Published in final edited form as:
Schizophr Res. 2012 August ; 139(1-3): 129–135. doi:10.1016/j.schres.2012.05.012.

Premorbid Multivariate Markers of Neurodevelopmental Instability in the Prediction of Adult Schizophrenia-Spectrum Disorder: A High-Risk Prospective Investigation

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Abstract

The authors examined whether multiple childhood indicators of neurodevelopmental instability known to relate to schizophrenia-spectrum disorders could predict later schizophrenia-spectrum outcomes. A standardized battery of neurological and intellectual assessments was administered to a sample of 265 Danish children in 1972, when participants were 10–13 years old. Parent psychiatric diagnoses were also obtained in order to evaluate the predictive strength of neurodevelopmental factors in combination with genetic risk. Participants were grouped into three categories indicating level of genetic risk: children with a parent with schizophrenia (n=94); children with a parent with a non-psychotic mental health diagnosis (n=84); and children with a parent with no records of psychiatric hospitalization (n=66). Variables measured included minor physical anomalies (MPAs), coordination, ocular alignment, laterality, and IQ. Adult diagnoses were assessed through psychiatric interviews in 1992, as well as through a scan of the national psychiatric registry through 2007. Adult diagnostic information was available for 244 members of the sample. Through a combination of multiple childhood predictors, the model correctly classified 73% (24 of 33) of the participants who eventually developed a schizophrenia-spectrum outcome in adulthood. Results suggest that, with replication, multivariate premorbid prediction could potentially be a useful complementary approach to identifying individuals at risk for developing a schizophrenia-spectrum disorder. Genetic risk, MPAs, and other markers of neurodevelopmental instability may be useful for comprehensive prediction models.

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Keywords

schizophrenia-spectrum; neurodevelopment; psychosis; premorbid; MPA

1. Introduction

Many researchers have targeted neurological dysfunction as not only a main feature of schizophrenia, but the primary expression of the neural pathology of the illness (Andreasen et al., 1998; Heinrichs et al., 1997; Heinrichs, 2005; Hugdalh and Calhoun, 2010). Post-mortem and imaging studies of individuals with schizophrenia typically demonstrate neural structural and functional abnormalities (e.g., Shenton et al., 2001). Formal neurological assessments administered to people with schizophrenia often reveal neurological “hard signs,” which indicate localized brain abnormalities, and neurological “soft signs,” which suggest global, non-specific, cerebral dysfunction (e.g., Flyckt et al., 1999).

The neurodevelopmental model of schizophrenia posits that the brain anomalies associated with schizophrenia are caused by genetically determined and/or environmentally influenced factors (e.g., heritable risk factors, genetic mutations, epigenetic effects, prenatal complications, structural abnormalities, see Walker et al., 2010) that interrupt typical neurodevelopment. Early neurodevelopmental anomalies may interact with typical maturational brain processes throughout childhood and adolescence, causing a range of relatively benign markers of developmental disruption. Though the clinical symptomatology resulting from this neural maldevelopment remains relatively dormant until psychosis onset (Weinberger, 1987), studies suggest the possibility of recognizing some neurodevelopmental signs premorbidly.

Many studies that examine neurological dysfunction and schizophrenia employ neurological assessments or post-mortem studies of the brains of adults after they have developed schizophrenia (Chan et al., 2010). Hospitalization, substance use, social isolation, long-term pharmaceutical treatment, and the potential neurotoxic effects of schizophrenia itself may, in part, account for the neurological dysfunction manifested by individuals with chronic schizophrenia (Madsen et al., 1999; van Haren et al., 2008). Additionally, comparing individuals with full schizophrenia to controls can unwittingly bias raters towards the study hypothesis during their assessment (Watt et al., 1984). It is difficult to ascertain, therefore, whether the dysfunctions observed are present before the onset of the disease or are byproducts of the illness.

Prospective studies involving individuals on a trajectory toward schizophrenia offer evidence that neurological dysfunction precedes schizophrenia onset. Assessments prior to illness onset avoid confounds such as rater bias and effects that are better attributed to treatment and/or course of illness, thereby providing a clearer view of developmental progression. Relative to children who do not go on to develop schizophrenia-spectrum disorders, children on a developmental trajectory toward schizophrenia have shown impairments in an array of areas such as cognitive abilities, motor coordination, lateral side preference, minor physical anomalies, and ocular alignment (see Amminger et al., 1999; Andreasen et al., 1999; Bearden et al., 2000; M. Cannon et al., 2002; Hans et al., 1999; Isohanni et al., 2001; Ott et al., 1998; Schiffman et al., 2004; Sørensen et al., 2010).

