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Premorbid indicators and risk for schizophrenia: A selective review and update

Matcheri S. Keshavan^{a,b,*}, Vaibhav A. Diwadkar^b, Debra M. Montrose^b,
Rajaprabhakaran Rajarethinam^a, John A. Sweeney^c

^a Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, 4201 St Antoine, Suite 9B, Detroit, MI 48201, United States

^b Department of Psychiatry, University of Pittsburgh School of Medicine, 3811 O'Hara Street, Pittsburgh, PA 15213, USA

^c Center for Cognitive Medicine, University of Illinois at Chicago, Chicago, IL, United States

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Abstract

Prospective studies of young relatives at risk for schizophrenia (high-risk studies, HR) can shed light on premorbid precursors of schizophrenia. Early HR studies pointed to a wide prevalence of schizophrenia spectrum psychopathology among young relatives at increased genetic risk. Recent studies suggest that young HR relatives have neurobehavioral deficits and structural, physiological, and neurochemical brain abnormalities that may date back to childhood or earlier. In this paper, we provide a selected overview of the lessons and limitations of early “first generation” studies and the beginning insights from recent “second generation” studies. We also provide an interim summary of data from the ongoing studies of young relatives at risk for schizophrenia in Pittsburgh. Collectively, such data may help us to predict the eventual emergence of schizophrenia, and schizophrenia spectrum or non-spectrum psychopathology.

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1. Introduction

The view that schizophrenia is a neurodevelopmental disorder suggests that pathogenetic biological events may be detectable in individuals at risk before

the typical onset of features of the illness (e.g., psychosis) during childhood, adolescence or early adulthood (Chua and Murray, 1996; Murray and Lewis, 1987; Weinberger, 1987). Genetic factors are among the best-established etiological risk factors in schizophrenia. The heritability of schizophrenia is estimated to be 60–90% (Gottesman, 1991; McGuffin et al., 1984; Kendler, 2002). The risk of schizophrenia increases in proportion to the familial proximity and the number of affected relatives. Offspring of schizophrenic parents have about a 13% risk of developing

* Corresponding author. Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, 4201 St Antoine, Suite 9B, Detroit, MI 48201 USA. Tel.: +1 313 993 6732; fax: +1 313 577 5900.

E-mail address: mkeshava@med.wayne.edu (M.S. Keshavan).

schizophrenia, and having two schizophrenic parents increases the risk to about 40% (Gottesman and Shields, 1982). Having a schizophrenic first-degree relative increases the risk by 5 times in parents, and 8 times in siblings. The challenge for learning how genetic risk impacts brain and behavioral functions is addressed by assessing specific premorbid alterations in the appropriate group of subjects. Prospectively studying relatives of schizophrenia patients with high genetic risk (the high-risk, or HR approach) will continue to be instructive in our search of markers that predict the onset of the illness. In this report, we provide a limited review of the HR studies and an interim summary of methods and findings from the Pittsburgh HR studies in the context of this literature. This paper is not intended as a comprehensive or detailed review of the vast literature on high-risk research; the reader is referred to other works (Niemi et al., 2003; Cornblatt et al., 1999; Sarfati and Hardy-Bayle, 2002).

2. Early, or “first generation” high-risk studies

The idea of examining young relatives at risk for schizophrenia is not new, and goes back to Emil

Kraepelin who said: “In children ... one might think of ... prophylaxis especially if the malady had been already observed in the parents or brothers or sisters. Whether it is possible ... to ward off the outbreak of the threatening disease, we do not know. But in any case it will be advisable to promote to the utmost of one’s power general bodily development and to avoid one-sided training in the brain work” (Kraepelin, 1919). Several high-risk (HR) studies were initiated in the early 1960s and 1970s, and some of these “first generation” studies have continued to date (Table 1). These studies typically involved follow-up of offspring of schizophrenic parents, though younger siblings and discordant monozygotic (MZ) twins have also been studied as at risk populations. Three HR studies, the New York Infant Study (Fish et al., 1992), the Swedish High-risk Study (McNeil et al., 1993) and the Israeli Infant Study (Marcus et al., 1993), have followed the offspring of parents with schizophrenia from birth onwards. The New York High-risk Project (NYHRP) (Erlenmeyer-Kimling et al., 1995) and the Israeli Kibbutz High-risk Study (Mirsky et al., 1995) studied offspring from elementary school ages, and the Copenhagen High-risk Project (CHRP) (Mednick et al., 1987) and the Edinburgh High-risk study (Johnstone et al., 2003)

