

Genetically predisposed offspring with schizotypal features: An ultra high-risk group for schizophrenia?

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Abstract

Biomarkers proposed in the schizophrenia diathesis have included neurocognitive deficits in domains such as working memory that implicate prefrontal systems. However, the relationship between these biomarkers and psychopathological markers such as schizotypy has not been systematically assessed, particularly in adolescent offspring of schizophrenia patients. Convergence between these markers may identify individuals at especially high risk for schizophrenia. In the current study the authors assessed whether functional deficits in working memory assessed using the oculomotor delayed response task (ODR) and executive function assessed using the Wisconsin Card Sort task (WCST), and structural deficits in prefrontal cortex, in the adolescent offspring of patients were predictive of schizotypy. Schizotypal offspring made more perseverative errors on the WCST ($p < .002$) and showed age-related deficits on the ODR task ($p < .02$) compared to their non-schizotypal counterparts or healthy controls. Reduced gray matter concentration in prefrontal cortex ($p < .001$) was also associated with schizotypy. Schizotypy in offspring of schizophrenia patients appears to be highly associated with known biomarkers of the illness such as executive function impairment and reductions in cortical gray matter. Furthermore, schizotypy appears to interact with development leading to greater impairment in working memory in schizotypal offspring closer to the typical age of onset of schizophrenia than non-schizotypal offspring. Thus, clinical and neurocognitive biomarkers of the illness appear to be highly interrelated in this sample of at-risk offspring. We propose that schizotypy may define a hyper vulnerable sub-sample among individuals genetically predisposed to schizophrenia and that future studies that attempt to assess risk may benefit from such a convergent approach.

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1. Introduction

Schizophrenia is increasingly being seen as a neurodevelopmental disorder (Lewis and Levitt, 2002). While psychotic symptoms typically manifest in the second and third decade of life, many individuals manifest premorbid cognitive, neuro-motor and interpersonal difficulties dating back to early childhood.

Brain abnormalities in the illness may primarily stem from intra- or early-perinatal developmental factors (Marengo and Weinberger, 2001; Murray and Lewis, 1987; Randall, 1980; Weinberger, 1987). According to the early neurodevelopmental model, the onset of the illness is preceded by a progressive loss of neuroregulatory control, occurring early in life. An

Abbreviations: CPT, Continuous Performance Task; HC, Healthy Controls; HR-S, High Risk Offspring of Schizophrenia Patients; HR-S_{NSSB}, High Risk Negative for Schizophrenia Spectrum Psychopathology; HR-S_{SSB}, High Risk with Schizophrenia Spectrum Psychopathology; K-SADS, Structured Interview for Schizophrenia and Affective Disorders; MRI, Magnetic Resonance Image; SPD, Schizotypal Personality Disorder; SCID, Structured Clinical Interview for DSM Disorders; ODR, Oculomotor Delayed Response Task; SSP, Schizophrenia Spectrum Psychopathology; SPM, Statistical Parametric Mapping; WCST, Wisconsin Card Sort Task.

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alternative model suggests an exaggerated loss of synapses through an exaggeration of normative synaptic pruning occurring during adolescence (Keshavan et al., 1994). As support for this, schizophrenia is associated with decrements in gray matter volume (Zipursky, 1992) and frontal metabolism (Andreasen et al., 1992) compared to healthy control subjects. Similarly, post mortem studies of schizophrenia brains show a reduction in neuropil (Selemon et al., 1995) and dendritic spine density (Garey et al., 1998). Collectively, these results suggest a possible alteration in the neurodevelopmental profile in schizophrenia in key regions of the cortex such as the prefrontal cortex (Lewis, 1997b). This abnormality in neurodevelopment and neuroregulatory control during childhood and adolescence may evolve into a clinically latent brain disorder, predisposing an individual to the later expression of psychosis (Cannon and Marco, 1994).