Each of these markers reflects unique neurodevelopmental processes, often implying some form of early neurodevelopmental disruption relevant in the etiology of the illness. For instance, MPAs have been associated with disruptions in neural migration during the first trimester of fetal life (e.g., Green et al., 1994), and atypical lateral-side preference has been linked with atypical cerebral hemispheric lateralization that may in part be influenced by

prenatal exposure to various levels of sex hormones (Cohen-Bendahan et al., 2005). Neurological markers may also be useful toward prediction of illness. Previous efforts to combine early neurodevelopmental markers with genetic risk toward prediction of schizophrenia have yielded mixed levels of success (Erlenmeyer-Kimiling et al., 2000; Isohanni et al., 2005). An emerging body of research suggesting that earlier intervention is associated with better treatment response (Marshall et al., 2005) provides a compelling rationale to attempt to improve prediction models using early markers of psychosis risk. In recent longitudinal studies, the most reliable indicators of pending psychosis are the presence of "prodromal" symptoms, sometimes conceptualized as the "Attenuated Psychosis Syndrome" (APS) (Cannon et al., 2008). This model, however, depends on the recognition of attenuated psychotic symptoms in individuals already experiencing psychological distress, and actual prediction of psychosis using the clinical high-risk paradigm is still less than ideal. Across studies, rates of psychosis onset among clinical high-risk participants vary widely from 7–52% (Correll et al., 2010). Successful identification of "premorbid" risk markers may help to further refine prediction models and improve early intervention paradigms.

Findings from prospective studies have provided useful insight into premorbid markers of schizophrenia risk by examining the relation of individually assessed variables to future psychiatric outcome (e.g., Cannon et al., 1997; Ott et al., 1998). Combining several related neurodevelopmental markers, rather than examining the relationship of each variable with the outcome of interest, may improve prediction of schizophrenia and related spectrum disorders (e.g., Mäki et al., 2005). The objective of the current study is to use prospective data collected over nearly fifty years to examine the combined strength of multiple premorbid markers of neurodevelopmental instability toward prediction of adult psychiatric status.

2. Materials and methods

2.1 Participants

The current study utilized data from the Copenhagen Perinatal Cohort, which included 9,125 individuals born between September 1, 1959, and December 31, 1961, at Rigshospitalet, in Copenhagen, Denmark (Schiffman et al., 2009). Recruitment, psychiatric evaluations, and neurological assessments were carried out by researchers and clinicians associated with University of Copenhagen as well as the Rigshospitalet and the Institute of Preventive Medicine. Participants received a complete description of the study and provided written informed consent. See online material for flowchart describing participant recruitment, selection, and group categorization.

2.2 Assessment of genetic risk

Parents' psychiatric status was assessed through hospital record reviews and face to face interviews in order to determine participants' level of genetic risk. At the inception of the project, all adults in the Copenhagen region who were part of the Copenhagen Perinatal Cohort study and who had been admitted to a mental hospital for schizophrenia were recruited for the current study. In 1972, the Danish Psychiatric Central Registry was scanned to further ascertain diagnostic information for participants' biological parents (see Dalman et al., 2002, for comments regarding the validity of register scans for identifying cases of schizophrenia and other psychiatric illnesses). On the basis of this information, 265 participants were categorized into three genetic risk groups: 1) children whose mother or father had a psychiatric hospital diagnosis of schizophrenia ("high-risk;" n=72), 2) children with a parent with a psychiatric record of hospitalization for a non-psychotic disorder ("other risk;" n=72), and 3) children with parents without records of psychiatric

hospitalization ("low-risk;" n=121). In the original design of the study, an effort was made to match the control subjects to the high-risk subjects on the basis of race, gender, socio-economic status, and parents' age.

In 1992, 207 mothers and 172 fathers were administered the Structured Clinical Interview for DSM-III-R (SCID) (Spitzer et al., 1990), and an additional Central Registry scan was performed in 2007 to further validate parental diagnoses. Some shifts occurred as a function of 1992 and 2007 efforts to capture parents' lifetime diagnoses. Prior to attrition (see below), the final risk groups were as follows, high-risk, n=102; other risk, n=89; low-risk, n=74. To assess whether groups were still equivalent based on demographic information, the final risk groups were compared on the demographic characteristics mentioned above. No significant differences between risk groups were found.