Table 1

“First generation” high-risk studies of offspring at risk for schizophrenia providing data on psychopathological outcome at follow-up

	Study population	Study began	Follow-up duration	Main findings
New York Infant HR Study (Fish et al., 1992)	12 HR offspring/12 controls	1952	30 years follow-up from infancy	Scz — 8%; Spectrum PD — 50%; pandysmaturation; predicted outcome
Copenhagen HR Project (Carter et al., 2002)	212 HR offspring/99 controls, mean age 15	1962	30+ years	33 subjects had lifetime diagnoses of schizophrenia
Israel HR Study (Mirsky et al., 1995)	50 HR/50 controls, all raised in Kibbutz, age 8–14 years	1964	27 years	Scz — 8%; Aff — 24%. Children raised in the group atmosphere of a Kibbutz were at a higher risk
New York HR Project (Erlenmeyer-Kimling et al., 1995; Amminger et al., 1999; Cornblatt et al., 1999; Erlenmeyer-Kimling, 2000)	63 HR offspring; 100 controls; and 43 psychiatric controls	1971	20+ years	Psychosis — 18.6%; Spectrum PD — 18.1%; attention, memory, motor skills and behavioral disturbance in childhood predicted schizophrenia spectrum disorders
Finnish Adoptive Family Study (Wahlberg et al., 1997; Tienari et al., 2003)	190 adopted away offspring of schizophrenic mothers; 192 offspring of mentally well mothers	1974	20+ years	Scz — 5.34%; risk for a schizophrenia spectrum disorder was 22.46% for high-risk adoptees

HR=High-Risk; Scz=Schizophrenia; PD=Personality Disorder; Aff=Affective Disorder.

studied subjects from adolescence onwards. Some, but not all, of these studies have followed subjects through the risk period, and have provided data on risk for schizophrenia and related disorders. Rates of schizophrenia and related psychotic disorders among the offspring of schizophrenia patients have ranged from 8% (NYHR studies) to 21% (CHRP study), which are substantially higher than prevalence rates in control offspring. Offspring of schizophrenia parents also have significantly elevated risk for cluster A personality disorders (Erlenmeyer-Kimling et al., 1995).

The holy grail of high-risk studies is the ability to predict schizophrenia at follow-up in a cost-effective manner with a high level of confidence. Many early HR studies had limited numbers of predictive measures that necessitated limited univariate prediction models of schizophrenia. However, using data from the Danish high-risk study, Carter et al. (2002) examined 25 premorbid variables (including genetic risk, birth factors, autonomic responsiveness, cognitive functioning, rearing environment, personality, and school behavior). A quarter century later, 33 of the 212 subjects had received diagnoses of schizophrenia. Using discriminant function analyses, schizophrenia was predicted by the interaction of genetic risk with rearing environment, and disruptive school behavior. Thus, having comprehensive data at the beginning and the use of multivariate prediction models maximize our ability to predict schizophrenia from premorbid measures and allow us to evaluate the relative importance of various predictors.

Earlier HR studies often suffered from a lack of statistical power, and were therefore relatively modest in cost effectiveness. The difficulties in these studies stemmed from the long interval, spanning decades before beginning follow-up and the time when the participants entered the age range of risk for schizophrenia. Further, the findings were highly variable across studies, and often lacked specificity (see Cornblatt et al., 1999; and Keshavan, 2004 for reviews). Additionally, predictive information from these studies was limited by the state of neurobiological understanding of the schizophrenic illness at the time the studies were initiated. In a review of these “first generation” HR studies, Norman Garmezy stated over a quarter century ago “Imagine that the year is 2006... . . . As the new century dawns, a youthful,

callow invitee, intent on publishing rather than perishing, is asked to review the early studies on risk-for-schizophrenia research for the Intergalactic Institute of Mental Health. He sets out to trace early longitudinal investigations, surveys the now definitive follow-up data, assigns the children now grown to middle age into disordered and adaptive groups, and comes to the inescapable conclusion that efficiency of predictions, based on their biologic and psychologic statuses, is depressingly low” (Garmezy, 1978).