A promising approach to understand the developmental basis of schizophrenia is to assess neurobiological and neurodevelopmental abnormalities in young individuals who are likely to be at elevated risk for the illness, thereby permitting the discovery of possible neurodevelopmental mechanisms of risk for the illness (Gottesman and Gould, 2003). Adolescent first-degree relatives of schizophrenia patients form an important sample for this effort. The incidence of schizophrenia is significantly higher in this group than in the general population. Whereas the incidence of the illness in the general population is about 1%, adolescent offspring of patients are up to 15 times more likely to develop the illness than the general population (Erlenmeyer-Kimling et al., 1995; Gottesman and Shields, 1982). Retrospective analyses of this group suggest that the vulnerability to schizophrenia “spectrum” psychopathology (SSP) is higher still, with predicted conversion rates as high as 40%. Examining the predictive value of a clinical variable that more generally captures predisposition to schizophrenia may enrich the study of this vulnerable group. Schizotypy, which may underlie predisposition to schizophrenia (Gottesman, 1991) and which is considered a common phenotype for the genetic diathesis of the schizophrenia “spectrum” psychopathology is such an important variable.

Schizotypic psychopathology defined by measures such as perceptual aberration and magical ideation (Coleman et al., 1996) has emerged as an important predictor of liability for illness in investigations of psychosis and has been associated with increased aberrant performance on neuropsychological tasks. For example, schizotypal traits have been associated with abnormalities in the oculomotor delayed response (ODR) task, a measure of spatial working memory, in college-age healthy subjects (Larrison et al., 2000; O’Driscoll et al., 1998), as well as slightly impaired verbal working memory performance (Park and McTigue, 1997). These results suggest that these deficits indicate a predisposition to aberrant performance on tasks that are known to be abnormal in schizophrenia. Schizotypy has also been associated with poorer sustained attention measured using the Continuous Performance Task (CPT; Lenzenweger, 2001; Lenzenweger et al., 1991), as well as reductions in the amplitude of the P300 component in event-related potential studies (Kimble et al., 2000).

Non-affected first-degree relatives of patients (henceforth HR-S; *High Risk for Schizophrenia*) manifest many behavioral and neurobiological abnormalities, albeit in milder form, that are characteristics of schizophrenia (Faraone et al., 1995, 1999). HR-S subjects show impairments in spatial working memory (Park et al., 1995), attention (Cornblatt et al., 1999), and executive function (Faraone et al., 2000). These abnormalities foreshadow many of those observed in first-episode subjects, are considered to be central features of schizophrenia, and may underlie predisposition to this disorder (Frith, 1995). These impairments are indicative of frontal and more generally distributed dysfunction of fronto-parietal-temporal circuits (or heteromodal association cortex) in the brain (Mesulam, 1998). The nature of these abnormalities in first-degree relatives is similar to abnormalities documented in schizotypal individuals. It is therefore logical to assume that schizotypy may be an important mediating variable in the search for biomarkers of schizophrenia in this high-risk group (Cadenhead and Braff, 2002). Neurobehavioral studies have begun to document relationships between measures of schizotypy and impaired function in first-degree relatives of patients. Impaired executive function has been observed (Laurent et al., 2001) and schizotypal components have been identified in high-risk samples (Miller et al., 2002). However, no studies have assessed the relationship between schizotypy, abnormal neurobehavioral performance and structural measures of cortical integrity.

The authors investigated the relationship between schizotypy scores and neurobehavioral and structural brain abnormalities in young first-degree relatives of schizophrenia patients. Schizotypy was measured by combining the Perceptual Aberration and Magical Thinking subscales of the Chapman and Chapman scales (Chapman and Chapman, 1980; Eckblad and Chapman, 1983). Neurobehavioral performance was assessed using the Wisconsin Card Sort (WCST), a robust measure of prefrontal function; we also used the oculomotor delayed response task (ODR) that assesses spatial working memory and can be used as an index of neurodevelopmental maturation of frontal systems (Luna and Sweeney, 2001). Brain structure was assessed using morphometric analyses of magnetic resonance images (MRI). We predicted that HR-S who scored high on our measures of schizotypy would perform poorly on our measures of working memory and executive function. Furthermore, we predicted that schizotypal HR-S would show greater reductions in heteromodal gray matter concentration.

2. Methods

2.1. Subjects

Thirty-three first-degree HR-S relatives of patients (15 females) and thirty-four healthy control (HC) subjects (16 females) with no family history of mental illness participated (Table 1). The study was approved by the University of Pittsburgh’s Institutional Review Board. All subjects (and/or their parents/guardians) provided informed consent. Groups did not differ in terms of age or gender.