2.3 Diagnostic outcome

In 1992, when the participants were between 31 and 33 years of age, a psychiatrist administered two structured clinical psychiatric interviews, the SCID, and the psychosis section of the Present State Examination (Wing et al., 1974). Danish psychiatric hospital records of the participants were examined at that time. In 2007, an additional diagnostic status update was completed through a scan of the Danish Psychiatric Central Registry for psychiatric admissions between the years 1994 and 2007. [1] On the basis of the interviews and/or hospital records, adult diagnostic outcomes data was available for 244 of the 265 subjects (92% successful follow-up after 48 years). Follow-up rate did not significantly differ by risk status (94 of 102 High-Risk; 84 of 89 Other-Risk, 66 of 74 Low-Risk). Thirty-three participants were diagnosed with a schizophrenia-spectrum disorder ("spectrum"), 78 were identified as having a non-psychotic disorder ("other disorders"), and 133 were not identified as having a mental health diagnosis ("no mental illness"). Diagnostic outcome information and demographic information is presented in Table 1. All participants were Caucasian.

2.4 Neurological examination

In 1972, when participants were between 10 and 13 years old, they participated in a one-day examination at a laboratory at the Institute of Preventive Medicine (N=265). Participation involved assessment of coordination, cognitive abilities, laterality, minor physical anomalies, and ocular alignment (see Schiffman et al., 2002, 2004, 2005, 2006, 2009). Nine tests of coordination were used to create the coordination scale: right and left diadochokinesia, right and left finger opposition test, right and left index finger and right and left foot tap, and right hand-left hand opens-closes (Boks et al., 2000; Rosso et al., 2000; Schiffman et al., 2009). Coordination scores were the sum of the standardized scores of coordination tests, with higher scores indicating more coordination dysfunction. The laterality examination included assessment of eye and foot dominance (e.g., Cannon et al., 1997; Crow et al., 1996; Elias et al., 1998). Footedness was assessed by asking subjects to kick a ball, balance, and hop on one foot. The foot used for each task was noted and scored (1=left, 0=right), and scores were summed to give a footedness score for each subject. Crider's Ring, Crider's Card, and Crider's Box (Crider, 1944) were employed to measure eye dominance. Subjects' choice of eye was observed for each task. Responses for tasks were scored (1=left, 0=right) and scores were summed to give a total eye dominance score for each subject. The total of both modalities were standardized and summed to form a

[1]As a function of the 2007 registry scan, we identified six additional participants who met the ICD-10 criteria for schizophrenia, schizotypy, paranoid psychosis or delusional disorder, and ten who met criteria for a non-psychotic other psychopathology disorder. By May 2007, 33 subjects were identified who met criteria for a disorder within the schizophrenia-spectrum. Fifteen participants were assessed through registry only; all others participated in face to face clinical interviews.

laterality score (Schiffman et al., 2005). Participants underwent a neuropsychological assessment consisting of the Wechsler Intelligence Scale for Children (WISC) (Sørensen et al., 2010; Wechsler, 1949). The WISC provides a measure of verbal, performance, and full scale intelligence quotients, with a mean of 100 and a standard deviation of 15. Subscales included in this assessment were Similarities, Vocabulary, Block Design, and Maze. Each subscale provides a scaled score based on normative data, with a mean of 10 and a standard deviation of 3. The MPA examination was conducted using the Waldrop Scale and measures included: epicanthus, hyperteliorism, adherent ear lobes, low-seated ears, malformed ears, asymmetrical ears, soft pliable ears, single transverse palmar crease, high-steepled palate, third toe longer than second, partial syndactylia of two middle toes, fundus abnormalities, fine electric hair or two or more hair whorls, and furrowed tongue or tongue with smooth-rough spots (Waldrop & Halverson, 1971; Gottesman and Gould, 2003; Compton and Walker, 2009). Each MPA was scored as either present or absent and summed. Higher scores indicated more MPAs (Schiffman et al., 2002). Participants were administered several tests of ocular alignment functioning, including monocular covering/uncovering, the Worth 4-Dot Test, and the Titmus Fly Test (Flach et al., 1992; Toyota et al., 2004). A general ocular alignment score was calculated by summing the standardized scores from the three tests, with higher scores indicating greater dysfunction (Schiffman et al., 2006).