3. Recent, “second generation” studies: the Edinburgh HR study

It would be instructive to reexamine Garmezy’s pessimistic projections as we draw close to 2006. Eventhough an inter-galactic institute is yet to be realized, recent developments in biological psychiatry have significantly advanced our understanding of schizophrenia, and have set the stage for more effective strategies to ascertain premorbid neurodevelopmental vulnerability. First, schizophrenia is now increasingly viewed as a disorder of brain development during the critical period of the 2nd and 3rd decades of life (Lewis and Levitt, 2002). The onset of the illness may be preceded by a progressive loss of neuroregulatory control, possibly associated with a disruption in the programming of normal neurodevelopment, coupled with neuroregressive processes, perhaps in late childhood and adolescence (Keshavan, 1999). This suggests that beginning prospective ascertainment of premorbid risk indicators may be fruitful if begun during adolescence, relatively close to illness onset. Second, the advent of in vivo neuroimaging and electrophysiological studies over the past two decades has raised the possibility of elucidating altered brain structure and function in the premorbid phase of the illness. Schizophrenia is increasingly viewed as a disconnection syndrome (Friston, 1999) possibly arising from failure to appropriately integrate functional information across brain regions. In support of this, numerous morphometric studies have documented volumetric reductions of cortical gray matter in several areas, particularly in the heteromodal association cortices (McCarley et al., 1999). Also, white matter integrity is compromised in schizophrenia patients with abnormalities documented along cortico-cortical

white matter tracts and in the corpus callosum (Foong et al., 2000; Lim et al., 1999). Working memory which is particularly implicated in the pathophysiology of the illness may be specifically impaired by dysfunctions of critical neurocircuitry (Goldman-Rakic, 1999). These observations highlight the importance of incorporating in vivo biobehavioral markers as predictive measures in the next generation of HR studies. Two prospective HR follow-up studies have been initiated in recent years: the Edinburgh High-risk Study (EHRS) and the Pittsburgh Risk Evaluation Program (PREP). Data from these studies have provided preliminary evidence for premorbid clinical, neurobehavioral, electrophysiological, structural, functional, and neurochemical brain alterations in young HR relatives, and will be reviewed here (see Table 2).

EHRS prospectively investigated a high-risk Scottish sample of 163 young adults age between 16 and 25, with at least two relatives with schizophrenia and 36 healthy controls (see Johnstone et al., 2003 for a review). A group of age-matched subjects with first schizophrenic episodes was also included. They were serially examined every 18 months to track psychopathological and neurobiological outcome. Baseline measurements included childhood behavioral traits, schizotypy, soft neurological signs, minor physical anomalies, neurocognitive battery and Magnetic Resonance imaging scans (MRI).

The whole high-risk sample differed from the control group on a variety of neurodevelopmental and neuropsychological variables. Neuropsychological

measures were most impaired in the individuals with first-episode schizophrenia, with high-risk subjects performing better and well controls better still. The greater the genetic liability of the high-risk subjects, the poorer the neuropsychological performance. MRI data analyses revealed amygdala and thalamic volume reductions; Voxel Based Morphometric analyses showed reductions in grey matter (GM) density bilaterally in the anterior cingulate, and a trend in the left parahippocampal gyrus for the high-risk vs. control subjects (Job et al., 2003).

By the time of the most recent report, the investigators had follow-up information on 173 participants (including 27 healthy controls). Among those at high-risk, 20 had developed schizophrenia (Johnstone et al., 2005). A larger proportion experienced isolated or partial psychotic symptoms. Individuals who developed schizophrenia differed from those who did not on social anxiety, withdrawal and other schizotypal features. Neuropsychological differences were identified in many areas of function between high-risk relatives and controls but did not differ between those with vs without psychotic symptoms (Byrne et al., 2003). In high-risk subjects with two scans, there was a significantly greater reduction in temporal lobe size in those with psychotic symptoms than in those without. It was suggested that in high-risk subjects, the change from vulnerability to psychosis may be preceded by reduction in size and deteriorating function of the temporal lobe. Additionally, increases in gyral folding ratios predicted the development of schizophrenia (Harris et al., 2004; Job et al., 2005).

