Premorbid characterization in schizophrenia: the Pittsburgh High Risk Study

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Prospective studies of young relatives at risk for schizophrenia can shed light on the possible premorbid precursors of the disease. Ongoing studies in Pittsburgh suggest that young non-psychotic high risk relatives have neurobehavioral, brain structural, physiological, and neurochemical deficits that may date back to childhood or earlier. We summarize these data, review the relevant literature in this emerging field, and provide some new data suggesting alterations in sleep architecture in young relatives at risk for schizophrenia. Collectively, such data are likely to help us to predict the eventual emergence of schizophrenia, schizophrenia spectrum or non-spectrum psychopathology.

Key words: High risk, schizophrenia, imaging, sleep, psychopathology

Genetic factors are among the best-established etiological factors in schizophrenia (1-3). The risk of schizophrenia increases relative to the general population in proportion to the proximity of the relationship and the number of affected relatives. Offspring of schizophrenic parents have about a 13% risk of developing the illness, and having two schizophrenic parents increases the risk to about 40% (4). Having a schizophrenic first-degree relative increases the risk by 5 times in parents, and 8 times in siblings. Prospectively studying relatives of schizophrenia patients with high genetic risk should therefore be instructive in our search of markers that may predict the onset of the illness.

Several high risk (HR) studies 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 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 (5), the Swedish High Risk Study (6) and the Israeli Infant Study (7), followed the offspring from birth onwards. The New York High Risk Project (NYHRP) (8) and the Israeli Kibbutz High Risk Study (9) studied offspring from elementary school ages, and the Copenhagen High Risk Project (CHRP) (10) and the Edinburgh High Risk Study (EHRS) (11) 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 axis I schizophrenia and related psychotic disorders among the offspring of schizophrenia patients have ranged from 8% (NYHR study) to 21% (CHRP study), and these risks have been substantially higher than in control offspring. Offspring of schizophrenia parents also have significantly elevated risk for cluster A personality disorders (8).

Earlier HR studies, however, suffered from a lack of statistical power, and were therefore relatively modest in cost effectiveness. Further, the findings are highly variable across studies, and often lack specificity (see 12-16 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 had been initiated.

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 schizophrenia. New *in vivo* approaches to examine the brain biology of abnormal neurodevelopment are beginning to be developed. In recent years, two prospective HR follow-up studies have been initiated: the EHRS and the Pittsburgh Risk Evaluation Program (PREP). Cross-sectional and early longitudinal 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. We briefly summarize our approaches for assessment of the HR subjects and provide summary data on the results thus far. We also provide some previously unpublished sleep polysomnographic data showing alterations in HR subjects that are indicative of prefrontal dysfunction.

METHODS

Subjects

HR relatives were defined as subjects who had never had a diagnosis of a psychotic disorder, and had at least one first- or second-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, and a series of healthy control subjects of similar age and gender distribution, from the same neighborhoods, have been recruited. We excluded subjects with a 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) for children below age 15 and the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) in older subjects. Parental psychopathology was determined using the SCID-I. The subjects were diagnosed by DSM-IV criteria at consensus conference meetings.

Neurobehavioral and clinical assessments

The choice of neurobehavioral and clinical instruments was driven by the need to assess attentional impairments (known to be compromised in HR subjects), neurological soft signs (that are diagnostic for schizophrenia), and schizotypy, which may suggest a predisposition to psychosis (17).

The Continuous Performance Task (CPT) – Identical Pair version (18) was selected for its ability to detect attentional impairments in the HR population. The Buchanan and Heinrichs Neurological Evaluation Scale (NES) (19) is a structured instrument for the assessment of neurological signs in schizophrenia and was administered to all subjects. Schizotypy was assessed using two of the Chapman psychosis-proneness scales. The Perceptual Aberration and Magical Ideation Scales (20-21), in particular, were chosen because they have been shown to have some predictive power for future psychosis (17).