2.5 Statistical Analyses

Less than 0.4% of the data were missing (26 of 6,588 cells). In the case of missing values, group mean substitution was used for data imputation. An analysis of variance was implemented to examine mean differences in neurological variables between outcome groups (i.e., spectrum, other diagnosis, no mental illness). Chi square tests were employed to explore systematic differences between sex and outcome group, as well as risk and outcome group. As previous literature has suggested the possibility of sex differences in some neurological measures including neuromotor coordination (Schiffman et al., 2004), handedness (M. Cannon et al., 1997), and MPAs (Weinberg et al., 2007), t-tests were used to assess for differences on dependent variables by sex. Univariate ANOVAs with Bonferroni's adjusted alpha level post hoc analyses were performed to test for specific pair-wise differences. Distributional properties and homogeneity of variance were also assessed and addressed. When data were sufficiently non-normal, non-parametric equivalents were performed.

The primary analysis was a multinomial logistic regression used to assess the ability of premorbidly collected neurological variables to predict adulthood diagnostic outcome. Using the results of the regression model, a receiver operating characteristic (ROC) analysis was performed to determine a statistically derived "optimal" cut-off score using the predicted probability of a schizophrenia-spectrum outcome. The ROC analysis with the cut-off score also allowed for the examination of the sensitivity and specificity in detecting the presence of an adulthood spectrum disorder relative to any other outcome. Given the number of predictors relative to the number of participants in our model, lack of statistical power may impede detection of significant effects in some cases; for this reason, effect sizes (Cohen's *d* and odds ratios) are presented throughout.

3. Results

An analysis of variance comparing group means for the three outcome groups (spectrum, other disorder, no mental illness) revealed significant differences for laterality, MPAs, IQ, and coordination [see Table 2]. Post-hoc comparisons were performed to identify significant between-group differences using Bonferroni correction to reduce type I error. Effect sizes (d) associated with mean differences among the three outcome groups were also obtained [see Table 3].

Due to significant kurtosis associated with the ocular alignment variable, non-parametric tests were used to examine group differences for this measure. A Kruskal-Wallis test indicated a significant omnibus difference across the three groups (χ^2 [2, 244]=10.24, p<.01). Post-hoc comparisons were performed using two-sample Kolmogorov-Smirnov tests. Alpha was set at .017 (Bonferroni correction) to minimize type I error. Ocular alignment deviation scores were highest among the spectrum group, and showed a trend toward significance when comparing those with spectrum disorders relative to those with other psychiatric disorders (z=1.45, p=.03) and those with no mental illness (z=1.45, p=.03). Differences in ocular alignment ratings were not significant when comparing those with other disorders to those with no mental illness (z=.26 p>.99).

3.1 Sex

There were 120 male participants and 124 female participants. To examine whether there was a significant relation between sex and outcome, a chi square analysis was employed. There was not a significant association between sex and adult psychiatric outcome [χ^2 (2, 244) = .20, p=.90]. Similarly, there was no significant relationship between sex and parental risk status [χ^2 (2, 244) =.59, p=.74].

T-tests, adjusted using a Bonferroni correction, demonstrated significant differences on two dependent variables between male and female participants. Male participants had significantly higher IQ scores (M=111.33, SD=14.31) than female participants (M=102.48, SD=14.56; t_{242}=4.79, p<.001) and significantly higher coordination scores (M=1.01, SD=6.64) than female participants (M=−.97, SD=6.38; t_{242}=2.38, p<.05). Given the potential influence of sex differences, sex was examined within the subsequent analyses as a predictor variable.

3.2 Logistic Regression

Multinomial logistic regression was performed to assess the ability of the premorbid variables (sex, parental risk status, laterality, MPAs, ocular alignment, IQ scores, and coordination) to predict adult diagnostic outcome (spectrum, other disorder, or no mental illness). The overall model was significant [χ^2 (16, 244) =53.70, p<.01)]. The likelihood ratio test indicated significant main effects for the overall model predicting outcome from the following variables: parent psychiatric status (i.e., having a parent with schizophrenia rather than no mental illness) [χ^2 (2, 244) =12.22, p<.01)]; IQ [χ^2 (2, 244) = 6.23, p<.05]; and MPAs [χ^2 (2, 244) = 8.37, p<.05]. See Table 4.

Probablistic diagnostic categorizations were predicted from the multivariate model for each participant, yielding 33.3% accuracy for those with a spectrum outcome and a total correct classification rate of 59.8%. See Table 5.

