Published in final edited form as:
Curr Psychiatry Rep. 2004 August ; 6(4): 296–302.

Approaches for Adolescents with an Affected Family Member with Schizophrenia

Vaibhav A. Diwadkar, PhD, **Konasale M. Prasad, MD**, and **Matcheri S. Keshavan, MD**
Department of Psychiatry, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Room 441, Pittsburgh, PA 15213, USA

Matcheri S. Keshavan: keshavanms@upmc.edu

Abstract

Prospective studies of adolescents at risk for schizophrenia (high-risk studies) can shed light on the possible premorbid precursors of schizophrenia. Recent studies have provided evidence of neurobehavioral, brain structural, physiologic, and neurochemical deficits in adolescent nonpsychotic high-risk relatives that may date back to childhood or earlier. These results are collectively providing a critical window into the inter-relationships between genetic predisposition, neurodevelopment, and premorbid indicators of risk in schizophrenia. Convergent approaches are inherently powerful in mutually informing each other in enriching the knowledge of the risk factors that predict the eventual onset of schizophrenia. Defining such reliable predictors of the onset of schizophrenia may provide us with the tools to better understand the etiology and pathophysiology of the illness, and may pave the way for innovative methods of treatment and possibly prevention. The authors review the relevant literature in this promising field of inquiry and summarize recent findings from high-risk studies.

Introduction: Schizophrenia, Adolescence, and Neurodevelopment

Schizophrenia is a complex and dynamic illness [1,2], with a presumed polygenic basis, that is thought to arise from a combination of genetic, epigenetic, and environmental factors [3]. The illness has high personal and societal costs and an estimated lifetime prevalence of 1% in the general population [4]. With no known cure, recent efforts have focused on early therapeutic intervention in the prodromal phase of the illness, which may lead to better long-term outcome for patients [5]. Early intervention may be better served if the nature of the illness' precursors, its development, and pathways to its clinical manifestation are understood.

Recently, progress in several important technical and conceptual issues has greatly advanced the scientific investigation of schizophrenia. The development and application of in vivo neuroimaging techniques [6] has helped identify structural and physiologic alterations in cortical and subcortical regions [7–9]. With an increased understanding of the pathophysiology of the illness has come an increased emphasis on understanding its pathogenesis. Abnormal neurodevelopment has emerged as a key construct [3].

The idea of abnormal neurodevelopment in schizophrenia dates to the earliest modern conceptions of the illness. For example, the observation of deficits in social interaction, as well as other behavioral deficits in childhood, was reported by Bleuler and Kraepelin (*see*

Correspondence to: Matcheri S. Keshavan, keshavanms@upmc.edu.

[10••,11]). More recently, the argument of neurodevelopment has been articulated in a series of influential papers. The prevailing models differ in regard to the timing of the developmental deviations. Some authors have argued that schizophrenia arises from a “fixed lesion” early in life that interacts with developmental processes occurring in adolescence and young adulthood [12]. Others have argued that the illness arises from alterations in the program of synaptic pruning in key areas of the brain during adolescence [13,14] that may result from a combination of genetic and epigenetic factors that cause abnormal neurodevelopment of cortical networks [15]. These models conform to the broad view of schizophrenia as a neurodevelopmental disorder because they predict psycho- and biopathologic events as being present much earlier in life than the phenotypic features of the illness required for diagnosis [16]. Because the typical onset of schizophrenia is in young adulthood, adolescence is a key developmental period in which to investigate possible precursors of the illness, and it has been argued that schizophrenia is a disorder of brain development during the critical period of adolescence.

Human neurodevelopment occurs along a complex yet systematic schedule that is dictated by a combination of genetic and environmental influences [17,18], and adolescence in particular is marked by substantial refinement in brain structures in conjunction with rapid increases in cognitive proficiency in basic systems such as memory and language [19]. Because schizophrenia is marked by pathophysiologic deficits in key cortical and subcortical regions and by neurocognitive deficits in memory and language, this suggests that there may be an abnormal profile of neurodevelopment in these structures during adolescence. Therefore, a promising approach to understanding the developmental basis of schizophrenia is to comprehensively assess adolescent individuals who are known to be at highly elevated risk for the illness. Adolescent first-degree relatives of schizophrenia patients form the most important sample to fit this description.

