15 years for language development.^{36,37} The increased risk occurred across the entire range of values reflecting some underlying general risk rather than a 'threshold' effect.³⁷

Retrospective and clinical studies show that speech and language deficits increase in frequency and severity as age of onset declines.³⁹ Further, only 15% of COS/early onset patients do not exhibit such delays.^{40–42} Finally, motor abnormalities appear to be trait markers for schizophrenia as they have been noted in both drug-free patients and in their unaffected first-degree relatives.^{43,44}

Social and cognitive development

Impairments in social development have been noted in a variety of studies most notably the British cohort studies: the National Survey of Health and Development, and the National Child Development study,^{37,38} and the Danish High Risk Study.⁴⁵ All three document poor peer relationships, social isolation, and social anxiety and a gender effect with boys being more disruptive and girls being more withdrawn. Again, these studies generally indicate increasing risk over the whole range of developmental measures suggesting some underlying general risk for psychosis rather than a threshold model.³⁷

General cognitive ability, assessed between the ages of 7–17 years either by formal cognitive tests or by using educational achievement as a proxy measure, is lower in preschizophrenic children compared to their healthy contemporaries.^{37,38,46} Decline in general intellectual function (between ages 4 and 7 years)⁴⁷ and persistently low scores in cognitive testing³⁵ during early childhood (between ages 3 and 11 years) show some specificity for schizophrenia and schizophrenia spectrum disorders, while emotional and social problems seem to be nonspecific indicators of a variety of different adult psychiatric outcomes.³⁵

Wilke *et al*⁴⁸ found that in 146 healthy children aged 7–11 years, measures of general intellectual ability (IQ) correlated with the volume of subcortical GM structures and not cortical GM. In the adolescent group, who had a mean age of 15 years, there was a strong correlation between IQ with overall GM volume; in addition, they noted a strong positive correlation between IQ and anterior cingulate volume. The observation that *higher* cognitive ability appears related to *lower* GM volumes in posterior areas also supports the notion of a progressive 'frontalization' of cognitive function with higher cognitive abilities being associated with greater reliance on frontal regions. In schizophrenia, these volumetric relationships are different for *selected regions* and may reflect a functional compensation secondary to early neurodevelopmental impairment. For example, in early onset schizophrenia, IQ remains stable (after an initial

decline associated with illness onset) in spite of continuing cortical GM loss.^{49–51}

The presence of cognitive abnormalities in very young preschizophrenic children (even before age 2 years), while strongly suggestive of disturbance in cortical and subcortical brain development, is not necessarily of prenatal origin. As noted earlier, these brain regions mature early and the consequences of their disturbed function could become most evident at the age when the relevant brain systems are going through a period of rapid change. These developmental changes appear to be trait markers, as abnormalities in smooth pursuit eye movements (SPEM) and in selected neurocognitive tasks were seen in healthy siblings of childhood onset schizophrenia patients.^{52,53} In summary, subtle neurodevelopmental problems are common in schizophrenia, although their nonspecificity and high frequency in the general population (over 15% of children) make them weak predictors of full psychosis. Yet, these measures show promise as endophenotypic markers for genetic studies as addressed below.

Premorbid psychopathology

Kim-Cohen *et al*⁵⁴ have contributed to our understanding of premorbid psychopathology in schizophrenia by including Diagnostic and Statistical Manual (DSM) diagnostic data in a prospective study at ages 11, 13, 15, 18, 21, and 26 years for a representative birth cohort of 1037 individuals participating in the Dunedin Multidisciplinary Health and Development Study. In this study, nearly 53% of individuals who were diagnosed as having schizophrenia or schizophreniform disorders at age 26 years already had another psychiatric diagnosis when seen at age 15 years. Unlike mood and anxiety disorders in childhood, which generally preceded their adult forms, schizophreniform disorder was preceded by a broad array of juvenile diagnoses including anxiety, depression, conduct disorder/oppositional defiant disorder, and attention deficit hyperactivity disorder.

Premorbid diagnoses for the NIMH childhood onset patients ($N = 75$) similarly included anxiety disorders (57%) and pervasive developmental disorders (26%, J Rapoport, unpublished data). There was no predictive specificity of these earlier diagnoses for schizophreniform disorder, as elevated rates for these disorders were also seen in individuals with other adult psychiatric outcomes. These varied premorbid diagnoses, given their lack of specificity to schizophrenia, suggest a generalized early impairment and most probably reflect the greater potency of the developmental risk genes. Alternate interpretations include locus heterogeneity, varied environmental stressors or toxins, and 'noise' in the developmental system.²

In the Dunedin cohort, and in contrast to the nonspecific pattern described above, it was also noted that at age 11 years nearly 15% of the sample ($n = 126$) reported some delusional or hallucinatory experience.⁵⁵ According to the strength of the psychotic experience, these individuals were divided into those

with weak ($n = 103$) and those with strong symptoms ($n = 13$). At 26 years of age, 2% of individuals without prior psychotic experiences, 9.5% of the weak, and 25% of the strong symptoms group were diagnosed with schizophreniform disorder. Early psychotic symptoms increased the risk specifically for schizophreniform disorder by a factor of 5 and 16.4 in the weak and strong symptom groups, respectively. This is an important finding since previously it had been accepted that psychotic symptoms occurring in nonpsychotic children had little predictive power for future schizophrenia,⁵⁶ and indeed the presence of isolated and transient psychotic experiences should not be equated with the more systematic, pervasive, and persistent psychotic symptoms that herald the onset of schizophrenia. However, these new data showed predictive power for 'strong' psychotic symptoms, apparently contradicting the predominant view that psychotic symptoms associated with schizophrenia are produced only when higher order association systems 'come on line' later in development. Cannon *et al*³⁵ noted that those reporting strong psychotic symptoms at age 11 years also had significant impairments in motor development, receptive language, and intelligence.³⁵ Again, the degree of premorbid impairment is associated with schizophrenia severity and earlier age of onset and thus reflects an ongoing earlier process directly related to the cause of schizophrenia.