3.3 Receiver operating characteristics (ROC) analysis

Using the predicted probability of a spectrum outcome among the three possible predicted probabilities (i.e., spectrum, other disorders, no mental illness), a ROC curve was plotted to predict spectrum versus non-spectrum outcomes (ROC curves do not afford the possibility to consider three outcomes, so the other disorders and no mental illness groups were combined). Using the predicted probabilities as the ROC curve predictor variable, the AUC was .80 (95% C.I. =.72–.88, p<.001), superior to pure chance and in the “good” range (Hosmer and Lemeshow, 2000). See Figure 1.

In an effort to empirically derive the optimal cut-point to discriminate an outcome of spectrum from not spectrum (i.e., other disorders and no mental illness groups), the distance for each cut-off point relative to point (0, 1) on the curve was calculated [$d=\sqrt{[(1-s_n)^2}$ +

$(1-s_p)^2]$ where s_n is the sensitivity of a given cut-off point and s_p is the associated specificity of the cut-off point (Zhou et al., 2002). The "optimal" statistically derived cut-off was identified as the one with the smallest value of d (d=.38, cut-off predicted probability =.14). This cut-point yielded specificity of .75, sensitivity of .73, positive predictive value of .32, and negative predictive value of .95. Overall, this model was able to accurately classify 75% of participants into spectrum vs. "other" outcome groups. See Table 6.

4. Discussion

The current study examined the combined ability of neurodevelopmental markers toward the prediction of schizophrenia-spectrum disorders in an effort to evaluate the potential usefulness of such variables as premorbid indicators of risk. Although several of the variables that predicted schizophrenia-spectrum disorders in univariate analyses did not contribute unique variance in the overall multivariate multinomial logistic model, all contributed to the model in the hypothesized direction and none fell notably far from significance. Genetic risk, MPAs, and at a trend level, coordination, laterality, and ocular alignment were all found to be significant predictors when considering either the full model or the parameter estimates comparing those with a spectrum disorder to the other two outcome groups.

Genetic risk and MPAs were significant predictors of schizophrenia-spectrum disorders in the current model, indicating that these variables contributed unique predictive power above and beyond the other indices included in the model. A robust literature supports differences in MPAs between those with schizophrenia-spectrum disorders and individuals with no mental illness (e.g., Weinberg et al., 2007), and between those with schizophrenia-spectrum disorders and other psychopathology (e.g., Trixler et al., 2001). Although the origins are not entirely understood, prenatal insults are purported to lead to morphological abnormalities such as MPAs through the disruption of neural migration between the 7^{th} and 22^{nd} weeks of gestation (Green et al., 1994; Lane et al., 1997). There is evidence to suggest that MPAs can be either genetically or environmentally mediated. From a genetic perspective, previous research supports the conceptualization of MPAs as heritable endophenotypes associated with spectrum disorders (Gottesman and Gould, 2003). Alternatively, MPAs are also known to have environmental causes in some cases as well, suggesting the importance of prenatal care, especially for those with known genetic risk for schizophrenia (e.g., Wide et al., 2000). Regardless of the specific origins, our finding that genetic risk and MPAs contributed significantly to prediction of outcomes is consistent with evidence from a wealth of studies suggesting that schizophrenia is a neurodevelopmental disorder characterized by anomalous fetal neural development (Compton & Walker, 2009).

Laterality and coordination showed non-significant trends in distinguishing the individuals who developed a spectrum disorder from the no mental illness group. Although not consistently replicated, researchers have observed decreased rates of right-lateral side preference in people with schizophrenia compared to control populations (Dragovic and Hammond, 2005). Further, studies have found increased rates of abnormal lateralization in relatives of individuals with schizophrenia (Orr et al., 1999), which supports the notion that these anomalies may be related to inherited pathophysiology (Keshavan et al., 2008). Among the many potential explanations, exposure to sex hormones during pregnancy, specifically testosterone, is hypothesized to play a role in the abnormal lateralization sometimes seen in schizophrenia (Cohen-Bendahan et al., 2005). Coordination deficits in schizophrenia are associated with prenatal neurodevelopmental disruption, which are believed to have implications for subsequent maldevelopment of the cortico-cerebellar-thalamic-cortical circuit (e.g., Schiffman et al., 2009).

4.1 Prediction of schizophrenia-spectrum disorders

In the current study, the use of multiple predictors across all three risk groups combined yielded a correct classification rate of 75% based on a ROC analysis, with sensitivity of .73 and specificity of .75; in other words, the model correctly classified 24 of the 33 spectrum cases and 159 of the 211 non-spectrum cases. The negative predictive value was .95, and the positive predictive value was .32, indicating that of the 76 predicted cases of spectrum disorders, 24 were 'true' positives. The relatively lower positive predictive value may be a function of the relatively few spectrum disorder outcomes, and is a pattern seen in prior work (e.g., Erlenmeyer-Kimiling, et al., 2000). Practical implications of a low positive predictive value would suggest that any clinical actions taken as a function of prediction models similar to this should involve strategies that are relatively low-cost and carry low risk of adverse effects (e.g., enhanced clinical monitoring).