Table 1
Demographic information for the 34 HC and 33 HR-S subjects including the mean schizotypy scores for the two HR-S sub-groups

	HC group <i>n</i> =34	HR-S group <i>n</i> =33	
Mean Age (sd; range)	16.8 (5.3; 7–25)	15.2 (3.65; 8–22)	
Mean Age (sd; range)		HR _{NSSP} ; <i>n</i> =16 16.5 (3.7; 12–22)	HR _{SSP} ; <i>n</i> =17 14 (3.2; 8–18)
Mean schizotypy score	.09	.08	.37

2.2. Clinical assessment

The HR-S and HC subjects were diagnosed using the Structured Interview for Schizophrenia and Affective Disorders (K-SADS) or Structured Clinical Interview for DSM Disorders (SCID) interviews and consensus meetings including all available clinical information (Ambrosini et al., 1989; Kaufman et al., 1997). The diagnoses in the index parent(s) were ascertained using SCID interviews and consensus conferences. The self-rating questionnaires, Chapman and Chapman schizotypy subscales (Chapman and Chapman, 1980; perceptual aberration and magical ideation) were administered to each subject to evaluate schizotypy. We did not use the physical anhedonia scale because of the age-inappropriateness of some items in this subscale. Measures on the two subscales were highly correlated, $r = .54$, $F(1,31) = 12.7$, $p < .001$, and the subscales were subsequently combined to generate a composite schizotypy score. The HR-S subjects were split into schizotypal ($n = 17$; henceforth HR_{SSP}, High Risk with Schizophrenia Spectrum Psychopathology) and “non”-schizotypal ($n = 16$; henceforth HR_{NSSP}, High Risk Negative for Schizophrenia Spectrum Psychopathology) based on a median split of composite schizotypal score. HR_{NSSP} subjects did not differ significantly from HC subjects on schizotypal scores (.08 vs. .09, $p > .25$).

2.3. Neurobehavioral measures

Neuropsychological assessments included ODR and WCST (Diwadkar et al., 2001; Keshavan et al., 2002; Koren et al., 1998) and were conducted within a week of the subjects’ MRI. A computerized administration of the WCST was used. Details of the ODR task are presented elsewhere (Diwadkar et al., 2001; Sweeney et al., 1998). In short, subjects sat in a darkened room, and needed to remember briefly cued peripheral locations over delay periods of 1, 2, 4 or 8 s, and then make saccades to those remembered locations. Eye movements were monitored and recorded, and the accuracy of the saccades was measured off-line.

2.4. MRI

MR structural images were collected on all subjects using the 1.5 T G.E. scanner at the MR Research Center of the University of Pittsburgh Medical Center. MR parameters were: 124 1.5-mm coronal slices; (SPGR sequence) TR=25 ms,

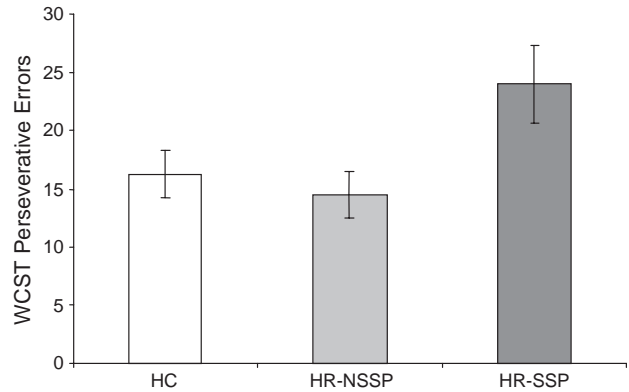


Fig. 1. Schizotypal HR-S subjects (HR_{SSP}) made significantly more errors of perseveration on the WCST task than their non-schizotypal counterparts (HR_{NSSP}) or healthy control (HC) subjects.

TE=5ms, flip angle=40°, matrix=256 × 192. Brain images were analyzed using voxel-based morphometry (Ashburner and Friston, 2000), a computational technique that permits the assessment of gray or white matter concentration on a voxel-by-voxel basis in standardized stereotactic space.

Image processing and analyses were performed using SPM99 (Wellcome Department of Cognitive Neurology, London, UK). Each anatomical scan was normalized to the Montreal Neurological Institute (MNI) template using an automated spatial normalization (12-parameter affine transformation followed by nonlinear iterations using 7 × 8 × 7 basis functions). The spatially normalized images had isotropic voxels of 1 mm. Each normalized image was segmented into gray, white, and CSF compartments. The segmented gray matter images were spatially smoothed (12-mm FWHM isotropic Gaussian kernel) to normalize the distribution of voxel’s values and facilitate parametric analysis (Ashburner and Friston, 2000; Salmond et al., 2002).