Brain morphology in schizophrenia

Neuroimaging

There is a large body of research on brain structural abnormalities in schizophrenia most recently using MRI techniques, which has been covered in qualitative reviews and meta-analytic studies.^{57–59} There are many methodological issues relevant to the neuroimaging studies in schizophrenia including sampling biases, differences in imaging protocols, small sample sizes, and heterogeneity of patient samples with regards to illness characteristics and medication. It is not our intention to provide a detailed critical appraisal of this literature but here too, we focus on the patterns emerging in relation to the neurodevelopment model of schizophrenia.

Adult onset schizophrenia While there is controversy as to the nature of the neurobiological 'lesion', there is general agreement as to the widespread effects of the illness on many and diverse brain regions with subtle pathology that is still poorly understood.^{60–62} The most consistent brain MRI findings are increased volume of the lateral ventricles and slightly decreased overall brain, gray and white matter volumes (between 2 and 3%).^{57,58} Meta-analytic studies noted regional volume decreases in the hippocampus,⁶³ thalamus,⁶⁴ and frontal lobes.⁶⁵ Deficits are present in patients with first episode psychosis (usual mean age of patient groups was about 26 years) in the volume of the total

GM, hippocampus, and superior posterior temporal gyrus.^{66–69}

Longitudinal studies in adult onset patients provide evidence for progressive GM changes although the number of studies and sample sizes are small and the follow-up periods are relatively short.^{7,59} Pantelis *et al*⁷⁰ have published the only study examining the same group of individuals before and after the onset of psychosis. They obtained brain MRI data from 10 individuals at high risk for schizophrenia (mean age 18.9 years), by virtue of family history and/or presence of attenuated positive symptoms, who became psychotic within a 12-month period from their initial assessment. Transition to psychosis was associated with significant bilateral reduction in the cingulate gyri, left parahippocampal, and left orbitofrontal cortex. Longitudinal studies of first episode patients (mean age between 26 and 30 years) have provided evidence of increase in ventricular volume over a 2–4-year period,^{71,72} and small bilateral decrease (about 3%) in the frontal lobes over a 30 month period.⁷³ Similar decline in frontal lobe volume and posterior superior temporal GM volume has also been reported in chronic schizophrenia patients (mean age 39 years) over a 4 year period.⁷⁴

Early onset schizophrenia (A) Normal brain developmental trajectories. In the last decade, there has been a concerted effort to obtain normative data for human brain growth across the understudied child and adolescent age period. The anatomic development of subcortical structures, including the amygdala, basal ganglia, and thalamus, has been shown to be relatively complete by late childhood,^{75,76} with cortical regions having substantially longer developmental trajectories. GM volume increases in late childhood and decreases during puberty following a consistent ‘back to front’ pattern.⁷⁷ Based on studies of primate and human cerebral cortical development, these volumetric changes are thought to reflect initial overproduction followed by selective elimination and structural alterations of dendritic synapses.^{78,79} This wave of GM maturation is first seen in the dorsal parietal cortices, particularly the primary sensorimotor areas. It then progresses rostrally over the frontal cortex moving caudally and laterally over the parietal, occipital, and finally the temporal cortices. Within the frontal lobes, the frontal pole and precentral gyrus lose GM first with the dorsolateral prefrontal and orbitofrontal regions maturing last, towards the end of the adolescent period. Medial aspects of the temporal lobe mature early while the lateral areas representing higher integrative areas are among the last regions to mature.⁷⁷

(B) Clinical studies of early onset schizophrenia. Anatomic MRI studies of childhood onset schizophrenia cases show GM reduction and ventricular enlargement typical of that seen in adults.⁸⁰ In contrast to adult onset schizophrenia, changes in temporal lobe structures do not appear to be a key feature of childhood schizophrenia. Four independent reports find no hippocampal volume reduction

in this age group.^{81–84} One study has found right-sided superior temporal gyrus volume reduction,⁸⁵ while in another study this finding was absent at baseline but present at a 2-year follow-up.⁸⁶ In contrast, the thalamus appears to be reduced in volume or area in EOS.^{80,87}

Longitudinal data from EOS subjects, mostly available from the NIMH cohort, show striking progressive changes. In the most sophisticated analysis to date, Thompson *et al*⁸⁸ examined longitudinal structural changes over a follow-up period of 5 years in 12 COS subjects and 12 matched controls. The earliest deficit was striking parietal GM loss, which then progressed anteriorly into the temporal lobes, sensorimotor and dorsolateral prefrontal cortices, and frontal eye fields. Moreover, this difference is diagnostically specific as it is not seen for children with atypical and affective psychoses who are receiving the same medications.⁷⁷ In the same cohort of patients there was also progressive increase in ventricular volume and decrease in hippocampal volume.⁷⁶ These changes appear to be exaggerations of normal cortical development as shown in Figure 1.