Genetic factors are among the best-established etiologic factors in schizophrenia. Previous twin, family, and adoption studies have provided data on the degree of risk for an individual as the proximity to the schizophrenia proband and the number of affected relatives increase. Epidemiologic studies indicate that first-degree relatives (HR-S) of schizophrenia patients are at highly elevated risk for developing schizophrenia [20]. Consistent with the genetic hypothesis, twin studies have revealed that the concordance rate for schizophrenia is much higher in monozygotic twins (46%) than in dizygotic twins (14%). More generally, the incidence of schizophrenia in the offspring and first-degree relatives of patients is significantly higher than in the general population. Whereas the lifetime risk of developing the illness in the general population is approximately 1%, offspring of patients are 12 to 40 times more likely to develop the illness than the general population [21,22]. Recent advances in the understanding of genetic contributions to schizophrenia help further elucidate the value of studying adolescent relatives of schizophrenia patients.

Although genetic factors are necessary, they are not sufficient to produce the illness. The heritability of schizophrenia is estimated at 60% to 90% [20,23,24]; that is, 60% to 90% of the total phenotypic variance is accounted for by the genetic variance. It must be emphasized here that heritability tells us the contribution made by the genetic factors to account for the population’s variance in a phenotype but not the relative contribution of genotype and environment to an individual’s phenotype. Therefore, using genetic factors alone to predict who would develop illness in the future is beset with the problem of false-positives. Nature-nurture interactions are extremely important to consider in such predictions and are complex. Although the risk of schizophrenia increases with greater proximity to the relative with the illness, it also increases the possibility of sharing the environment. Earlier studies sought to focus on teasing apart the genetic and environmental contributions to the etiology of schizophrenia using family and adoption studies. Further studies clarified that it was the

shared genetic material that was more important than the shared external [25] or in utero [26] environments. These family studies also demonstrated that genetic materials are not specific to schizophrenia as is classified in the diagnostic systems, but may be associated with a variety of disorders and traits that are phenotypically closer to schizophrenia. These findings led investigators to study such high-risk subjects using prospective follow-up studies (the high-risk strategy).

Several studies of adolescents at high risk (HR) for schizophrenia were initiated in the early 1960s and 1970s, and some of these "first generation" studies have continued to date. These studies typically involved follow-up of offspring of parents with schizophrenia, though younger siblings and discordant monozygotic (MZ) twins also have been studied as at-risk populations. Three HR studies—the New York Infant Study [27], the Swedish High-Risk Study [28], and the Israeli Infant Study [29]—observed the offspring from birth onward. The New York High-Risk Project (NYHRP) [30] and the Israeli Kibbutz High-Risk Study [31] studied offspring from elementary school ages, and the Copenhagen High-Risk Project (CHRP) [32] and the Edinburgh High-Risk study [33•] studied subjects from adolescence onward. Some, but not all, of these studies have observed subjects through the risk period, and have provided valuable data on risk for schizophrenia and related disorders. The authors summarize some of the recent findings in the HR literature including their own work from ongoing studies in Pittsburgh.

Psychopathology

Early HR studies showed that the risk for schizophrenia and related disorders and the cluster A personality traits/disorders were elevated in relatives of patients with schizophrenia. Rates of Axis I schizophrenia and related psychotic disorders among the offspring of schizophrenia patients have ranged from 8% (NYHRP studies) to 21% (CHRP study), and these risks have been substantially higher than in control offspring. Offspring of schizophrenia parents also had significantly elevated risk for cluster A personality disorders [30]. An important message from these studies was that schizophrenia in a relative gives rise to a risk for a variety of psychopathology that can be subsumed under a broad rubric of schizophrenia-spectrum psychopathology.

The recent studies in first-degree relatives clearly reveal advances in identifying endophenotypic markers of the illness and discovering its premorbid precursors. The authors' Pittsburgh High-Risk Project has documented many of the initially identified endophenotypes in adolescent relatives and continues to expand in scope. The essential nature of the results is tabulated in Table 1, and some of the findings are discussed in more detail in subsequent sections.

Neurocognitive Deficits

The strongest evidence of impairment in relatives of schizophrenia patients appears to be in sustained attention, abstract thinking, and perceptual motor speed [34]. Among the various neuropsychologic measures, the continuous performance test appears to be consistently associated with liability to schizophrenia [35]. In the NYHRP, attentional impairment in childhood predicted 58% of the HR subjects who developed schizophrenia spectrum disorders in adulthood [36]. Attentional impairment is trait-related, stable over time, and related to genetic vulnerability [37]. Gross motor skills also were abnormal in 75% of offspring, while false-positive rates were 27%. Short-term verbal memory was impaired in 83% of offspring who later developed schizophrenia [38], showing a high sensitivity, but with relatively high false-positive rates (28%). By contrast, attentional impairments had lower sensitivity (58%) and also lower false-positive rates (18%). In summary, therefore, attentional impairments may be among the most useful neurobehavioral measures for

prediction of outcome in offspring at risk for schizophrenia. Data from the Pittsburgh study indicate attentional (continuous performance test) and executive function (Wisconsin Card Sorting Test) alterations as well as increased soft neurologic signs in young HR relatives [38].