Table 2

Main biobehavioral findings in young relatives of schizophrenia patients from the “second generation” high-risk studies

Domain	Main findings
Clinical	High proportions of axis I psychopathology, especially ADHD and conduct disorders (Keshavan et al., 2002b); increased schizotypy (Johnstone et al., 2005)
Neurocognitive	Impaired attention, spatial working memory and executive functions; increased NES (Keshavan et al., 2002a; Johnstone et al., 2002; Byrne et al., 2003; Niemi et al., 2003; Sarfati and Hardy-Bayle, 2002)
Brain structure	Volume reductions in amygdala and hippocampus, and in the STG; prefrontal gray matter reductions in schizotypal HR subjects (Lawrie et al., 1999; Lawrie et al., 2004; Keshavan et al., 2002a; Johnstone et al., 2002; Rajarethinam et al., 2004)
Brain function	Decreased prefrontal activation with executive function tasks with fMRI (Keshavan et al., 2002c; Whalley et al., 2004)
Brain chemistry	Decreased NAA/choline ratios; decreased PME and increased broad PDE (Keshavan et al., 1997, 2004a,b)
Electrophysiology	Decreased SWS; abnormal oculomotor delayed response performance (Diwadkar et al., 2001; Ross, 2003)

ADHD — attention deficit/hyperactive disorder; fMRI — functional magnetic resonance imaging; HR — high-risk; NAA — *N*-acetyl aspartate; NES — Neurological Evaluation Scale; PDE — phosphodiester; PME — phosphomonoester; STG — superior temporal gyrus; SWS — slow wave sleep.

These findings suggest that significant clinical and neuroimaging predictors of the development of schizophrenia may be identifiable years before onset.

4. The Pittsburgh high-risk study

The goals of the Pittsburgh high-risk study were to characterize the neurobehavioral, psychopathologic and biological features of young relatives of schizophrenia patients with matched healthy comparison subjects and to identify potential predictors of emergent psychopathology during follow-up. The study is ongoing, all data are not available in every subject, and therefore the analyses presented must be viewed as preliminary.

4.1. Methods

4.1.1. Subjects

High-risk relatives were defined as subjects who had never had a psychotic disorder, and had at least one first-degree relative with schizophrenia or schizoaffective disorder. HR subjects were identified by approaching parents or older relatives who were patients at the Western Psychiatric Institute and Clinic (WPIC) or related clinical sites. Eighty one young first-degree relatives, aged 6 to 25 years were recruited. Eighty age- and sex-matched healthy control subjects (mean age=16.2±4.4; 40 males/40 females) with no family history of mental illness, and drawn from the same neighborhoods, also participated. We excluded subjects with a Diagnostic and Statistical Manual-fourth edition (DSM-IV) diagnosis of mental retardation, significant head injury, significant history of or current medical or neurological illness. All experimental protocols were approved by the University of Pittsburgh School of Medicine Institutional Review Board. All subjects provided written informed consent following full description of the studies. The parent or guardian also provided informed consent for subjects aged less than 18. Diagnoses were ascertained by using the Schedule for Affective Disorders and Schizophrenia for Children (K-SADS) (Kaufman et al., 1997) for children below age 15 and the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-P) (Spitzer et al., 1992) in older subjects. Parental psychopathology was

determined using the SCID-I. The subjects were diagnosed by DSM-IV criteria at consensus conference meetings. Parental emotional interactions were also evaluated using the Camberwell family interview (Vaughn and Leff, 1976).

4.1.2. Neurobehavioral and clinical assessments

The choice of neurobehavioral and clinical instruments was driven by the need to assess attentional and other neurocognitive impairments (known to be compromised in HR subjects) and neurological soft signs (that are seen across schizophrenia and non-schizophrenia and non-schizophrenic disorders). The Continuous Performance Task (CPT)–Identical Pair version (Cornblatt et al., 1989) was selected for its ability to detect attentional impairments in the HR population. The Buchanan and Heinrichs Neurological Evaluation Scale (NES) (Buchanan and Heinrichs, 1989) is a structured instrument for the assessment of neurological signs in schizophrenia and was administered to all subjects. We have also been quantifying schizotypy, which may suggest a predisposition to psychosis (Erlenmeyer-Kimling, 2000). Specifically, we use the self-administered Chapman Psychosis Proneness Scales, which have been found to have some, albeit modest, predictive ability in longitudinal studies of population at risk for psychosis. The Perceptual Aberration and Magical Ideation Scales (Chapman et al., 1978; Eckblad and Chapman, 1983) were chosen because of their predictive power for future psychosis (Chapman et al., 1994).