2.5. Analysis

Two analytical approaches were employed: categorical and correlational. In the categorical approach three groups, Healthy Controls (HC), HR_{NSSP} and HR_{SSP} were compared on

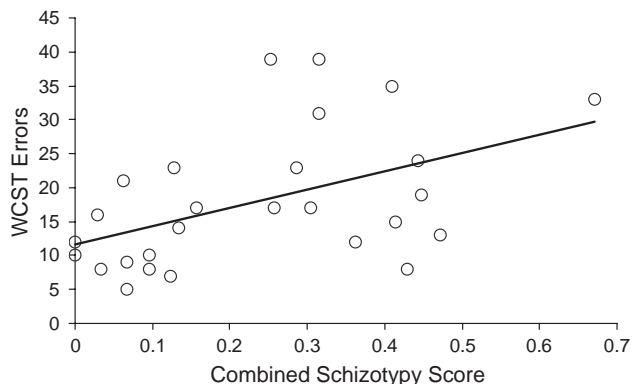


Fig. 2. Within the HR-S group, performance on the WCST was positively correlated with increase in schizotypy. Subjects who scored high on measures of schizotypy also made more perseveration errors on the task.

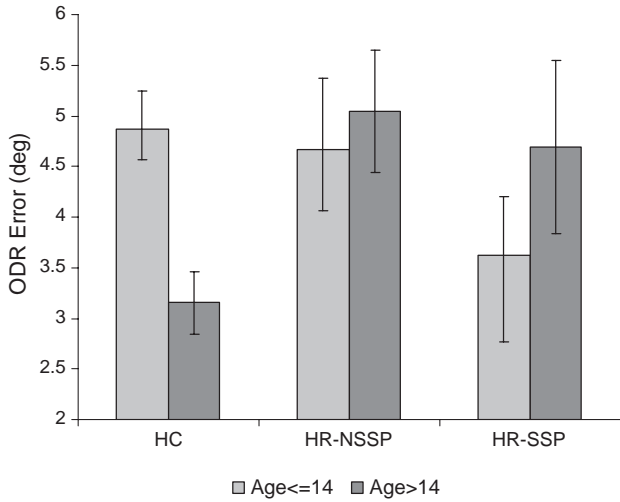


Fig. 3. Schizotypy was also associated with age-related decrements in performance on the spatial working memory task. Whereas older HC subjects (age >14) performed better on the task than their younger counterparts, older subjects in both HR-S groups performed worse with the older schizotypal subjects performing most poorly. These data suggest that as opposed to normal developmental trends, HR-S subjects perform worse on working memory tasks later in adolescence, and the degree of this deficit is related to the degree of measured schizotypy (error bars are ±s.e.m.).

performance on the WCST and the ODR performance. In the correlational approach, the relationship between schizotypal scores and neurobehavioral and gray matter measurements was assessed in the HR-S subjects.

3. Results

3.1. Schizotypy and neurocognitive performance

As shown in Fig 1, whereas HC and HR_{NSSP} groups performed comparably, HR_{SSP} made significantly more perseverative errors on the WCST than HR_{NSSP} and HC, $F(2, 52)=7.13, p<.002$.

Correlational analyses within the HR-S group, revealed that the number of errors on the WCST was highly positively correlated with schizotypy scores ($r=.49, F(1, 25)=7.58, p<.01$; Fig 2). These results indicate a continuous relationship between measured schizotypy and impairment on the WCST task suggesting a definitive interplay between this neurocognitive biomarker and clinical markers for schizophrenia in HR-S.

The oculomotor delayed response task is a robust index of normal neurodevelopment of frontal systems in adolescence (Luna et al., 2001), with task performance improving with age