Longitudinal data from the Maudsley EOS study ($N=??$) also show that, over an average interval of 4 years, patients present with significant reductions bilaterally in the dorsal and ventral prefrontal cortex, the superior parietal cortex, the middle and inferior temporal gyrus, and the thalamus and cerebellum. Left-sided reductions were observed in the anterior cingulate and paracingulate gyrus, cuneus and precuneus, and the superior temporal gyrus (S Frangou, unpublished data).

The above data show that (1) the disease process continues throughout the lifespan and (2) the pattern/trajectory of brain changes in schizophrenia appears to represent an exaggeration of normal brain development. As noted previously, the GM changes, both early and late, may be useful endophenotypes for future genetic, prenatal risk,⁸⁹ and/or treatment studies.

Postmortem brain findings in schizophrenia and neurodevelopmental models

Early postmortem findings reported neuronal disarray, especially in lamina II of the entorhinal cortex, and abnormal migration of subplate neurons in the neocortical white matter, which were strongly supportive of prenatal neurodevelopmental abnormalities in neuronal migration and organization. However, the current consensus is that in schizophrenia abnormalities in neuronal size, arborization, and synaptic organization are far more reliable findings but offer no specific information with regards to their timing.⁶⁰ Abnormalities have recently been reported in associated glial elements, particularly oligodendrocytes, which contribute to myelination and synaptic integrity.^{89,90} The current emphasis in neuropathological studies is on synaptic structure and function, based in part on the observation that nearly all susceptibility genes identified for

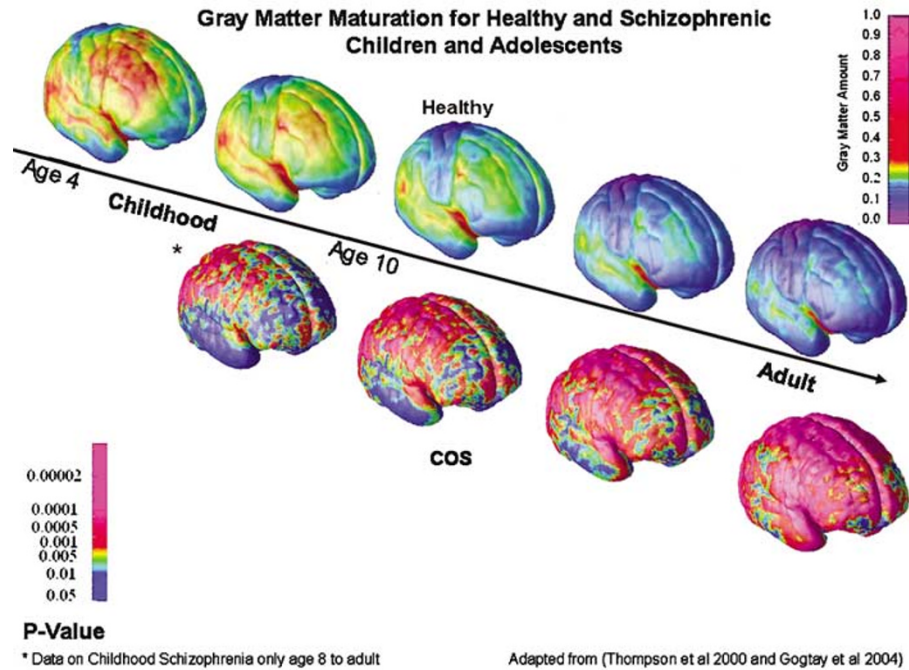


Figure 1 Gray matter maturation for healthy and schizophrenic children and adolescents.

schizophrenia affect on cell signaling.⁶² The application of microarray technology to postmortem brain studies also has led to the hypothesis of schizophrenia as ‘a disease of the synapse’.^{91–95} Mimics’ group found a consistent decrease in the number of transcripts encoding proteins that regulate synaptic function. That model postulates that impaired synaptic transmission during childhood and adolescence results in altered synapse formation or pruning (or both), which leads to the clinical onset of the disease. This formulation is consistent with the imaging studies discussed previously documenting a relative and progressive GM loss during adolescence through adulthood. Moreover, as described in greater detail below, GM loss in childhood onset cases has been associated with risk alleles in *GAD1*,⁹⁶ a gene under-expressed in prefrontal cortex of patients with schizophrenia.⁹⁷

Recent developmental human brain studies document changing BDNF expression across different developmental periods with increased expression paralleling maturation of the prefrontal cortex.^{98,99} It is likely that the identification of more of these new ‘developmental intermediate phenotypes’ will be particularly important in the evaluation of candidate genes.

Genetics

Candidate genes

Genetic studies are rapidly advancing our understanding of neurodevelopment. Genetic research on schizophrenia has been strengthened by the recent reproducibility of susceptibility genes for this illness.

Currently, the best replicated schizophrenia susceptibility genes are *COMT*, *DTNBP1*, *NRG1*, *RGS4*, *DISC1*, and *G72*, while others, *GAD1*, *DAO*, *GRM3*, *PPP3CC*, *CHRNA7*, *PRODH2*, *AKT1*, *CAPON*, and *MRDS1* (*OFCC1*) require further study.⁶² Given several recent reviews on this subject,^{62,100} we will not go into detail about these genes, but rather expand on those that seem most relevant to neurodevelopmental models.