4.1.3. Imaging studies

Integrated Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) studies were carried out using a GE Signa 1.5 T whole body MR scanner. In a small group of subjects, we have also conducted blood oxygen level dependent contrast (BOLD) functional MRI (fMRI) during oculomotor delayed response tasks (see below) using a GE Signa 3.0 Tesla whole body scanner. T1 weighted images were used for region of interest (ROI) based morphometric analyses conducted using the National Institute of Health (NIH) IMAGE software (See Keshavan et al., 2002a, 2002c for details). Neuroanatomical changes were also assessed on a voxel-wise basis by voxel based morphometry (VBM) (Ashburner and Friston, 2000). This involves normalization of

brain scan data to stereotactically standard space, followed by segmentation into gray, white and cerebrospinal fluid compartments; and smoothing of the data with a Gaussian kernel.

MRS offers a noninvasive way of quantifying in vivo metabolism. Using Proton MRS, several studies have shown reductions in *N*-acetyl aspartate (NAA), an in vivo marker of neuronal integrity, in prefrontal and temporal brain regions in schizophrenia (see Keshavan et al., 2000 for a review). Our initial Proton MRS studies were done using a single voxel placed in the anterior cingulate region. In vivo Phosphorus (^{31}P) MRS studies have shown abnormal membrane phospholipid metabolism in the prefrontal cortex in the early course of schizophrenia. A doubly tuned transmit/receive volume head coil was used to acquire multi-voxel phosphorus (^{31}P) MRS data. MRS data were processed using fully automated methods by research assistants blind to clinical data.

4.1.4. Electrophysiological studies

The methodology for the oculomotor delayed response (ODR) task is described in detail elsewhere (Diwadkar et al., 2001; Sweeney et al. 1998). Briefly, subjects fixated on a central marker on a computer display in a dark room. Following a brief delay, a target was presented briefly (100 ms) at a point 9° , 18° , or 27° to the left or right of center fixation. Subjects remained fixated on the central fixation marker when the peripheral target appeared but were instructed to encode the peripheral target's location. After a varying delay period (1, 2, 4 or 8 s), the central light was extinguished. This provided a cue for subjects to direct their eyes to where the peripheral target had been presented. The principal dependent variable of interest was the distance in degrees of visual angle between the location of the final resting eye position after subjects made saccades to the remembered location and the actual cued location. These measurements of the absolute error of each saccade were utilized because they reflect the degree of failure to hold spatial information in working memory with high fidelity.

4.2. Findings

4.2.1. Axis I psychopathology

To date, we have clinical data on 81 HR relatives (offspring, siblings) including 39 males (age $15.0 \pm$

3.1 years) and 42 females (16.0 ± 4.2 years). In the order of frequency, the observed Axis I disorders included attention-deficit/hyperactivity disorder ($n=19$), depression ($n=13$), oppositional defiant disorder ($n=11$), anxiety disorder ($n=9$), and conduct disorder ($n=7$). About 45% of the subjects ($n=37$) did not have any Axis I disorder (note that the total adds up to >81 because of subjects having more than one disorder). Less frequent diagnoses included bipolar, adjustment and substance use disorders and uncomplicated bereavement. Male HR relatives had higher rates of psychopathology. The increased frequency of Axis I disorders in our sample suggests that children from families of schizophrenia and schizoaffective patients are at a greater risk for developing psychopathology. Interestingly, externalizing disorders such as ADHD and conduct disorder were more likely to be associated with schizotypal symptoms (Montrose et al., 2005). The increased frequency of Axis I disorders in our sample confirms previous work showing that young non-psychotic relatives from families of schizophrenia and schizoaffective parents are at a greater risk for developing a broad spectrum of psychopathology (Aminger et al., 1999). Longitudinal follow-up is needed to determine whether the non-specific psychopathological manifestations as noted here will predict the eventual emergence of schizophrenia or related psychotic disorders.

We have observed that increased psychopathology in young HR relatives is associated with higher amounts of pathological emotional reactivity (i.e. expressed emotion) among parents (Montrose et al., 2001). This is consistent with data from the Danish high-risk study which suggested that environmental factors, such as family relationships, may contribute to later schizophrenia in high-risk individuals, and that having positive relationships with both the mother and father may be protective (Schiffman et al., 2002). Data from EHRS also point to an association between upsetting life events and psychotic symptoms among young relatives at risk for schizophrenia (Miller et al., 2001). In the Finnish high-risk study, among the genetically at risk offspring of the adoptive parents with high levels of communication deviance, a higher proportion of high-risk than comparison adoptees showed evidence of thought disorder (Wahlberg et al., 1997). These observations suggest that genetic

risk interacts with psychosocial environmental risk factors leading to heightened vulnerability.