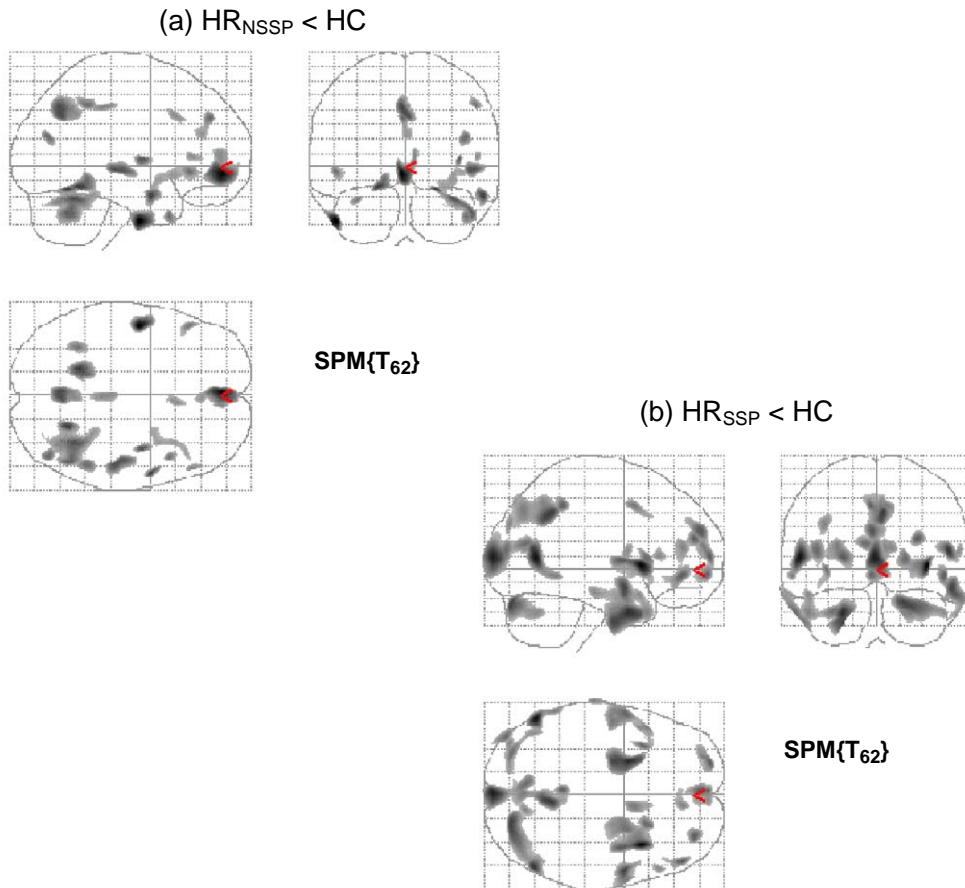


Fig. 4. Reductions in gray matter concentration as measured by voxel-based morphometry indicated reductions in gray matter concentration across heteromodal association cortex in both groups of HR-S subjects. The reductions were more pronounced in HR_{SSP} (b) than HR_{NSSP} (a), suggesting a relationship between gray matter deficit and schizotypy in subjects at risk for schizophrenia.

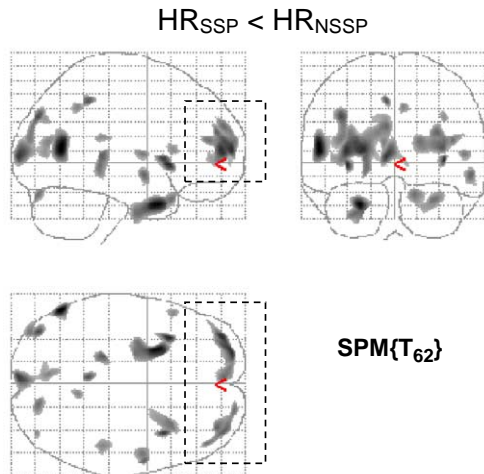


Fig. 5. Gray matter reductions were further compared between the two HR-S sub-groups. As can be seen, reductions in the HR_{SSP} subjects were particularly prominent in the prefrontal cortex (inset). Reductions in the prefrontal areas (insets) are further explored and depicted in Fig. 6.

through late adolescence to mid-adolescence. We assessed the relationship between age-related changes on the ODR task as they related to schizotypy in the HC and HR-S group. Following the developmental labeling scheme used by Luna et al. (2001), each group was subdivided by age (age ≤ 14 or age > 14) into younger and older sub-groups. Mean performance on the ODR task was analyzed in a two-way repeated measures analysis of variance with age (young vs. old) and group (HC vs. HR_{SSP} vs. HR_{NSSP}) as factors. Though HC on average were

more accurate than either of the HR sub-groups, no significant difference between groups was observed (HC: 3.90° vs. HR_{NSSP}: 4.67° vs. HR_{SSP}: 4.3°). However, an interaction between group and age was significant, $F(2, 52) = 5.8, p < .02$. Whereas older HC subjects showed an age-related improvement in performance (evidenced by decreased error on the ODR task), older subjects in either HR-S sub-group performed worse than their younger counterparts. Furthermore, this age-related decrement in performance was greater in the HR_{SSP} sub-group than the HR_{NSSP} suggesting that developmental progressive deficits were most closely associated with schizotypy. These data are depicted in Fig 3. The decrease in errors with age in the HC group is notable in the face of an increase in error with age in the two HR-S sub-groups.