Imaging studies

T_1-weighted magnetic resonance imaging (MRI) (using the GE Signa 1.5 T whole body MR imager) was used for region of interest (ROI) based morphometric analyses conducted using the National Institute of Health (NIH) IMAGE software. Neuroanatomical changes were also assessed on a voxel-wise basis by voxel based morphometry (VBM). Proton magnetic resonance spectroscopy (MRS) studies were done using a single voxel placed in the anterior cingulate region. A doubly tuned transmit/receive volume head coil was used to acquire phosphorus (^{31}P) MRS data. MRS data were processed using fully automated methods by research assistants blind to clinical data. In a small group of subjects, we have also conducted blood oxygen level dependent contrast (BOLD) functional MRI (fMRI) during oculomotor delayed response tasks using a GE Signa 3.0 Tesla whole body scanner.

Sleep polysomnographic studies

Subjects underwent two consecutive nights of polysomnographic recording in the WPIC sleep laboratory. Daytime napping was avoided. Sleep times used in the laboratory were based on their habitual "good night" and "good morning" times, determined using a subject diary of recent sleep patterns. Electrodes were placed about one hour before bedtime. Sleep was recorded in the laboratory on a 24-channel polygraph (78B Grass Instruments) comprising an electroencephalogram (EEG), an electrooculogram (EOG), and a submental chin electromyogram (EMG). The EEG consisted of a C4 scalp placement referenced to linked mastoids. Sleep continuity, rapid eye movement (REM) sleep and slow wave sleep were measured using standard scoring methods as well as by power spectral and period amplitude analyses (for details see 22). Using the latter approach, which is a more sensitive measure of sleep indices, we can compute the number of delta sleep and REM waveforms (total and average per minute) during the night.

RESULTS

Table 1 provides an overall summary of findings derived from subsets of the dataset in the Pittsburgh HR studies thus far.

Table 1 Main findings from the Pittsburgh High Risk studies

Domain	Main findings
Clinical	High proportions of axis I psychopathology, especially ADHD and conduct disorders (23)
Psychosocial	Increased EE among relatives; trend for more psychopathology in offspring of high EE relatives (24)
Neurocognitive	Impaired attention, spatial working memory and executive functions; increased NES (25)
Brain structure	Volume reductions in amygdala and hippocampus, and in the STG; prefrontal gray matter reductions in schizotypal HR subjects (23,26-28)
Brain function	Decreased prefrontal activation with ODR on fMRI (25)
Brain chemistry	Decreased NAA/choline ratios; decreased PME and increased broad PDE (25,26)
Electrophysiology	Decreased SWS; decreased amplitude in P300

ADHD – attention deficit/hyperactivity disorder; EE – expressed emotion; fMRI – functional magnetic resonance imaging; HR – high risk; NAA – N-acetyl aspartate; NES – Neurological Evaluation Scale; ODR – oculomotor delayed-response; PDE – phosphodiester; PME – phosphomonoester; STG – superior temporal gyrus; SWS – slow wave sleep

Axis I psychopathology

HR relatives (n=81; offspring or siblings) were highly more likely to have a diagnosable disorder. Ten subjects, five of whom already had a psychotic disorder, were not included, as they did not meet study criteria. The sample of 71 eligible subjects included 36 males (age 14.3 ± 2.9 years) and 35 females (15.7 ± 4.5 years). In the order of frequency, the observed axis I disorders included attention-deficit/hyperactivity disorder (n=21), oppositional defiant disorder (n=11), depression (n=11), conduct disorder (n=8), and anxiety disorder (n=7). About a third of the subjects (n=27) did not have any axis I disorder (please note

that the total adds up to more than 71 because of many 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. Subjects with axis I disorders had higher scores on schizotypy, soft neurological signs and ratings on teacher or parent observed behavioral disturbance (Child Behavior Checklist). The increased frequency of axis I disorders in our sample suggests that children from families of schizophrenic and schizoaffective patients are at greater risk for developing psychopathology. Longitudinal follow-up is needed to determine whether non-psychotic psychopathology would predict schizophrenia spectrum disorders, and eventually schizophrenia or other related psychotic disorders.