Discovery of schizophrenia susceptibility genes was achieved through different strategies, including positional cloning, functional genomics, cytogenetics, and expression studies on postmortem brains. While these candidate genes are biologically plausible and appear to have convergent effects on glutamatergic and other synapses, with the exception of *COMT*, no known polymorphism has been demonstrated to have a functional effect that could be involved in the development of schizophrenia. Neither specific alleles nor haplotypes in these genes are universally associated with schizophrenia in different populations, underscoring the need to identify true functional variants. Large-scale sequencing efforts of an entire gene in large samples of schizophrenics will be necessary to identify the disease-causative variants, and it remains to be seen which genes will prove to be of clinical importance. Newer brain imaging findings, however, now allow us to examine these genes in association with more completely characterized subject profiles, and together with postmortem brain expression studies permit analyses of gene effects closer to the underlying brain abnormalities. It is likely that many of these genes will prove to have an important role in neurodevelopment generally and

will be constructive for studying other neurodevelopmental disorders.

Genetic studies using the NIMH COS population were motivated by observations across pediatrics and medicine that early onset cases may be caused by more salient and fewer genetic defects with higher penetrance.^{101–103} As with breast cancer and Alzheimer's Disease, the familial risk for schizophrenia spectrum disorders appears higher for COS than in adult onset contrast groups.^{104,105} Given the extreme early onset and severity of the COS cases, more detrimental and/or penetrant mutations in known schizophrenia susceptibility genes were hypothesized for the COS sample, and this would enable detection of significant associations even in the face of reduced power due to relatively small sample size. The role of schizophrenia risk genes in the neurodevelopmentally impaired COS population suggests a greater 'hit' to underlying neurodevelopmental processes. Finally, given the high prevalence of pervasive developmental disorders within the NIMH COS sample, we tested genes that have been associated with autism risk to determine whether or not these genes might also be acting in this unique cohort and perhaps act as general risk factors for the neurodevelopmental problems in COS. In fact, this does not appear to be the case.¹⁰⁶

Using family-based association studies, several risk genes that were identified in adult onset schizophrenia (AOS) groups have been replicated for COS. In contrast, there is little evidence for an association between COS and genes associated with autism.¹⁰⁶ These findings support the biological continuity between childhood onset and adult onset schizophrenia. The use of biologically related endophenotypes may also aid in parsing out differential gene effects to different aspects of the schizophrenia syndrome. For early onset cases, developmental measures, in spite of the nonspecificity at a population level, appear to be particularly useful genetic endophenotypes for studying the influence of individual susceptibility gene risks (see below).

One gene not highlighted in the most recent review⁶² that deserves mention is *GAD1*. Postmortem brain studies have shown deficits in the cortical GABA (gamma-aminobutyric acid) system in schizophrenic individuals. Expression studies have shown a decrease in the major GABA-synthesizing enzyme (*GAD67*) mRNA levels in neurons in dorsolateral prefrontal cortex in schizophrenics relative to controls. Glutamic acid decarboxylase (GAD) is the key enzyme in the synthesis of GABA in inhibitory interneurons. In the COS sample, Addington *et al*⁸⁹ observed significant overtransmission of alleles at several adjacent SNPs in the 5' region of the *GAD1* gene. Further, the same risk alleles were associated with MRI measures of abnormal GM loss in the COS patients as shown in Figure 2.

In addition, one SNP was associated with a poor qualitative eye-tracking score, thought to reflect impaired frontal lobe function. These observations,

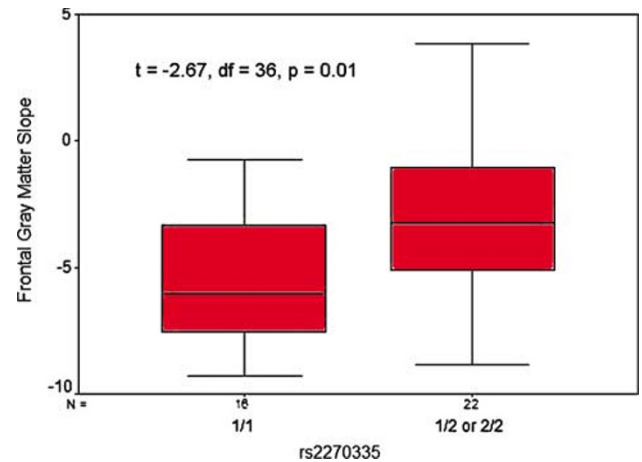


Figure 2 Slope of frontal gray matter loss during adolescence for the risk (1/1) vs non-risk (1/1 and 2/2) alleles of *GAD1* for children with schizophrenia.

when taken together with the postmortem expression studies and the positive results obtained from two independent adult onset schizophrenia pedigree samples,¹⁰⁷ suggest that the gene encoding *GAD67* may prove to be a fairly common genetic risk factor for schizophrenia and deserves more investigation in other samples. Straub *et al*¹⁰⁷ found evidence for association with individual SNPs and haplotypes in *GAD1* and schizophrenia in both the CBDB Sibling Study and the NIMH Genetics Initiative samples.