4.2.2. Schizotypy and other behavioral measures

We have observed elevations in magical ideation and perceptual aberration scores in young HR relatives, especially in those with attentional impairments (Keshavan et al., 2002b). These schizotypal measures represent a set of personality dimensions that may underlie the predisposition to schizophrenia. About 16–20% of high-risk offspring develop cluster A personality disorders (Erlenmeyer-Kimling et al., 1995); adolescents with schizotypal personality traits appear to be at a particularly higher risk for future psychosis (Chapman et al., 1978; Kwapil, 1998). In the Edinburgh High-risk study, 20 out of 163 young relatives developed schizophrenia in a span of 2.5 years (Johnstone et al., 2005). Social anxiety, withdrawal and other schizotypal features were more frequent in those who developed schizophrenia. These data point to the value of schizophrenia spectrum psychopathological measures in predicting schizophrenia among individuals at increased genetic risk.

4.2.3. Cognition and language

Data from the Pittsburgh study indicate attentional (CPT) and executive function (Wisconsin Card Sorting Test) alterations as well as increased soft neurological signs in young HR relatives (Keshavan et al., 2002b). These are consistent with observations of impairment in sustained attention, abstract thinking and perceptual motor speed in relatives of schizophrenia patients (Kremen et al., 1994). Among the various neuropsychological measures, CPT appears to be consistently associated with liability to schizophrenia (Cornblatt and Keilp, 1994). In the New York High-risk study, attentional impairment in childhood predicted 58% of the HR subjects who developed schizophrenia spectrum disorders in adulthood (Erlenmeyer-Kimling, 2000); relatively low false positive rates were seen (18%). Attentional impairment is trait related, stable over time, and related to genetic vulnerability (Michie et al., 2000). However, the Edinburgh high-risk study failed to confirm an association between attentional impairment and later frequency of schizophrenia (Cosway et al., 2002) though decline in IQ and verbal memory at follow-up were predictive of the development of psychotic symptoms (Cosway et al., 2000). In

the New York High-risk study, gross motor skills 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 (Erlenmeyer-Kimling, 2000), showing a high sensitivity, but with relatively high false positive rates (28%). Further research is needed to confirm the value of attentional and other cognitive impairments for prediction of outcome in offspring at risk for schizophrenia.

Language and thought impairments may also characterize the premorbid vulnerability to schizophrenia. A study of long term follow-up of all children born in a small town during one year in Dunedin, New Zealand has shown that receptive language deficiencies predict future development of schizophrenia (Cannon et al., 2002). Thirty six of 1037 subjects developed schizophreniform disorder at follow-up. Receptive language and cognitive development were significantly impaired in children who later developed schizophreniform disorder. In a study of clinically at risk individuals during premorbid phase, thought interference, and disturbances of receptive language were found to predict future onset of schizophrenia, with a probability up to 91% (Klosterkotter et al., 2001a,b). Additionally, follow-up studies of children with developmental language disorders have shown a tendency for later development of schizophrenia and schizotypy (Clegg et al., 2005). Hallett et al. (1986) reported that high-risk children showed deficits in binaural relative to monaural comprehension, impaired overall speech comprehension, and deficient speech sound perception compared to controls and proposed that this might reflect an abnormal interhemispheric integration in the high-risk children. Verbal fluency impairments are also common in schizophrenia patients and their relatives. Further investigation of the development of language and thought is needed in the genetically at risk individuals.

4.2.4. MRI studies

Children at risk for schizophrenia, and non-psychotic adult relatives of patients with schizophrenia, manifest structural brain abnormalities to a milder degree than patients with frank psychosis. Both younger and older non-psychotic relatives manifest volumetric abnormalities, especially in the prefrontal

tal and temporal regions, suggesting that these abnormalities, at least in part, reflect vulnerability to the illness (Lawrie et al., *in press*). Our data indicate reductions in amygdala and hippocampal volumes (Keshavan et al., 2002a) and in superior temporal gyrus (Rajarethinam et al., 2004); we have also seen more prominent prefrontal gray matter reductions in HR subjects with schizotypal characteristics (Diwadkar et al., 2003). We have also observed reductions in the gyral folding index in adolescent HR subjects (Jou et al., *in press*). VBM analyses have revealed relationships between the severity of prefrontal gray matter reductions and etiological variables, such as obstetric complications (Gilbert et al., 2003). Data from the Edinburgh studies also reveal hippocampal volume reductions in HR subjects (Lawrie et al., 1999); in those high-risk subjects with follow-up scans, there was a significantly greater reduction in temporal lobe size in those with psychotic symptoms than in those without (Johnstone et al., 2002).