Recent longitudinal studies predicting schizophrenia-spectrum disorders have relied more heavily on clinical criteria as defined by the Structured Interview for Psychosis Risk States (SIPS), Comprehensive Assessment of At-Risk Mental States (CAARMS), and basic symptoms model (Klosterkötter et al., 2001; Miller et al., 2003; Ruhrmann et al., 2010; Yung et al., 2005). Clinical high-risk models aim to detect the emergence of 'prodromal' symptoms which are thought to appear more proximally (e.g., one to two years) to onset of the full threshold disorder. One notable advantage of the clinical high-risk prediction model is that it has been developed using a general clinical population rather than a specialized high-genetic risk sample. In contrast, our study's model relies heavily on genetic risk, and likely would not generalize to individuals with no familial risk for psychopathology. It is worth noting, however, that prediction in the clinical-risk model is substantially more accurate when genetic risk for psychosis is present (T. Cannon et al., 2008).

Although the clinical-risk model for early detection of psychosis has some concrete clinical advantages over the neurodevelopmental model tested in the current study, results from this study may still be of clinical value for assessing psychosis risk during the earlier premorbid phase of illness rather than in the year or so prior to psychosis onset. Genetic risk can be identified prior to birth, and the markers of early neurodevelopmental disruption are reliably stable in school-age children. Premorbid identification of individuals with indicators of psychosis risk (including family history) could enable earlier monitoring or intervention in the course of illness for some (e.g., Mäki et al., 2005), thus potentially shortening or eliminating the duration of untreated illness and improving outcomes for those on a trajectory toward psychosis (Marshall et al., 2005). If replicated, results from the current study suggest that individuals who have a parent with a psychotic illness, elevated MPAs, and perhaps other neuro-behavioral indicators may warrant continued clinical monitoring, especially as they reach the age of greatest risk for first-episode psychosis (around 15–25 years).

Further, neurological indicators might combine with more proximal risk indicators to enhance the predictive accuracy of existing assessment tools. There is room for improving the predictive accuracy of assessment tools such as the SIPS and CAARMS that use attenuated symptoms as the primary indicator of psychosis risk. Preliminary findings suggest that the inclusion of neurological risk indicators such as abnormal movements, history of obstetric complications, neurocognitive deficits, and MPAs in "prodromal" assessment protocols may incrementally improve the predictive accuracy of risk diagnoses (Mittal and Walker, 2007, 2011; Mittal et al., 2009; Pukrop et al., 2007). Results from the current study might encourage further exploration with regard to whether additional screening for neurological dysfunction, MPAs in particular, might be used in combination with clinical instruments like the SIPS to potentially minimize false-positive predictions of

psychosis onset, especially in individuals known to have a genetic vulnerability to the disorder.

4.2 Limitations

As is typical in longitudinal high-risk studies, generalization may be limited as the sample was selected for increased genetic risk for psychopathology. Efforts to reliably identify premorbid risk markers for schizophrenia in general population samples have met with limited success (Isohanni et al., 2005). Findings from this high-risk sample, however, likely generalize to many individuals with schizophrenia given the robust findings of parental genotypic risk transfer as well as the neurological abnormalities seen in healthy first-degree relatives (T. Cannon et al., 1995). Small sample size is also a typical problem in longitudinal high-risk designs, and in the current study prevented the possibility of examining potentially interesting interactions. Additionally, it is possible that insufficient power impacted the ability of the multinomial logistic regression to more accurately classify participants. Nonetheless, the number of participants with an outcome of a schizophrenia-spectrum disorder exceeds that of other similar studies (e.g., Amminger et al., 1999; Fish et al., 1992). It should also be noted that the combination of logistic regression with ROC analyses can lead to highly tailored results that should be interpreted as preliminary and with caution, and that the theoretical model tested in the current study has limited practical application with regard to suggesting ‘cutoffs’ at which MPAs or coordination difficulties (for example) might be considered as indicators of elevated risk. Future related work, from independent samples, would be required to validate this approach and these results.