Polymorphisms in the 13q33.2 gene *G72* (also called *DAOA*, or D-amino-acid oxidase (DAO) activator) has also shown associations with the NIMH-COS and psychosis not otherwise specified (NOS) groups,¹⁰⁸ consistent with previous studies in adult patients with schizophrenia and bipolar disorder. Note that half of the NIMH psychosis NOS group later developed bipolar disorder. The action of the *G72* gene is poorly understood although it appears to activate the enzyme *DAO*. While the *DAO* gene was not associated with the NIMH-COS group, it has been associated in other samples.¹⁰⁹ A recent study by Korostishevsky *et al*¹¹⁰ documented overexpression of the *G72* gene in the postmortem brains of adult onset schizophrenics as compared to controls. In the NIMH-COS sample, while QTDT analyses indicated association with age of onset of psychosis, the overtransmitted allele was associated with *later* age of onset and with *lower* score on the Autism Screening Questionnaire. It is intriguing to speculate that *G72* may discriminate COS cases with greater continuity with relatively later onset, more adult type of schizophrenia.

Also of interest are the associations observed in the NIMH-COS sample between SNPs in dysbindin (*DTNBP1*, 6p22.3) and premorbid endophenotypes assessing poor social and academic adjustment during grade school and the years before the onset of psychosis, measured by the social withdrawal and peer relationship subscales of the Premorbid Adjustment Scale (PAS).¹¹¹

Thus, we have shown that intermediate phenotypic measures of impaired neurodevelopment are associated with the same susceptibility genes identified for schizophrenia and that the use of such phenotypes can help clarify the role some of these genes play in shaping the developmental trajectories leading to schizophrenia. To date, in the NIMH-COS sample three different schizophrenia susceptibility genes each demonstrated a distinct pattern of association with phenotypic measures. Specifically, the *G72* gene was associated with (later) age of onset and (lower/better) scores on the Autism Screening questionnaire, while SNPs in the gene *dysbindin* were associated with higher scores on the Premorbid Development Scale (indicating greater impairment). The *GAD1* gene was associated with (greater) frontal GM loss in adolescence and more severe smooth pursuit eye movement abnormalities. While these findings are all preliminary, it is likely that quantitative intermediate neurodevelopmental phenotypes may elucidate the unique effects of each gene and how it relates to illness.

Cytogenetic abnormalities

Cytogenetic abnormalities may provide a valuable clue to the identification of target loci. One such success story was the discovery of the overlapping genes *DISC1* and *DISC2* (disrupted in schizophrenia) where an inherited translocation segregated with schizophrenia and other psychiatric disorders in a large multigenerational pedigree from Scotland.^{112,113} Other researchers have found a relatively high rate of chromosomal abnormalities generally in schizophrenia.^{114,115} As most cytogenetic syndromes have their clinical appearance during infancy or childhood, it may not be surprising that a higher rate of cytogenetic abnormalities was found in a screening of COS patients.¹¹⁶ In addition to a 1;7 translocation,¹¹⁷ four cases of 22q11DS and one case of Turner's syndrome (XO) have been identified in the COS sample.¹¹⁶ There was a relatively high rate of 22q11 microdeletions (5%) in the NIMH-COS series of 80 cases compared with an estimated rate of 0.36% in a combined series of four studies with over 1100 unscreened adult schizophrenic patients and 0.025% in the community.¹¹⁸

Velocardiofacial syndrome (VCFS) has been proposed as a disease model for a genetically mediated subtype of schizophrenia.¹¹⁹ The literature is mixed as to whether 22q11DS is associated with early illness^{100,120} although none of these studies included childhood onset. Since the 22q11DS carries an approximate 25-fold risk for schizophrenia,^{121–123} it represents the highest known genetic risk factor for the disorder (second only to having an affected monozygotic twin). Brain imaging studies of non-psychotic children with 22q11DS show cortical GM loss (as seen in COS).¹²⁴ It is probable that haploinsufficiency of a neurodevelopmental gene or genes mapping to 22q11 underlies the susceptibility to psychosis in this syndrome. The 22q11DS is also

associated with progressive brain cortical GM loss during childhood and adolescence for patients not yet psychotic,¹¹⁸ which may be an intermediate phenotype of importance for early onset cases. The actual gene(s) responsible for psychoses in VCFS remains unclear, as there are approximately 30 genes in this 3Mb hemizygotously deleted region. Distinct clinical features of the 22q11 deletion syndrome can show variable expressivity and incomplete penetrance. Recent studies have provided compelling evidence that haploinsufficiency of *TBX1* is likely to be responsible for many of the physical features associated with the deletion. However, although a number of genes have been implicated as possible schizophrenia susceptibility loci, further confirmatory studies are required. Initially studies of *PRODH* seemed promising, particularly for COS populations,^{125,126} but subsequent studies have failed to confirm this (J Rapoport, unpublished data).^{127,128}

To assess the contribution of 22q11 genes to cognitive and psychiatric phenotypes, Maynard *et al*¹²⁹ determined the CNS expression of 32 mouse orthologs of 22q11 genes from the 1.5Mb minimal critical region consistently deleted in the 22q11DS.¹²⁹ Many genes continue to be expressed in the fetal, postnatal, and adult brain, but expression levels of some genes (eg *TBX1*) increase specifically in adolescence. Thus, gene expression may be disrupted in 22q11DS during development with maturation accounting for the varied phenotype across the age range.¹²⁹ This important study probably reflects a common pattern for most if not all schizophrenia susceptibility genes and may explain the highly variable phenotype before psychosis onset.