Advances in understanding the biological 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 and/or environmental factors. Increased frequency of obstetric complications known to be an environmental risk factor for schizophrenia is associated with grey matter deficits in HR subjects (Gilbert et al., 2003). In recent years, several replicable genes have been associated with the susceptibility to schizophrenia (Harrison and Owen, 2003). Studies in Pittsburgh have identified Regulator of G-Protein Signalling (RGS4), a potential gene for schizophrenia risk (Chowdari et al., 2002). We have recently observed an association between RGS4 polymorphisms and gray matter volume reductions in first episode schizophrenia (Prasad et al., 2004). Ongoing studies in the PREP program include molecular genetic studies of HR relatives to examine relations between putative genetic polymorphisms and neurobiological indicators of risk.

4.2.5. *Magnetic Resonance Spectroscopy (MRS) studies*

Cross-sectional data from the PREP study suggest reductions in the ratio of NAA to choline in offspring

at risk for schizophrenia (Keshavan et al., 1997). Similar observations have been reported in adult relatives of patients with schizophrenia (Callicott et al., 1998). Using high field (3 Tesla) MRS, Tibbo et al. (2004) have observed increases in the glutamate/glutamine signal in adolescent offspring at risk for schizophrenia. These findings are of considerable interest in view of the glutamatergic model of vulnerability to schizophrenia (Keshavan, 1999). MRS can potentially shed light on the neurochemical underpinnings of the heritable diathesis in this illness.

We have recently reported *in vivo* ^{31}P MRS data on HR children and adolescents (Keshavan et al., 2003). 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 due to less mobile molecules with PDE and PME moieties (e.g., synaptic vesicles and phosphorylated proteins). Compared to 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 (Klemm et al., 2001). These data provide new evidence for decreased synthesis of membrane phospholipids and possibly increased synaptic vesicles and/or phosphoproteins in the prefrontal cortex of young offspring at risk for schizophrenia. These findings are similar to those observed in early course schizophrenia (Keshavan et al., 2000). Follow-up studies are needed to examine the predictive value of these measures for future emergence of schizophrenia in at risk individuals.

4.2.6. *Functional Magnetic Resonance Imaging (fMRI) studies*

Using fMRI, one can study abnormal regional brain activation in adolescent HR subjects during performance of specific cognitive tasks of interest. While some fMRI data have been reported in the literature in adult relatives (Callicott et al., 2003), few studies have investigated child and adolescent relatives. In a preliminary study, we observed reduced activation in prefrontal brain regions in HR adolescents during a spatial working memory task (Keshavan et al., 2002c). Recent work from the Edinburgh

group suggests reduced task-related activation in medial prefrontal–thalamic–cerebellar regions in the high-risk group as a whole compared with control subjects (Whalley et al., 2004). Interestingly, high-risk subjects with isolated or “fleeting” psychotic symptoms showed hyperactivation in the left inferior parietal lobule compared with controls and non-symptomatic HR subjects. This may reflect a compensatory activity of this brain region which is involved in attentional maintenance, given that HR subjects, especially those with early manifestations of psychopathology, have significant attentional impairments. (Keshavan et al., 2002b).

4.2.7. Electrophysiological studies

The oculomotor delayed response task (ODR) is a test of spatial working memory that depends on intact fronto-parietal communication. In this task, subjects must maintain memory for a spatial location in the periphery of vision for a brief delay period; at the end of the delay, they are required to make an eye-movement to the remembered location. Electrophysiological studies have shown that sustained activity of neurons in prefrontal cortex is crucial for maintaining this spatial information in working memory, in parallel with spatial encoding in the parietal lobe (Chafee and Goldman-Rakic, 2000).