These neurobehavioral results indicate that offspring of patients who score high on measures of schizotypy show greater deficits on tasks of executive function and spatial working memory, suggesting impaired function in prefrontal systems. Our next aim was to assess whether HR-S subjects with measured schizotypy also demonstrated greater neuropathology as measured by more extensive reductions in gray matter in heteromodal and particularly prefrontal areas of the cortex.

3.2. Schizotypy and morphometric analyses

Whole-brain voxel-based morphometric analyses were conducted using SPM '99 (Ashburner and Friston, 2000). An overall analysis of covariance (age and gender as covariates) revealed significant reductions in gray matter in the HR-S group

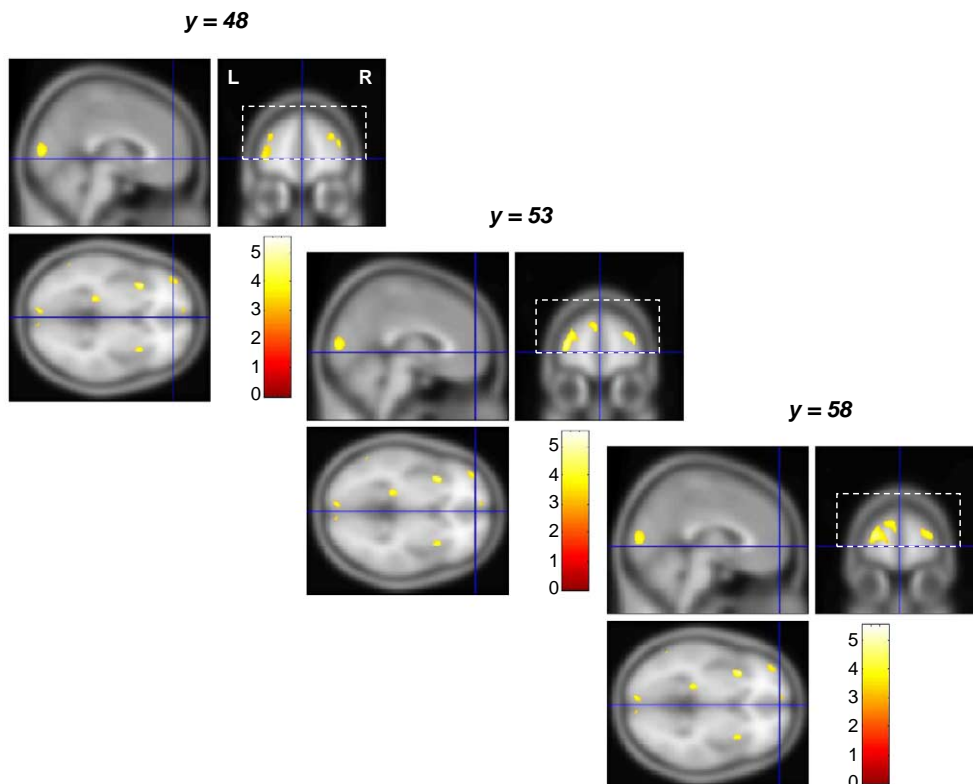


Fig. 6. Significant reductions in gray matter concentration in the prefrontal cortex are rendered in three successive coronal views ($y = 48, y = 53, y = 58$) of a T₁ template image.