Magnetic Resonance Imaging Studies

Children and adolescents at risk for schizophrenia, and nonpsychotic adult relatives of patients with schizophrenia, manifest structural brain abnormalities to a milder degree than patients with frank psychosis. A few magnetic resonance imaging (MRI) studies of the brain in relatives have demonstrated abnormalities in structures relevant to schizophrenia, and many of them agree with the neuropsychologic deficits associated with HR for the illness. Younger and older nonpsychotic relatives manifest volumetric abnormalities, especially in the prefrontal and temporal regions, suggesting that these abnormalities, at least in part, reflect vulnerability to the illness (*see* [39] for a review). The authors' data indicate reductions in amygdala-hippocampal volumes [40•] and superior temporal gyrus [41]; we also have seen more prominent prefrontal gray matter reductions in HR subjects with schizotypal characteristics [42]. Parahippocampal regional abnormalities have been demonstrated in HR individuals and are emerging as a possible vulnerability indicator [43,44]. Such findings are important because the parahippocampal region is involved in verbal declarative memory. Such convergent findings of structure-function impairments enhance the confidence with which future research may be pursued. Advances in understanding the biologic vulnerability to schizophrenia will be facilitated by increasing the precision of measurement of the abnormalities, by evaluating whether putatively linked risk factors are related to each other, and by determining whether these deficits are associated with genetic or environmental factors.

Magnetic Resonance Spectroscopy Studies

Magnetic resonance spectroscopy (MRS) offers a noninvasive way of quantifying in vivo metabolism. Several studies using proton (^{1}H) MRS have shown reductions in N-acetyl-aspartate, an in vivo marker of neuronal integrity, in prefrontal and temporal brain regions in schizophrenia (*see* [45] for a review). Cross-sectional data from the authors' studies in Pittsburgh suggest reductions in the ratio of N-acetyl-aspartate to choline in offspring at risk for schizophrenia [46]. Similar observations have been reported in adult relatives of patients with schizophrenia [47], suggesting that MRS can potentially shed light on neurochemical underpinnings of the heritable diathesis in this illness.

In vivo phosphorous (^{31}P) MRS studies have shown abnormal membrane phospholipid metabolism in the prefrontal cortex in the early course of schizophrenia. It is unclear, however, whether these alterations also represent premorbid risk indicators in schizophrenia. The authors have recently reported in vivo ^{31}P MRS data on HR children and adolescents. We quantified the freely-mobile phosphomonoester (PME) and phosphodiester (PDE) levels, reflecting membrane phospholipid precursors and breakdown products, respectively, and the relatively broad signal underlying PDE and PME peaks, which is caused by less-mobile molecules with PDE and PME moieties (*eg,* synaptic vesicles and phosphorylated proteins). Compared with healthy comparison subjects, HR subjects had reductions in freely mobile PME and increases in the broad signal underlying the PME and PDE peaks in the prefrontal cortex. Similar observations have been reported by others [48]. These data provide new evidence for decreased synthesis of membrane phospholipids and possibly increased synaptic vesicles or phosphoproteins in the prefrontal cortex of young offspring at risk for schizophrenia. These findings are similar to those observed in early course

schizophrenia. Follow-up studies are needed to examine the predictive value of these measures for future emergence of schizophrenia in at-risk individuals.

Functional Magnetic Resonance Imaging Studies

Using blood oxygenation level–dependent and contrast functional MRI (fMRI), it has now become possible to study abnormal regional brain activation in adolescent HR subjects. Although some fMRI data have been reported in the literature in adult relatives [49], few studies have investigated child and adolescent relatives. In a preliminary study, the authors have observed reduced activation in prefrontal brain regions in HR adolescents during a spatial working memory task [50]. Preliminary fMRI studies have shown that performance on these tasks of eye-movement control and working memory in these subjects result in aberrant fMRI-measured activation in the frontal and parietal regions of the brain [51] and the frontal eye fields, which are thought to regulate eye movement control [52]. Studies have shown that the response of the prefrontal cortex in adult relatives is similarly inefficient to increases in working memory demands [49], providing a measure of convergence with fMRI results of child and adolescent relatives. Recent and future work may seek to narrow the nature of the frontal deficit in relatives by assessing whether the presence or absence of specific allelic genotypes modulates prefrontal function, and thereby the risk for the illness [53].