The ODR task provides a window into neurodevelopment, and its performance is impaired in young relatives at risk for schizophrenia (Diwadkar et al., 2001). Therefore, relative impairments in ODR performance may be associated with alterations in cortico-cortical connectivity and may be expressed as changes in white matter microstructure. Our goal was to use voxel based morphometry (VBM) (Ashburner and Friston, 2000) to assess the relationship between alterations in white matter microstructure and ODR performance in 19 HR relatives compared to a healthy control sample. Significant negative correlations between white matter density and ODR errors were observed in several regions of cortical and sub-cortical white matter, including the frontal, parietal and cerebellar regions. These negative correlations indicate that white matter density *decreased* in these regions in relation to increasingly pronounced impairments in the ability to hold spatial information in working memory over time when performing the ODR task. These results provide intriguing evidence

suggestive of relative fronto-parietal disconnection during adolescence in high-risk individuals who show impairments in spatial working memory measured by the ODR task (Diwadkar et al., 2004). The reductions in white matter density may reflect aberrant tissue microstructure resulting from processes such as abnormal myelination (Flynn et al., 2003). That the extent of the observed white matter reductions was related to performance deficits in spatial working memory suggests a relationship between impaired cognitive function and impaired brain structure in individuals at risk for the illness.

Other electrophysiological markers of schizophrenia diathesis are also of interest. We have observed reductions in slow wave sleep in HR subjects that were also observed in early course schizophrenia patients (Keshavan et al., 2004a). Cognitive evoked potentials have been proposed as measures of liability to schizophrenia; prolonged latency and reduced amplitude of N100, P300 and P50 components have been observed among relatives (Friedman and Squires-Wheeler, 1994). Defects in gating or inhibition of the P50 auditory evoked potential have also been found in adolescent genetically at risk offspring of schizophrenic patients (Myles-Worsley et al., 2004). Abnormal auditory event-related potentials (Schreiber et al., 1989) and electrodermal hypo- or hyper-responsiveness (Dykes et al., 1992; Hollister et al., 1994) have also been demonstrated albeit less consistently. Our own unpublished data suggest reductions in visual P300 amplitudes in HR subjects. Temporoparietal P300 amplitude reductions and frontal P300 amplitude increases have been seen in unaffected adult relatives of schizophrenia patients (Winterer et al., 2003).

5. Conclusions

In summary, the first generation HR studies were instrumental in characterizing the frequency and patterns of psychopathological outcome in young at risk relatives, and offered some broad clues to neurocognitive and behavioral predictors of later schizophrenia spectrum disorders. Nevertheless, the limited predictive data and long follow-up periods reduced the cost-effectiveness of these studies. Recent HR studies have begun to yield valuable data concerning the possible

premorbid neurobiological precursors of schizophrenia. Observations of neurobehavioral, brain structural, physiological, and neurochemical alterations in young non-psychotic HR relatives strongly suggest that the neurobiological diathesis of this illness may have its beginnings in childhood or earlier. Future studies with the convergent application of neuroimaging and electrophysiological techniques may help elucidate the nature of cortico-cortical disconnection within the developmental context in schizophrenia.

Several caveats need to be considered in discussing the future directions in HR research in schizophrenia. First, one of the limitations of the HR strategy cited in the literature is that only a small proportion of these individuals will eventually develop schizophrenia. However, as our review indicates, a much larger proportion will likely develop features of schizophrenia spectrum disorders or other non-spectrum psychopathology; a broader definition of the outcome measures is therefore likely to increase the “yield” of HR studies. Second, the recent identification of replicable candidate genes conferring susceptibility, such as catechol-*O*-methyl transferase (COMT) and RGS4 (Harrison and Owen, 2003; Prasad et al., 2004), provides an additional and powerful set of possible predictive measures to examine in longitudinal HR studies. Third, the use of high field neuroimaging and spectroscopy studies (4T or higher) (Theberge et al., 2002) may allow us to more precisely delineate the neurochemical and microstructural alterations that may characterize the premorbid phase of schizophrenia. Fourth, while we now have a wealth of data on potential premorbid biobehavioral predictors for the illness, we still do not know which of these measures reflect inter-related vs. independent markers of risk. A critical question for the field is to know which of the HR subjects are likely to develop the illnesses later in life, and which measures, singly, or in combination, will provide us the best predictive power. Sample sizes large enough to allow multivariate analyses of putative predictive measures are needed. Prospective multi-center studies of carefully ascertained HR subjects, using uniform neurobiological and genetic methods, are critical. Finally, genetic HR studies are still limited by the inability to generalize the findings to all those who develop the illness. Studies of individuals with prodromal manifestations of schizophrenia (the “clinical” HR strategy, Keshavan et al.,

200a,b) need to be considered in combination with the genetic HR strategy to maximize our efforts toward prediction and eventually, early diagnosis and intervention.

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