Schizotypy and other behavioral measures

Schizotypy represents a set of personality dimensions that may underlie the predisposition to schizophrenia. Adolescents with schizotypal personality traits appear to be at a particularly higher risk for future psychosis (21,29,30). We have observed elevations in magical ideation and perceptual aberration scores in young HR relatives, especially in those with attentional impairments (23).

Neurocognitive measures

The strongest evidence of impairment in relatives of schizophrenia patients appears to be in sustained attention, abstract thinking and perceptual motor speed (31). Among the various neuropsychological measures, the CPT appears to be consistently associated with liability to schizophrenia (32). In the NYHR study, attentional impairment in childhood predicted 58% of the HR subjects who developed schizophrenia spectrum disorders in adulthood (16). Attentional impairment is trait related, stable over time, and related to genetic vulnerability (33). Gross motor skills were also 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 (16), 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 PREP study indicate attentional (CPT) and executive function (Wisconsin Card Sorting Test) alterations as well as increased soft neurological signs in young HR relatives (34).

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. A few MRI studies of the brain in relatives have demonstrated abnormalities in structures relevant to schizophrenia. Both younger and older non-psychotic 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 35 for a review). Our data indicate volume reductions in amygdala and hippocampus (23) and superior temporal gyrus (27); we have also seen more prominent prefrontal gray matter reductions in HR subjects with schizotypal characteristics (28). 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.

MRS studies

MRS offers a noninvasive way of quantifying *in vivo* metabolism. 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 36 for a review). Cross-sectional data from the PREP study suggest reductions in the ratio of NAA to choline in offspring at risk for schizophrenia (26). Similar observations have been reported in adult relatives of patients with schizophrenia (37), suggesting that MRS can potentially shed light on neurochemical underpinnings of the heritable diathesis in this illness.

In vivo ^{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. We have recently reported *in vivo* ^{31}P MRS data on HR children and adolescents (34). 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 (38). 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. Follow-up studies are needed to examine the predictive value of

these measures for future emergence of schizophrenia in at-risk individuals.

fMRI studies

Using BOLD and contrast fMRI, it has now become possible to study abnormal regional brain activation in adolescent HR subjects. While some fMRI data have been reported in the literature in adult relatives (39), few studies have investigated child and adolescent relatives. In a preliminary study, we have observed reduced activation in prefrontal brain regions in HR adolescents during a spatial working memory task (25).

Electrophysiological studies

A physiological measure that has received attention in HR studies is eye tracking abnormality (40), seen in about 50% of adult relatives. Studies of smooth pursuit eye movements in adolescent HR subjects have shown significant dysfunction compared to healthy comparison subjects (41). Eye movement studies have shown lack of age related improvements in oculomotor delayed response performance in young HR subjects (42). However, these measures have not been investigated as a predictor of schizophrenia risk in prospective studies.

Cognitive evoked potentials have also been proposed as measures of liability. Prolonged latency and reduced amplitude of N100, P300 and P50 components have been observed among relatives (43). Abnormal auditory event potentials (44) and electrodermal hypo- or hyper-responsiveness (45,46) have also been demonstrated, albeit less consistently. Our own data suggest reductions in P300 amplitudes in HR subjects.

Finally, several polysomnographic studies suggest reductions in slow wave sleep (SWS) in schizophrenia (see 47 for a review). Noted alterations include disrupted sleep continuity and reductions in SWS, but less consistently rapid eye movement (REM) sleep reductions. Sleep changes are frequently the earliest symptom heralding the onset of psychopathology in schizophrenia; studies of sleep in the premorbid and prodromal phases of this illness are therefore important to identify potential precursors of later illness. However, few studies have investigated sleep in young relatives at risk for schizophrenia. We have found delta sleep and REM sleep reductions but no sleep continuity alterations in a small series of HR adolescents (Table 2). We also observed a steeper decline in delta counts with age in the HR subjects compared to controls.