Electrophysiologic Studies

A physiologic measure that has received attention in HR studies is eye tracking abnormality [54], which is seen in approximately 50% of adult relatives; studies of smooth pursuit eye movements in adolescent HR subjects have shown significant dysfunction compared with healthy comparison subjects [55]. Eye movement studies have shown lack of age related improvements in oculomotor delayed response performance in young HR subjects [56]. However, these measures have not been investigated as a predictor of schizophrenia risk in prospective studies.

Cognitive evoked potentials also have been proposed as measures of liability; prolonged latency and reduced amplitude of N100, P300, and P50 components have been observed among relatives [57]. Abnormal auditory event potentials [58] and electrodermal hypo- or hyper-responsiveness [59,60] also have been demonstrated, albeit less consistently.

Molecular Genetic Approaches

Schizophrenia is a clinically heterogeneous disorder. No single gene or chromosome locus of major effect has been characterized, but several genes of small effects have been reported to be associated with schizophrenia. Some of the replicated associations are given in Table 2.

Several of these genes affect diverse brain and neurotransmitter functions, as well as neurodevelopmental processes. Some of them affect glutamate (*eg,* neuregulin, DAAO, G72), the dopamine function (*eg,* catechol-O-methyltransferase), whereas others affect signal transduction (*eg, RGS4*). Among these genes, there is evidence implicating *RGS4*, dysbindin, neuregulin, and *DISC1* as affecting neurodevelopmental processes. Furthermore, *DAAO* and *G72* affect glutamate signaling that is involved in neuronal migration [61,62]. By affecting neurodevelopmental processes, unique endophenotypes for each risk may result. More importantly, the combination of these genes that is necessary or sufficient to lead to schizophrenia is not known. The precise mechanisms linking genetic factors and neurodevelopment in schizophrenia remain unclear, and theories will continue to evolve in the face of rapidly accumulating data. Several studies linking genetic polymorphisms with

specific structural or functional abnormalities in schizophrenia patients exist (*eg,* catechol-O-methyltransferase, working memory, and dorsolateral prefrontal cortex perfusion) [63]. In preliminary analyses, the authors have demonstrated dorsolateral prefrontal cortex morphometric alterations in first-episode schizophrenia associated with specific genotypes of *RGS4* single nucleotide polymorphism in patients but not in controls [64]. This suggests that the *RGS4* polymorphisms may be interacting with other illness-related variables. Targeting HR individuals can potentially mitigate the effect of illness variables on the endophenotypes associated with genetic polymorphisms and could provide a clearer picture of the premorbid endophenotype.

Family studies clearly suggest that schizophrenia does not increase the risk for nonspecific psychopathology, but does increase the risk for phenotypes closer to schizophrenia and cognitive deficits associated with the illness. Recent findings suggest associations between specific genetic polymorphisms and impaired cognition and prefrontal function, suggesting one possible etiopathologic pathway [63]. A recent multivariate prediction study in children of parents with schizophrenia and those without reported that schizophrenia was predicted by an interaction of genetic risk with rearing environment and disruptive school behavior [65]. However, the genetic liability for schizophrenia-related disorders is widely dispersed [66], and suggests that there may be multiple pathways to the heterogeneous clinical phenotype that is currently termed *schizophrenia*.

Conclusions

Recent studies of adolescent relatives at risk for schizophrenia have begun to yield valuable data concerning the possible premorbid precursors of schizophrenia in adolescence. Observations of neurobehavioral, brain structural, physiologic, and neurochemical alterations in adolescent HR relatives suggest that the neurobiologic diathesis of this illness may have its beginnings in childhood or earlier. A critical question for the field is to know the subjects that are likely to develop the illnesses later in life, and the measures that, singly or in combination, will provide researchers with the best predictive power.