Array-based comparative genomic hybridization (CGH) technology measures submicroscopic DNA copy number changes and allows the simultaneous high-resolution mapping of these changes onto the genome.¹³⁰ This application of a technique developed for cancer genetics seems of potential importance for neurodevelopmental disorders generally. Recently, Vissers *et al*¹³¹ used this technology in a genome wide effort in order to detect submicroscopic chromosomal abnormalities in a sample of 20 mentally retarded cases and were successful in identifying and validating three microdeletions and two microduplications. Further, Shaw-Smith *et al*¹³² identified 12 copy number abnormalities out of 50 patients with learning disability/mental retardation and dysmorphic features (24% of the total): seven deletions (six apparently *de novo* and one inherited from a phenotypically normal parent) and five duplications (one *de novo* and four inherited from phenotypically normal parents).

There are several reasons why CGH should be of interest at least for very early onset cases of schizophrenia, for which dysmorphic features are common (J Rapoport, unpublished data). The high prevalence of premorbid abnormalities in COS patients and the high rates of other neurodevelopmental disorders

(totals 10.5%)¹⁰⁶ as well as schizophrenia/schizotypy (27%) in full COS siblings¹⁰⁵ suggests that two familial/genetic processes may be at work both increasing developmental disorders and schizotypy. Clearly this area has potential importance for schizophrenia and neurodevelopmental disorders more generally.

Routine karyotype analysis is not sensitive enough to detect subtle chromosome rearrangements that are less than 5 Mb, but methods are under development for rapid genome screening for small deletions/duplications.^{132–136} It is plausible that other micro-deletion/duplication syndromes will be found, particularly in early onset populations. Low copy number variations (LCVs) themselves may point to unstable regions of the genome where new disease-associated rearrangements may be found in the future.¹³⁷

Epigenetics

The study of twins has served to elucidate the involvement of genes in the etiology of schizophrenia and other psychiatric illnesses. The significantly higher concordance rates in monozygotic (MZ) twins as compared to dizygotic (DZ) twins has provided strong evidence of heritable factors, but at the same time, the observed concordance of only about 50% in MZ twins points to the unequivocal role of environmental factors as well. The epigenetic hypothesis suggests that in addition to disease-predisposing DNA sequence variants and hazardous environmental factors, epigenetic dysregulation of gene activity may make an important contribution to the etiopathogenesis of major psychoses.^{138,139} Dysfunction of epigenetic mechanisms fits well with a wide variety of non-Mendelian features of complex diseases, and epigenetic strategies can open new opportunities for the understanding of the phenotypic differences of MZ twins.¹⁴⁰ Unlike DNA sequences, which usually remain stable throughout the lifetime of an organism, DNA methylation and chromatin structure, two of the most investigated epigenetic mechanisms, are quite dynamic processes. Epigenetic regulation of gene activity is tissue-specific, age-dependent, and subject to developmental stage and environmentally induced changes as well as to stochastic events. Such epigenetic modifications of DNA and chromosomal proteins may have a significant impact on regulation of gene expression.

Recently, Petronis *et al*¹⁴¹ investigated DNA modification status in a fragment of the regulatory region of the dopamine D2 receptor gene (DRD2) in two pairs of MZ twins (one twin pair was discordant for schizophrenia, while the other was concordant). They found a higher degree of DRD2 methylation in lymphocytes of the unaffected co-twin as compared to his affected twin. Further, the affected twin from the discordant pair appeared epigenetically more similar to the unrelated affected twins than to his own unaffected MZ co-twin. While this study was limited to one particular gene, the concept may prove to be useful for future studies on a larger scale.

Animal models not specifically addressing schizophrenia have been particularly exciting in indicating the promise of highly specific interactions between genetic and environmental measures. The mechanism of how parental behavior translates into offspring behavioral effect remains controversial. Recently, Meaney and co-workers reported that increased pup licking and grooming altered the rat offspring epigenome at a glucocorticoid receptor gene promoter in the hippocampus.¹⁴² Offspring of 'high grooming' vs 'low grooming' mothers had differences in DNA methylation. These differences were reversed with cross-fostering, persisted into adulthood and were associated with altered histone acetylation and transcription factor (NGFI-A) binding to the glucocorticoid receptor. Thus, they show that an epigenomic state of a gene can be established through behavioral programming. While there is no evidence at all for crossfostering effects in schizophrenia,¹⁴³ the general epigenetic concept is of major potential importance as it shows how changes in gene expression induced by relatively brief exposure to a particular environment can become lifelong.

An alternative to epigenetic actions is variation in human gene expression regulatory elements. A 'gene expression phenotype' shows abundant natural variation and familial aggregation, thus making it a heritable quantitative trait worthy of study,¹⁴⁴ as discussed in the following section.