Table 2
Bilaterally significant prefrontal clusters in the voxel-based analysis (HR_{SSP} < HR_{NSSP}) were explored using small volume correction

Left DLPFC		Right DLPFC	
Voxel location (x, y, z)	T ₆₂ value	Voxel location (x, y, z)	T ₆₂ value
–24, 61, 7	4.97	35, 56, 8	4.4
–28, 57, 10	4.67	36, 54, 12	4.18
–32, 56, 8	4.67	30, 58, 11	4.06
–32, 57, 5	4.56	32, 53, 17	4.04
		39, 51, 13	3.97

Voxel coordinates (Talairach) and corresponding T values are indicated.

compared to HC ($p < .001$, uncorrected; $t_{63} > 3.23$; extent threshold = 125 voxels) in key brain regions including inferior and dorso-lateral frontal cortex, anterior cingulate and the cerebellum. These analyses were extended for this study by analyzing data of the three groups (HC, HR_{NSSP} and HR_{SSP}) in a single analysis of covariance (Ancova) with gender and age as covariates. Contrasts were used to identify differences between groups and suprathreshold clusters were identified using a preset threshold ($p < .001$, uncorrected; $T_{62} > 3.23$; extent threshold = 125 voxels). Reductions in gray matter concentration are presented in maximum intensity projections in Fig. 4. At the same preset threshold and with the same power to detect differences, HR_{SSP} showed more widespread reductions in gray matter concentration compared with HR_{NSSP}, when each group was separately compared to HC. In both comparisons, reductions were observed in areas of the heteromodal cortex including the insula, the superior, middle and inferior temporal gyri, inferior frontal gyrus, and the precuneus.

Further analyses were conducted to compare each of the HR sub-groups directly. As seen in Fig 5, compared to their HR_{NSSP} counterparts, HR_{SSP} subjects showed significant gray matter reductions in middle and superior frontal cortex, thalamus, insula and cuneus, providing further evidence of increased impairment in this high-risk sub-group.

The reductions in prefrontal cortex are of particular relevance given the region's implication in schizophrenia and risk for the illness (Glantz and Lewis, 2000; Lewis, 1997a). The reductions in the insets (Fig. 5) are rendered on a T₁ template image in three successive coronal views (Talairach coordinates; $y = 48$, $y = 53$ and $y = 58$) in Fig. 6.

The bilateral prefrontal clusters in Figs. 5 and 6 were further explored for significance using small volume correction ($p < .001$, corrected; Job et al., 2002), using 10 mm spheres, placed at the centroid of the bilateral prefrontal clusters. Coordinates for significant voxels were converted from SPM-native Montreal Neurological Institute (MNI) coordinates to Talairach using non-linear transformations (www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml). As shown in Table 2, several voxel peaks in left and right dorsolateral prefrontal cortex emerged as significant.

4. Discussion

The aim of these studies was to assess the interrelationship between potential neurocognitive biomarkers of the schizo-

phrenia diathesis such as impairments in spatial working memory and executive function, and clinical markers such as schizotypy. We were also interested in assessing whether schizotypy was associated with neuroanatomic alterations, particularly in prefrontal cortex and other heteromodal association areas, as measured by MRI. The results provide strong evidence for convergent findings across the behavioral, clinical and neurobiological measures employed. Schizotypy in HR-S was associated with impaired performance on the WCST task (Figs. 1 and 2). Also HR-S subjects in late adolescence performed more poorly on spatial working memory tasks than their younger counterparts with the age-related decrement in performance being most closely related to schizotypy (Fig. 3). Schizotypy was also associated with decreased gray matter concentration in key areas of the cortex, particularly the prefrontal and temporal cortices (Figs. 4–6).

These results are consistent with studies of genetic risk for schizophrenia which have indicated that adolescent first-degree relatives demonstrate many of the abnormalities that are observed in first-episode schizophrenia (Johnstone et al., 2002). MRI morphometric studies have indicated reductions in the gray matter of key cortical regions in first-degree relatives of patients. These structures include the prefrontal cortex (Gogtay et al., 2003) and thalamus (Lawrie et al., 2001), both of which featured prominently in the current results (Figs. 4–6). The results are also consistent with other demonstrations of neurocognitive deficits in first-degree relatives, including spatial working memory abnormalities (Diwadkar et al., 2001; McDowell et al., 2001) and abnormalities of executive function (Wolf et al., 2002).

The life-time risk of offspring for developing disorders of the schizophrenia spectrum is approximately 15–30 times greater than the incidence in the normal population (Gottesman and Shields, 1982). However, with the incidence in the normal population being approximately 1%, this suggests considerable heterogeneity of the risk-profiles in the offspring population, with fewer developing schizophrenia spectrum disorders than do not. The reasons for this heterogeneity remain unclear and studies of this population may need to be further refined to identify possibly “ultra high-risk” sub-groups in which neurocognitive, clinical and neurobiological predictors of the illness converge. The present study is the first to attempt to relate a plausible clinical marker that captures disposition to schizophrenia, with neurocognitive and neurobiological markers in individuals at risk for the illness.