Several future directions in understanding such a complex illness may be discerned. The first is the concurrent application of multimodal imaging techniques within patients. Thus, fMRI and morphometric techniques can help uncover the relationship between abnormal function and structure in key regions of the brain. This may allow researchers to understand the precise structural deficit that causes the emergent functional abnormality. Similarly, the concurrent use of MRS, which identifies neurochemical abnormalities in the brain and fMRI, can provide further information on relationships between substrate pathology and its relationship to function [67]. Second, most HR studies have been limited by small sample sizes and cross-sectional designs. However, several groups including the Pittsburgh High-Risk Project are expanding sample sizes conducting longitudinal follow-up designs. Other welcome trends also are becoming evident. The fields of HR and prodromal research are beginning to converge, such that measures of early illness, derived from the latter, may potentially serve as outcome measures to be examined in HR subjects prospectively [68]. Third, the use of high-field neuroimaging and spectroscopy studies (4T or higher) [69] may allow researchers to more precisely delineate the neurochemical and microstructural alterations that may characterize the premorbid phase of schizophrenia. More sophisticated spectral acquisitions and analysis may provide additional evidence for in vivo neurochemical concentrations and metabolism. Fourth, the recent identification of replicable candidate genes conferring susceptibility, such as dysbindin, neuregulin, catechol-O-methyltransferase, and *RGS4* [70•,71], provides an additional and powerful set of possible predictive measures to examine in longitudinal HR studies. Fifth, efforts to develop preventive interventions in symptomatic adolescent relatives provide the promise of

preemptive illness onset and better illness management [72••]. Finally, given the large samples needed for statistical power in HR studies, prospective multicenter studies of carefully ascertained HR subjects, using uniform neurobiologic and genetic methods, are critically needed for effective and timely progress in this pivotal area of schizophrenia research.

Quite possibly the only way to understand the neurodevelopmental precursors of the illness are to assess adolescent individuals who are genetically predisposed to the illness and in whom this predisposition may be expressed in tangible and measurable neurodevelopmental anomalies. Several groups around the world remain focused on uncovering the complex epigenetic puzzle that is schizophrenia by studying adolescent relatives, and endeavor that clearly reflects a rich synergy between basic science and potentially important applications. A clearer understanding of premorbid alterations will help in the development of more accurate profiles of risk and assist in earlier identification and intervention.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Carpenter WT Jr, Buchanan RW. Schizophrenia. N Engl J Med. 1994; 330:681–690. [PubMed: 8107719]
2. Schultz SK, Andreasen NC. Schizophrenia. Lancet. 1999; 353:1425–1430. [PubMed: 10227239]
3. Lewis DA, Levitt P. Schizophrenia as a disorder of neurodevelopment. Annu Rev Neurosci. 2002; 25:409–432. [PubMed: 12052915]
4. Murray, CJL.; Lopez, AD. The Global Burden of Disease: Global Burden of Disease and Injury Series. Vol. vol 1. Boston: Harvard School of Public Health; 1996.
5. McGorry PD. "A stitch in time"…the scope for preventive strategies in early psychosis. Eur Arch Psychiatry Clin Neurosci. 1998; 248:22–31. [PubMed: 9561350]
6. Diwadkar VA, Keshavan MS. Newer techniques in magnetic resonance imaging and their potential for neuropsychiatric research. J Psychosom Res. 2002; 53:677–685. [PubMed: 12169342]
7. McCarley RW. MRI anatomy of schizophrenia. Biol Psychiatry. 1999; 45:1099–1119. [PubMed: 10331102]
8. Shenton ME. A review of MRI findings in schizophrenia. Schizophr Res. 2001; 49:1–52. [PubMed: 11343862]
9. Callicott JH. An expanded role for functional neuroimaging in schizophrenia. Curr Opin Neurobiol. 2003; 13:256–260. [PubMed: 12744982]
10. Marenco S, Weinberger DR. The neurodevelopmental hypothesis of schizophrenia: following a trail of evidence from cradle to grave. Dev Psychopathol. 2001; 12:501–527. [PubMed: 11014750] A review of the neurodevelopmental hypothesis of schizophrenia. This key conceptual model predicts the emergence of premorbid symptoms during childhood and adolescence. The authors review research pointing to prenatal and postnatal impairments that may contribute to illness development.
11. Malmberg A. Premorbid adjustment and personality in people with schizophrenia. Br J Psychiatry. 1998; 172:308–313. [PubMed: 9715332]
12. Weinberger DR. The biological basis of schizophrenia: new directions. J Clin Psychiatry. 1997; 58:22–27. [PubMed: 9265913]
13. Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? J Psychiatr Res. 1982; 17:319–334. [PubMed: 7187776]
14. Keshavan MS, Anderson S, Pettegrew JW. Is schizophrenia due to excessive synaptic pruning in the prefrontal cortex? J Psychiatr Res. 1994; 28:239–265. [PubMed: 7932285]