Gene expression throughout development

Eucaryotic cells use a variety of post-transcriptional mechanisms to expand the coding capacity of their genomes and to provide additional levels for regulation of gene expression. By developmentally regulated and tissue-specific alternative splicing, multiple protein forms can be produced from a single gene.^{145,146} It appears that many if not most genes act at more than one developmental period with different levels of expression and even different sites in the brain most active at different developmental time points.^{147,148} When these patterns are better understood for schizophrenia susceptibility genes (eg Maynard *et al*¹²⁹ for 22q11 region and development), it is likely that the range and timing of premorbid psychopathology seen many years before onset of psychosis will be understood as subtle abnormalities in early brain development that are mediated by the earlier expression, or lack thereof, of the various susceptibility genes.

For most of the identified susceptibility genes for schizophrenia, knowledge regarding their normal function is rudimentary. While progress is being made, some of the identified genes appear to have multiple roles and it is unclear which of the processes(es) they affect may be relevant to schizophrenia. For example, neuroregulin (*NRG1*), another susceptibility gene for schizophrenia,¹⁴⁹ is involved in neuronal migration and connectivity, cell signaling, and myelination.¹⁵⁰ The contribution of genes, such as *NRG1*, most probably differ in relation to

developmental stage. For example, *NRG1* could be involved in neuronal organization in prenatal life and synaptic function throughout the life cycle.¹⁵⁰ *GAD1* is less well studied, but preclinical studies show that it is involved with cortical, thalamic, cerebellar, and hippocampal development.^{151–154}

There is evidence of linkage and association with schizophrenia and the ‘Disrupted-in-schizophrenia 1’ (*DISC1*) gene,^{155,156} which may play an important role in hippocampal development. *DISC1* alleles associated with schizophrenia may result in compromised neuronal integrity and function.^{62,157}

Genetic variation in dysbindin (*DTNBP1*), shown to be associated with schizophrenia in multiple independent samples, was recently studied in primary cortical neuronal culture.¹⁵⁸ Numakawa *et al* found that Dysbindin influenced expression of presynaptic proteins, extracellular glutamate levels and release of glutamate, and protection of cortical neurons against cell death when overexpressed. These multiple functions that dysbindin is involved in indicates that it could play an important role in the pathogenesis of schizophrenia.

Similar findings have been reported for the ‘Metabotropic glutamate receptor-3’ (*GRM3*) gene. Although the cellular levels of expression of *GRM3* were not found to be altered in the prefrontal cortex of patients with schizophrenia,¹⁵⁹ Egan *et al*¹⁶⁰ reported that the SNP4 A allele of the *GRM3* predicted lower mRNA levels of the glial glutamate transporter *EAAT2*, an astrocytic protein regulated by *GRM3*. In the same study they found that the SNP4 A allele also predicted lower levels of *N*-Acetyl-Aspartate during *in vivo* examination of the prefrontal cortex of patients with psychosis, their unaffected siblings, and healthy controls. Poor performance on some cognitive tests (verbal fluency and verbal learning) was also predicted by the SNP4 A allele.

A study of the *GAD1* gene, which translates to GAD₆₇, the major GABA synthesizing enzyme, and a truncated form of GAD (GAD₄₄), only found during development, are both capable of synthesizing GABA. Two embryonic forms with a distinct temporal distribution are produced concomitantly from two embryo-specific mRNAs, a leader peptide (GAD₂₅) and a truncated GAD (GAD₄₄) that show a maximum of expression during the period of neuronal migration and differentiation.¹⁶¹ Inexplicably, the GAD₄₄ isoform is not seen beyond the embryonic developmental period. Another example includes insulin-like growth factor (IGF-1), which has a number of effects on cultured neural tissue, and transient IGF-1 gene expression is seen during the maturation of specific groups of functionally related sensory and cerebellar projection neurons. The specific timing and distribution suggest that IGF-1 may have a role in shaping synaptic connections or myelination.¹⁶² Neuregulin-1 (*NRG-1*) regulates numerous aspects of neural development and synaptic plasticity. Expression of *NRG-1* mRNAs is highest and broadest at P7 and is restricted during maturation to a few neuronal

populations. In the prenatal (P0-P7) mouse brain, *NRG-1* is highly expressed in the differentiating thalamus, cortex, and olfactory bulb, while in the adult brain, *NRG-1* is restricted to pretectal, thalamic, pontine, and lateral amygdala; low expression is observed in a few cells of the cerebral cortex, and hippocampus.¹⁶³ In the newborn cerebellum, *NRG-1* mRNA levels are highest in the molecular and Purkinje cell layers, and during maturation expression is restricted to cells in the internal granule cell layer.

It is clear that genes may have multiple developmental effects at different time points. This phenomenon is so widespread that simply extending the concept of neurodevelopment throughout the life cycle would avoid debate about neurodevelopmental vs neurodegenerative interpretations of CNS changes. This has clear implications for many stages of a disorder as specific abnormalities may be related only to a particular gene action at a particular developmental time point. In addition, certain regions of brain may be more susceptible to different environmental effects at different developmental stages. For example, in a study of intelligence, Plomin *et al*¹⁶⁴ reported a greater resemblance in adolescence than in childhood between adoptees and their biological parents, which is consistent with the finding that heritability of intelligence increases between childhood and adolescence.¹⁶⁵ Further, there is preliminary evidence that phenotypic variance in brain volume increases robustly during adolescence where white matter heritability increases while the heritability of GM remains stable. In addition, a longitudinal pediatric twin brain imaging study shows that different brain regions are susceptible to different environmental effects at different time periods. More specifically, the cerebellum is the least heritable brain structure and the only one quantified, which demonstrates a decrease in heritability across age with shared environmental influences more prominent in childhood and nonshared environmental factors more influential during adolescence (Dr Jay Giedd, personal communication, October 2004).