The current study is also limited by its exclusion of non-neurological variables (other than genetic risk status). The choice of variables for this analysis was based on previous literature showing an association of each of these indicators to future schizophrenia-spectrum outcomes. Further, although other measures of varying constructs might contribute to prediction, no other scales that might be gleaned from the Copenhagen Perinatal Cohort Dataset (for example, a scale based on composite social functioning variables) have been adequately validated to date.

Despite these limitations, the current multivariate approach combining premorbidly assessed markers of neurodevelopmental instability over the course of nearly 50 years provides a clinically relevant model for prediction of schizophrenia-spectrum disorders. The current study lends further support to previous findings that indicators of early neurodevelopmental disruption, as well as genetic risk for psychosis, can be etiologically informative, and perhaps clinically useful as well. Early screening and monitoring of individuals at genetic risk for schizophrenia-spectrum disorders manifesting markers of neurodevelopmental disruption may be helpful in early identification, which might lead to earlier and more effective treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported in part by grant R03MH076846 to Jason Schiffman; by a Research Seed Funding Initiative (RSFI) grant from University of Maryland, Baltimore County; by the Division of Child and Adolescent Psychiatry within the University of Maryland; and by Sygekassernes Helsefond (Health Insurance Foundation) by grant 9700093 from the Danish Research Council. NIMH, RSFI administrators, the Division of Child and Adolescent Psychiatry, and the Danish Research Council had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

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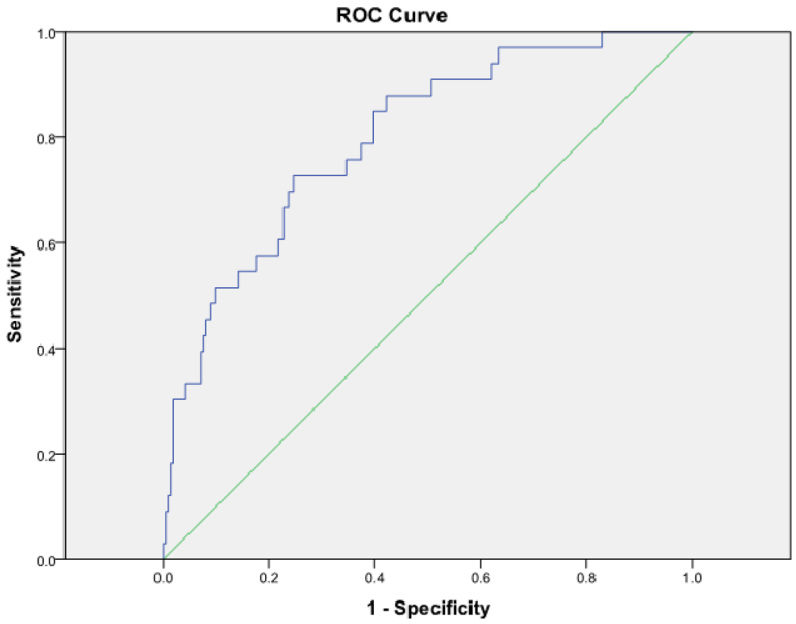

Figure 1.
ROC Curve predicting schizophrenia-spectrum vs. other outcomes

Table 1

Primary diagnosis by age, sex, and genetic risk status of subjects

	Age		Mother's Age		Sex		Genetic Risk			Total
	Mean	SD	Mean	SD	Male	Female	HR	OR	LR	
Schizophrenia-spectrum										
Schizophrenia	11.5	.77	27.5	7.7	10	8	15	2	1	**18**
Any psychosis or delusional disorder	11.7	.83	25.2	7.9	5	3	4	3	1	**8**
Schizotypal PD	11.6	.57	23.4	3.6	0	4	1	3	0	**4**
Paranoid PD	11.3	.61	25.2	3.2	0	2	2	0	0	**2**
Schizoid PD	10.5	n/a	38.6	n/a	1	0	0	0	1	**1**
Total Schizophrenia- spectrum	11.5	.74	26.6	7.3	16	17	22	8	3	**33**
Other Disorders										
Non-psychotic mood or anxiety disorder	11.7	.63	24.2	5.5	12	15	12	11	4	**27**
Non-psychotic alcohol/drug abuse	11.9	.63	24.2	5.7	23	11	9	17	8	**34**
Non-spectrum personality disorders	11.7	.80	26.9	6.4	5	12	7	6	4	**17**
Total Other Disorders	11.8	.68	24.8	5.9	40	38	28	34	16	**78**
No mental illness										
Total No Diagnosis	11.7	.64	27.4	6.9	64	69	44	42	47	**133**
All Participants	**11.7**	**.67**	**26.4**	**6.7**	**120**	**124**	**94**	**84**	**66**	**244**