Our observations of reduced SWS in HR subjects are consistent with those observed in the early course of the schizophrenic illness (22). Decreased SWS in nonpsychotic HR subjects suggests that this abnormality might be a trait related alteration that may underlie predisposition to the illness. Our observation of steeper reductions with age in the HR subjects is consistent with the view that adolescents at risk for schizophrenia might have an exaggeration of the normative peri-adolescent process of SWS reductions, perhaps related to synaptic pruning (see 48 for a review). Previous data suggest that SWS reductions may correlate with negative symptoms, brain structural alterations, reduced prefrontal metabolism and cognitive impairment (see 48 for a review). SWS is largely prefrontally generated (49). Thus, the polysomnographic changes convergently suggest altered prefrontal physiology in young relatives at increased risk for schizophrenia.

CONCLUSIONS

In summary, recent HR studies, such as the EHRS and PREP studies, have begun to yield valuable data concerning the possible premorbid precursors of schizophrenia. Observations of neurobehavioral, brain structural, physiological, and neurochemical alterations in young nonpsy-

Table 2 Sleep architecture in high risk (HR) relatives and healthy comparison (HC) subjects

	HR (n=9)	HC (n=10)	Group F (df=1,14)	P (two tailed)
Sleep continuity measures				
Total sleep time in minutes (mean ± SD)	496.1 ± 55.9	528.7 ± 48.7	0.7	0.41
Sleep latency in minutes (mean ± SD)	22.3 ± 12.1	18.2 ± 12.1	2.0	0.18
Awake time in minutes (mean ± SD)	14.2 ± 11.7	5.4 ± 3.4	4.0	0.065
Slow wave sleep measures				
Delta %, visually scored (mean ± SD)	23.1 ± 6.8	28.2 ± 8.2	1.3	0.27
Delta counts/minute (mean ± SD)	50.3 ± 16.5	68.5 ± 19.3	9.5	0.008
REM sleep measures				
REM latency in minutes (mean ± SD)	117.0 ± 53.5	87.6 ± 28.7	3.5	0.08
REM sleep % (mean ± SD)	20.7 ± 4.0	25.5 ± 4.0	6.9	0.02
REM counts/minute (mean ± SD)	4.6 ± 2.5	9.2 ± 4.0	4.8	0.04

REM – rapid eye movement

chotic HR relatives strongly suggest that the neurobiological diathesis of this illness may have its beginnings in childhood or earlier. However, only a small proportion of these individuals will eventually develop schizophrenia, though a much larger proportion will likely develop features of schizophrenia spectrum disorders or other non-spectrum psychopathology. A critical question for the field is to know which of these subjects are likely to develop the illnesses later in life, and which measures, singly, or in combination, will provide us the best predictive power.

The PREP study has been limited by small sample sizes and the cross sectional nature of the data thus far. However, efforts to expand this sample and to conduct longitudinal follow-up are currently in progress. Several other promising future directions are also worth outlining. First, 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 (50). Second, the use of high field neuroimaging and spectroscopy studies (4T or higher) (51) may allow us to more precisely delineate the neurochemical and microstructural alterations that may characterize the premorbid phase of schizophrenia. Third, the recent identification of replicable candidate genes conferring susceptibility, such as catechol-O-methyl transferase (COMT) and RGS4 (52,53) provides an additional and powerful set of possible predictive measures to examine in longitudinal HR studies. Finally, given the large samples needed for statistical power in HR studies, prospective multi-center studies of carefully ascertained HR subjects, using uniform neurobiological and genetic methods, are critically needed for effective and timely progress in this pivotal area of schizophrenia research.

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