15. Murray RM, Fearon P. The developmental 'risk factor' model of schizophrenia. J Psychiatr Res. 1999; 33:497–499. [PubMed: 10628525]
16. Chua SE, Murray RM. The neurodevelopmental theory of schizophrenia: evidence concerning structure and neuropsychology. Ann Med. 1996; 28:547–555. [PubMed: 9017114]
17. Rakic PT. The importance of being well placed and having the right connections. Ann N Y Acad Sci. 1999; 882:90–106. [PubMed: 10415888]
18. Rubenstein JL, Rakic P. Genetic control of cortical development. Cereb Cortex. 1999; 9:521–523. [PubMed: 10498269]
19. Case R. The role of the frontal lobes in the regulation of cognitive development. Brain Cogn. 1992; 20:51–73. [PubMed: 1389122]
20. Gottesman, II. Schizophrenia Genesis: The Origins of Madness. New York: WH Freeman and Company; 1991.
21. Erlenmeyer-Kimling L. The New York High-Risk Project. Arch Gen Psychiatry. 1995; 10:857–865. [PubMed: 7575106]
22. Gottesman, II.; Shields, J. Schizophrenia: The Epigenetic Puzzle. New York: Cambridge University Press; 1982.
23. McGuffin P. Twin concordance for operationally defined schizophrenia: confirmation of familiality and heritability. Arch Gen Psychiatry. 1984; 41:541–545. [PubMed: 6539584]
24. Kendler KS. Hierarchy and heritability: the role of diagnosis and modeling in psychiatric genetics. Am J Psychiatry. 2002; 159:515–518. [PubMed: 11925285]
25. Kety SS. Mental illness in the biological and adoptive families of adopted individuals who have become schizophrenic: a preliminary report based on psychiatric interviews. Proc Annu Meet Am Psychopathol Assoc. 1975; 63:147–165. [PubMed: 1242222]
26. Kety SS. Mental illness in the biological and adoptive families of adopted individuals who have become schizophrenic. Behav Genet. 1976; 6:219–225. [PubMed: 973827]
27. Fish B. Infants at risk for schizophrenia: sequelae of a genetic neurointegrative defect. A review and replication analysis of pandysmaturation in the Jerusalem infant development study. Arch Gen Psychiatry. 1992; 49:221–235. [PubMed: 1373598]
28. McNeil TF. Neuromotor deviation in offspring of psychotic mothers: a selective developmental deficiency in two groups of children at heightened psychiatric risk? J Psychiatr Res. 1993; 27:39–54. [PubMed: 8515388]
29. Marcus J. Children at risk for schizophrenia: the Jerusalem Infant Development Study, II: neurobehavioral deficits at school age. Arch Gen Psychiatry. 1993; 50:797–809. [PubMed: 7692835]
30. Erlenmeyer-Kimling L. The New York High-Risk Project: psychoses and cluster A personality disorders in offspring of schizophrenic parents at 23 years of follow-up. Arch Gen Psychiatry. 1995; 52:857–865. [PubMed: 7575106]
31. Mirsky AF. Overview and summary: twenty-five year follow-up of high-risk children. Schizophr Bull. 1995; 21:227–239. [PubMed: 7631170]
32. Mednick SA, Parnas J, Schulsinger F. The Copenhagen High-Risk Project 1962–1986. Schizophr Bull. 1987; 13:485–495. [PubMed: 3629202]
33. Johnstone EC. The Edinburgh High Risk Study: current status and future prospects. World Psychiatry. 2003; 2:45–49. [PubMed: 16946890] A useful summary of the findings and future directions of the Edinburgh High-Risk Project includes synopses of current MRI and clinical findings.
34. Kremen WS. Neuropsychological risk indicators for schizophrenia: a review of family studies. Schizophr Bull. 1994; 20:103–119. [PubMed: 8197409]
35. Cornblatt BA, Keilp JG. Impaired attention, genetics, and the pathophysiology of schizophrenia. Schizophr Bull. 1994; 20:31–46. [PubMed: 8197420]
36. Erlenmeyer-Kimling L. Neurobehavioral deficits in offspring of schizophrenic parents: liability indicators and predictors of illness. Am J Med Genet. 2000; 97:65–71. [PubMed: 10813806]
37. Michie PT. Phenotypic markers as risk factors in schizophrenia: neurocognitive functions. Aust N Z J Psychiatry. 2000; 34(suppl):S74–S85. [PubMed: 11129319]