Table 2

Means, standard deviations, and F values of predictor variables

Variable	Spectrum Outcome Mean (SD) N = 33	OD Outcome Mean (SD) N = 78	NMI Outcome Mean (SD) N = 133	F	*p*
Laterality	.61 (1.63)	.01 (1.53)	−.16 (1.44)	3.50	.03
MPA	3.50 (1.58)	2.73 (1.44)	2.57 (1.59)	4.79	.01
IQ	102.55 (17.96)	104.27 (15.11)	109.39 (13.85)	4.50	.01
Coordination	3.84 (8.35)	.15 (6.07)	−1.04 (6.02)	7.73	<.01

Note: OD=Other Disorders, NMI=No Mental Illness

Levene's tests for homogeneity of variances were as follows, Laterality: F(2, 241) = .40, p=.67; MPA: F(2, 241) = .31, p=.74; IQ: F(2, 241) = .90, p=.41; Coordination: F(2, 241) = 2.98, p=.05

Table 3

Post-hoc paired group comparisons

	Mean Difference Effect Size		
Variable	**Spectrum – NMI**	**Spectrum – OD**	**OD – NMI**
Laterality	.77 (p=.03) d=.43	.59 (p=.17) d=.26	.17 (p >.99) d<.01
MPA	.93 (p=.01) d=.53	.77 (p=.05) d=.38	.16 (p >.99) d<.01
IQ	−6.85 (p=.06) d=.37	−1.72 (p >.99) d<.01	−5.12 (p=.05) d=.27
Coordination	4.88 (p<.01) d=.79	3.70 (p=.02) d=.47	1.19 (p=.59) d=.08

Note: OD=Other Disorders, NMI=No Mental Illness; d=Cohen's d; α =.02 using Bonferroni correction

Table 4

Summary of multinomial logistic regression analysis

Group and Predictor	Wald χ^2	df	B	Odds Ratio	*p*	95% CI
Spectrum vs. OD Outcome						
Intercept	5.22	1	5.54		.02	
Parent w/Spectrum vs. NMI	3.33	1	−1.31	.27	.07	.07–1.10
Parent w/Spectrum vs. OD	3.71	1	−1.00	.37	.05	.13–1.02
Sex	.77	1	−.45	.64	.38	.24–1.74
Laterality	1.38	1	−.17	.84	.24	.63–1.12
MPAs	5.73	1	−.36	.70	.02	.52–.94
Ocular Alignment	3.92	1	−.21	.81	.05	.66–1.00
IQ	.28	1	−.01	.99	.60	.96–1.03
Coordination	3.15	1	−.06	.94	.08	.88–1.01
Spectrum vs. NMI Outcome						
Intercept	1.56	1	2.93		.21	
Parent w/Spectrum vs. NMI	8.49	1	−1.99	.14	<.01	.04–.52
Parent w/Spectrum vs. OD	2.50	1	−.81	.45	.11	.17–1.21
Sex	.01	1	−.06	.94	.91	.36–2.46
Laterality	3.16	1	−.26	.77	.08	.58–1.03
MPAs	7.82	1	−.40	.67	.01	.50–.89
Ocular Alignment	1.42	1	−.11	.90	.23	.76–1.07
IQ	1.42	1	.02	1.02	.23	.99–1.05
Coordination	4.03	1	−.07	.94	.05	.88–1.00

Note: OD=Other Disorders, NMI=No Mental Illness

Model R^2=.19 (Cox & Snell), .23 (Nagelkerke); Model x^2_{16}=52.51, p<.001

Table 5

Multinomial regression analysis classification summary

	Predicted Group Membership			
Observed	**Spectrum**	**OD**	**NMI**	**Σ**
Spectrum	11	2	20	33 (13.5%)
OD	2	20	56	78 (32.0%)
NMI	4	14	115	133 (54.5%)
Σ	17 (7.0%)	36 (14.7%)	191 (78.3%)	244 (100%)

Note: OD=Other Disorders, NMI=No Mental Illness

Table 6

ROC analysis classification summary: spectrum vs. all others

	Predicted Group Membership		
Observed	**Spectrum**	**Not Spectrum**	**Σ**
Spectrum	24	9	33 (13.5%)
Not Spectrum	52	159	211 (86.5%)
Σ	76 (31.1%)	168 (68.9%)	244 (100%)

Note: Not Spectrum = Other Disorders and No Mental Illness groups