The current results are also directly relevant to questions of the relationship between schizotypal personality disorder (SPD) and schizophrenia. Whereas this relationship between schizotypal personality disorder and schizophrenia itself is not yet well understood, studies have provided evidence of increased familial coincidence, suggestive of genetic relatedness (Kendler et al., 1993; Siever et al., 1990). Different models have speculated that the disorders are distinct, identical and characterized only by the degree of severity of expression, or related with partially overlapping etiologies (Siever and Davis, 2004; Siever et al., 2002). Increasingly, it appears that either of the last two models is consistent with

the emerging data. Individuals with SPD show less severe neuropsychological deficits or psychotic symptoms than individuals with schizophrenia (Voglmaier et al., 2000), suggesting that SPD may be part of the schizophrenia spectrum of disorders and represent a milder variant of the illness. Also, studies assessing neurobiological and neurocognitive impairment in SPD showed prefrontal deficits in structure and executive function that are characteristic of what is observed in schizophrenia itself (Raine et al., 1992). Recent studies have also indicated an increase incidence of schizotypal-related characteristics in first-degree relatives of schizophrenia patients. When schizotypal personality questionnaires (specifically the SPQ) are administered to non-psychotic first-degree relatives of schizophrenia patients and controls, social and interpersonal deficits differentiated relatives from control subjects (Calkins et al., 2004). This increased expression of schizotypal characteristics in relatives of patients, suggests a possible increased heritability of these traits in individuals at risk for the illness, further suggesting this disorder's position within part of the schizophrenia spectrum. Therefore, as our results suggest, first-degree relatives and particularly adolescent offspring of schizophrenia patients may provide an important group in which to assess the impact of genetic risk (which has presumably been conferred on these individuals), its expression in schizotypal features and the relationship between these features and other accepted biomarkers of the schizophrenia spectrum including working memory deficits and impaired prefrontal neurobiology.

5. Conclusions

The search to identify premorbid biomarkers of schizophrenia that may be predictive of illness onset is one of the topics of foremost importance in the scientific study of schizophrenia (Chapman and Chapman, 1987; Johnstone et al., 2003; Keshavan et al., 2004). Approaches that focus on adolescent offspring or relatives of schizophrenia patients may be one of the most important methods for trying to assess premorbid abnormalities in schizophrenia (Diwadkar et al., 2004). Serious challenges remain. Because of the presumed complex genetic basis of the illness (Harrison and Weinberger, 2005), attempts to study first-degree relatives as a homogenous group may be compromised by the latent genetic heterogeneity that may underlie this population. Alternatively, the study of precursors of the illness may be enriched by assessing cross-correlations between clinical scales known to be strongly associated with the schizophrenia spectrum, and biomarkers known to be strong correlates of the illness.

These results suggest that refining estimates of risk for the illness in the HR-S group may benefit from at least two strategies. Firstly, assessing multiple interrelated modalities of deficit, including neurobehavioral tasks, structural, functional and neurochemical imaging along with measures of psychopathology may reveal a better picture of emergent deficits in HR-S subjects. Secondly, subjects with the maximal degree of dysfunction across these measures may

be followed longitudinally to assess how these different variables may change through adolescence and into young adulthood.

Future directions may also assess the relationship between plausible genetic liability for the schizophrenia diathesis such as particular genetic polymorphisms (e.g., COMT, Egan et al., 2001) and the incidence of schizotypy in high-risk populations. Such genetic associations have already been identified in community samples (e.g., Avramopoulos et al., 2002) but have yet to be understood in first-degree relatives. Clearly, not all offspring have the same degree of risk for the illness. A challenge for the future will be to develop research strategies that better capture the latent heterogeneity in this group and lead to better techniques for early identification and intervention.

The present results provide the initial steps toward such a prospective approach. Other related strategies (Yung et al., 2004) have also attempted to enrich the prospective study of risk factors in individuals with a family history of schizophrenia using measures of functional decline and the expression of sub-threshold psychosis. These approaches that combine clinical and neurocognitive measures may help to identify specific sub-groups of young and adolescent offspring or relatives of schizophrenia patients at ultra high risk for schizophrenia. The sub-groups therefore, may particularly benefit from strategies of early intervention.

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