38. Keshavan MS. Psychosis proneness and ADHD in young relatives of schizophrenia patients. Schizophr Res. 2002; 59:85–92. [PubMed: 12413647]
39. Lawrie, SM. Premorbid structural abnormalities in schizophrenia. In. In: Keshavan, MS.; Kennedy, JL.; Murray, RM., editors. Neurodevelopment and Schizophrenia. London: Cambridge University Press; 2004. in press.
40. Keshavan MS. Decreased left amygdala and hippocampal volumes in young offspring at risk for schizophrenia. Schizophr Res. 2002; 58:173–183. [PubMed: 12409156] A study on volumetric alterations in the sizes of the amygdala and the hippocampus in offspring of schizophrenia parents. These alterations provide evidence of a loss of structural integrity in key regions of the cortex that are involved in memory and the processing of emotional valence.
41. Rajarethinam RP. Reduction of superior temporal gyrus volume in young offspring of patients with schizophrenia. Am J Psychiatry. 2004 in press.
42. Diwadkar VA. Cognitive impairments and structural MRI abnormalities in schizotypal first-degree relatives of schizophrenia patients. Biol Psychiatry. 2003; 53(suppl):500.
43. Seidman LJ. Left hippocampal volume as a vulnerability indicator for schizophrenia: a magnetic resonance imaging morphometric study of nonpsychotic first-degree relatives. Arch Gen Psychiatry. 2002; 59:839–849. [PubMed: 12215084]
44. Pantelis C. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. Lancet. 2003; 361:281–288. [PubMed: 12559861]
45. Keshavan MS, Stanley JA, Pettegrew JW. Magnetic resonance spectroscopy in schizophrenia: methodogical issues and findings, part II. Biol Psychiatry. 2000; 48:369–380. [PubMed: 10978720]
46. Keshavan MS. Magnetic resonance imaging and spectroscopy in offspring at risk for schizophrenia: preliminary studies. Prog Neuropsychopharmacol Biol Psychiatry. 1997; 21:1285–1295. [PubMed: 9460092]
47. Callicott JH. Hippocampal N-acetyl aspartate in unaffected siblings of patients with schizophrenia: a possible intermediate neurobiological phenotype. Biol Psychiatry. 1998; 44:941–950. [PubMed: 9821558]
48. Keshavan MS. Prefrontal membrane phospholipid metabolism of child and adolescent offspring at risk for schizophrenia or schizoaffective disorder: an in vivo 31P MRS study. Mol Psychiatry. 2003; 8:316–323. [PubMed: 12660804]
49. Callicott JH. Abnormal fMRI response of the dorsolateral prefrontal cortex in cognitively intact siblings of patients with schizophrenia. Am J Psychiatry. 2003; 160:709–719. [PubMed: 12668360]
50. Keshavan MS. A preliminary functional magnetic resonance imaging study in offspring of schizophrenic parents. Prog Neuropsychopharmacol Biol Psychiatry. 2002; 26:1143–1149. [PubMed: 12452537]
51. Raemaekers M. Neuronal substrate of the saccadic inhibition deficit in schizophrenia investigated with 3-dimensional event-related functional magnetic resonance imaging. Arch Gen Psychiatry. 2002; 59:313–320. [PubMed: 11926931]
52. O'Driscoll GA. Neural correlates of eye tracking deficits in first-degree relatives of schizophrenic patients: a positron emission tomography study. Arch Gen Psychiatry. 1999; 56:1127–1134. [PubMed: 10591290]
53. Egan MF. Relative risk for cognitive impairments in siblings of patients with schizophrenia. Biol Psychiatry. 2001; 50:98–107. [PubMed: 11527000]
54. Levy DL. Eye tracking and schizophrenia: a selective review. Schizophr Bull. 1994; 20:47–62. [PubMed: 8197421]
55. Ross RG. Early expression of a pathophysiological feature of schizophrenia: saccadic intrusions into smooth-pursuit eye movements in school-age children vulnerable to schizophrenia. J Am Acad Child Adolesc Psychiatry. 2003; 42:468–476. [PubMed: 12649634]
56. Diwadkar VA. Memory guided saccade abnormalities in young offspring and siblings at risk for schizophrenia. CNS Spectrums. 2001; 6:899–903. [PubMed: 15328471]
57. Friedman D, Squires-Wheeler E. Event-related potentials (ERPs) as indicators for risk for schizophrenia. Schizophr Bull. 1994; 20:63–74. [PubMed: 8197422]