With greater specificity and ability to study developmental effects across time with candidate genes and deletion/duplication syndromes, better neurodevelopmental formulations for schizophrenia can be proposed. Reiss and co-workers reported that non-psychotic patients with 22q11DS had greater GM loss, such that abnormal temporal lobe and hippocampal development in velocardiofacial syndrome is potentially concordant with MRI findings in the schizophrenia literature.¹⁶⁶ Temporal lobe and mesial temporal structures may represent a shared substrate for the effects of the 22q11 deletion and for the complex etiological pathways that lead to schizophrenia. As a genetic marker, it is nonspecific for psychosis at least for that syndrome.

Ultimately, screens for genes affecting early development will be invaluable in the study of human development as the trait of being a genetically

essential gene is conserved in evolution.¹⁶⁷ Gene and intermediate phenotype associations observed in the COS sample strengthen the neurodevelopmental hypothesis. Gene–environment interactions may explain some neurodevelopmental phenomena, and broaden our understanding of the role of epigenetics in development.²

Discussion

The neurodevelopmental model for schizophrenia (as for most other neurodevelopmental disorders) still operates at a relatively broad level but this is starting to narrow. Studies of early onset patients indicate greater salience for later development of brain changes. Several susceptibility genes for schizophrenia appear to have specific developmental correlates, and to have different regional brain expression at different developmental stages. Thus in addition to prenatal insults, both late genetic and late environmental (and of course interactive) models could account for the variable age of onset. Late genetic effects on behavior are well recognized in developmental human studies; for example, the age-related increase in the correlation of cognitive ability between adoptees and their biological (as compared to their adopting) parents.¹⁶⁴ A reasonable interpretation is that genes affecting brain development related to cognitive ability are operating more strongly in late adolescence. Increased understanding of normal brain development will allow alternate pathological models to be tested as it is expected that some risk alleles will be associated with later cortical changes,⁸⁸ while others will be related to earlier brain abnormalities.²⁹ Genetic studies in COS (including candidate gene and cytogenetic studies) make neurodevelopmental models increasingly diverse and clinical subgroups more probable. Hopefully future work can address the role of locus heterogeneity and of epistasis in producing these variants.

The few studies in the rare early onset populations are limited by small sample size. The data however is intriguing in supporting greater early and later developmental changes, and the relative importance of genetic effects such as microdeletions/duplications. The premorbid pathology also accompanies other neurodevelopmental disorders reflecting either nonspecific vulnerability or the limited ‘common path’ of early developmental impairment.^{118,166,168} The newer techniques such as CGH^{133,169} may be the most promising approach.

It is increasingly obvious that risk genes for schizophrenia have multiple actions and variable expression at different times and different brain locales (eg GAD67). This suggests that genetic factors model the brain across the lifespan and therefore distinctions between early and late models and between neurodevelopmental and neurodegenerative hypotheses have become outdated. The variable expression and actions of genes may also provide meaningful correlates for the pan neurodevelopmental delays, and widely varied

psychiatric symptoms seen years before the onset of schizophrenia.⁵⁴ We have increasingly specific formulations of how and when various etiological genetic and nongenetic factors may act and interact with increasingly well defined early and later onset environmental risk measures.¹⁷⁰

Animal models of schizophrenia are beyond the scope of this review. While initial studies focused on the early ‘lesion’ hypothesis,^{171–173} later work with this model has shown that transient inactivation of the ventral hippocampus at PD7 with tetrodotoxin (TTX), a reversible blocker of the voltage gated sodium channels, caused lasting changes in later life for juvenile and young adult rats that were similar to those produced by the excitotoxic permanent lesions in earlier studies. Alternate models have changed the timing (‘adolescent’) and site (entorhinal cortex) of lesions with somewhat similar sensitivities.¹⁷⁴ Other animal models interfere with brain development either with high glucocorticoid levels and/or other stressor components¹⁷⁵ are also attempting to address stress models and account for later onset disturbance without a brain ‘lesion’.

Gene expression studies also contribute to the complexity of neurodevelopmental models. Naturalistic studies across developmental brain stages in the rat find varying degrees of expression of BDNF, and GAD67 in different brain regions.^{153,176} Attempts to integrate both early, and late models and also focus on later brain development closer to age of onset of the illness have studied developmental gene expression as well as epigenetic effects.^{177,178} As gene expression may vary by tissue and developmental period, environmental stress may interact with gene expression at a particular developmental period to account for specific vulnerability.¹⁷⁹ Accordingly, animal models continue to be modified and extended to address the ‘epigenetic puzzle’ of schizophrenia.¹⁸⁰

Summary

Neurodevelopmental models remain dominant, and thanks to advances in epidemiology, imaging, and genetics, issues are now being addressed at a more specific level. Individual risk factors are being identified in increasingly specific time periods with identification of specific environmental and genetic risk factors at specific time points. It is likely that future whole genome association studies will greatly facilitate the study of gene–gene and gene–environmental interactions. Early onset cases are likely to be particularly helpful in understanding abnormal brain development and understanding the role of individual genes in brain development generally and unique cytogenetic risk factors.

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