58. Schreiber H. Prolonged latencies of the N2 and P3 of the auditory event-related potential in children at risk for schizophrenia: a preliminary report. Eur Arch Psychiatry Neurol Sci. 1989; 238:185–188. [PubMed: 2759150]
59. Dykes KL. Adult third ventricle width and infant behavioral arousal in groups at high and low risk for schizophrenia. Schizophr Res. 1992; 7:13–18. [PubMed: 1591192]
60. Hollister JM. Impaired autonomic nervous system-habituation in those at genetic risk for schizophrenia. Arch Gen Psychiatry. 1994; 51:552–558. [PubMed: 8031228]
61. Chumakov I. Genetic and physiological data implicating the new human gene G72 and the gene for D-amino acid oxidase in schizophrenia. Proc Natl Acad Sci U S A. 2002; 99:13675–13680. [PubMed: 12364586]
62. Stefansson H. Neuregulin 1 and susceptibility to schizophrenia. Am J Hum Genet. 2002; 71:877–892. [PubMed: 12145742]
63. Egan MF. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci U S A. 2001; 98:6917–6922. [PubMed: 11381111]
64. Prasad KMR. RGS4 gene polymorphism, cognition and in vivo neurobiology in first episode schizophrenia. Schizophr Res. 2004; 67(suppl):28.
65. Carter JW. A multivariate prediction model of schizophrenia. Schizophr Bull. 2002; 28:649–682. [PubMed: 12795497]
66. Tienari P. Genetic boundaries of the schizophrenia spectrum: evidence from the Finnish Adoptive Family Study of Schizophrenia. Am J Psychiatry. 2003; 160:1587–1594. [PubMed: 12944332]
67. Callicott JH. Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. Cereb Cortex. 2000; 10:1078–1092. [PubMed: 11053229]
68. Keshavan MS. Investigating risk for schizophrenia: how genetic high risk approaches can inform prodromal research. ACNP Scientific Abstract. 2003
69. Theberge J. Glutamate and glutamine measured with 4.0 T proton MRS in never-treated patients with schizophrenia and healthy volunteers. Am J Psychiatry. 2002; 159:1944–1946. [PubMed: 12411236]
70. Harrison PJ, Owen MJ. Genes for schizophrenia? Recent findings and their pathophysiological implications. Lancet. 2003; 361:417–419. [PubMed: 12573388] An excellent state-of- the-field review of results from genetic linkage studies, identifying key susceptibility genes that may confer risk for schizophrenia. Also discussed are the molecular processes controlled by these genes and the plausible mechanisms by which they confer risk for schizophrenia.
71. Prasad KMR. RGS4 gene polymorphism, cognition and in vivo neurobiology in first episode schizophrenia. Schizophr Res. 2004; 67(suppl):28.
72. McGorry PD, Yung AR, Phillips LJ. The"close-in" or ultra highrisk model: a safe and effective strategy for research and clinical intervention in prepsychotic mental disorder. Schizophr Bull. 2003; 29:771–790. [PubMed: 14989414] Outlines strategies for early intervention in prepsychotic young individuals at risk for schizophrenia includes a discussion on conceptual models of schizophrenia, prediction, and intervention.

Table 1

Main findings in adolescent relatives of patients with schizophrenia

Domain	Main findings
Clinical	High proportions of Axis I psychopathology, especially attention deficit and conduct disorders, and of Axis II psychopathology
Neurocognitive	Impaired attention, spatial working memory, and executive functions; increased neurologic abnormalities; language and motor coordination abnormalities
Brain structure	Volume reductions in amygdala and hippocampus, prefrontal cortex, thalamus, and in the superior temporal gyri
Brain function	Decreased prefrontal activation with spatial working memory tasks with functional magnetic resonance imaging
Brain chemistry	Decreased N-acetyl-aspartate; abnormal membrane phospholipid metabolism

Table 2

Main findings from molecular genetic approaches

Location	Gene	Population studied
1q23.2	*RGS4*	Pittsburgh, USA; National Institute of Mental Health Clinical Global Impression scale, USA; New Delhi, India; Wales, UK; Dublin, Ireland
6p22	*DTNBP1*	Ireland
8p12-21	*NRG1*	Iceland
13q34	*G72*	French-Canadian; Russia, USA
22q11	*COMT*	Israel; China
22q11	*PRODH*	USA
t(1q42.1; 11q14.3)	*DISC1*	Scotland; Finland