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Premorbid multivariate prediction of adult psychosis-spectrum disorder: A high-risk prospective investigation

Jason Schiffman [a,*], Emily Kline [b], Nicole D. Jameson [a], Holger J. Sorensen [c,d], Shana Dodge [e,1], Thomas Tsuji [a], Erik L. Mortensen [d,f], Sarnoff A. Mednick [f,g]

[a] Department of Psychology, University of Maryland, Baltimore County, United States
[b] Department of Psychiatry, Harvard Medical School, Beth Israel Deaconess Medical Center, United States
[c] Department of Psychiatry, Amager Hospital, Copenhagen University Hospital, Capital Region of Denmark, Denmark
[d] Institute of Public Health, Center for Healthy Aging, University of Copenhagen, Denmark
[e] University of Hawaii, United States
[f] Institute of Preventive Medicine, Copenhagen University Hospital, Denmark
[g] University of Southern California, United States

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ABSTRACT

Premorbid prediction of psychosis-spectrum disorders has implications for both understanding etiology and clinical identification. The current study used a longitudinal high-risk for psychosis design that included children of parents with schizophrenia as well as two groups of controls (children whose parents had no mental illness, and children with at least one parent with a non-psychotic psychiatric diagnosis). Premorbid neurological factors and an indication of social function, as measured when participants were 10–13 years of age, were combined to predict psychosis-spectrum disorders in adulthood. Through a combination of childhood predictors, the model correctly classified 82% (27 of 33) of the participants who eventually developed a psychosis-spectrum outcome in adulthood. With replication, multivariate premorbid prediction, including genetic risk, social, and neurological variables, could potentially be a useful complementary approach to identifying individuals at risk for developing psychosis-spectrum disorders.

1. Introduction

Research suggests that neurodevelopmental markers of psychosis are identifiable premorbidly during childhood despite clinical presentation emerging later in life (Walker et al., 2010; Koutsouleris et al., 2014). Previous research that has combined premorbid neurodevelopmental indicators with genetic risk in an effort to predict psychosis has met with mixed success (Erlenmeyer-Kimling et al., 2000; Isohanni et al., 2005). Using prospective data collected by Mednick and colleagues over nearly 50 years, we (Golembo-Smith et al., 2012) identified multiple neurodevelopmental markers as premorbid indicators of risk for a psychosis-spectrum disorder. In this analysis, minor physical anomalies, and at a trend level coordination, laterality, and ocular alignment, all contributed to the predictive model, which yielded a 73% correct classification rate in predicting future psychosis-spectrum disorders.

Non-neurological factors are also known to predate psychosis onset, and specific evidence for the influence of social risk factors is well-documented (Couture et al., 2006; Howes and Murray, 2014; Morgan et al., 2010). Tsuji et al. (2013), utilizing the same Mednick-led 50-year prospective dataset as Golembo-Smith et al. (2012), created a separate model in which childhood social functioning was identified as a significant predictor of adult psychosis-spectrum disorders (Tsuji et al., 2013).

The aim of the current study is to combine both premorbid neurological and social factors in a single, multivariate model. A combined model has the potential to inform how these variables interrelate, as well as to increase the accuracy of prediction over and above what any single variable could do alone (Shah et al., 2013).

2. Materials and methods

2.1. Participants

This study recruited from the Copenhagen Perinatal Cohort, which included 9,125 individuals born between September 1, 1959 and December 31, 1961 at Rigshospitalet, Copenhagen, Denmark (Schiffman et al., 2009). In 1972, 265 "high-risk" participants (having a biological parent identified with schizophrenia) from the larger cohort were recruited for a more detailed evaluation. Matched controls were also recruited.

* Corresponding author at: Department of Psychology, University Of Maryland, Baltimore County, Baltimore, MD, 21250, United States.
E-mail address: schiffma@umbc.edu (J. Schiffman).
[1] Currently works for Engility Corporation.

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Table 1
Description of main neurological and social variables.

Variable measured	Description of measurement
Laterality	Laterality was assessed during a detailed analysis of foot and eye dominance. Footedness was assessed by recording foot used (1 = left, 0 = right) when participant was asked to kick a ball, balance, and hop on one foot and then summing to yield a total footedness score. Total eye dominance scores were similarly calculated, by summing the individual scores (1 = left, 0 = right) from three eye preference tasks: Crider's Ring, Crider's Card, and Crider's Box tasks (Crider, 1944). The total of both assessments were standardized and summed to form an overall laterality score, with higher scores indicating more left side preference (Schiffman et al., 2005).
MPA	MPA examination was assessed 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 and Halverson, 1971; Gottesman and Gould, 2003; Compton and Walker, 2009). Each MPA was reported as present or absent, and summed, with higher scores indicating more MPAs (Schiffman et al., 2002).
IQ	The Wechsler Intelligence Scale for Children (WISC) was used to measure verbal, performance, and full scale intelligence quotients with a mean of 100 and standard deviation of 15 (Wechsler, 1974). Subscales included Similarities, Vocabulary, Block Design, and Maze. Each subscale provided a scaled score based on normative data with a mean of 10 and standard deviation of 3 (Sørensen et al., 2010).
Coordination	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). Coordination scores were the sum of the standardized scores of coordination tests, with higher scores indicating more coordination dysfunction (Schiffman et al., 2009).
Social function	Completed by participants' teachers, the social function scale is 5 questions selected and summed from within a larger 136-item questionnaire. The 5 functioning questions were recorded in Likert-type format with options between 1 and 5, yielding total scores between 5 and 25. Higher scores represented better social functioning (Tsuji et al., 2013).

Recruitment, psychiatric evaluations, and social functioning assessments were orchestrated by researchers at the Institute of Preventive Medicine as well as the Rigshospitalet and University of Copenhagen. Participants received written informed consent. A complete recruitment and selection flowchart can be found in the online supplement to Golembo-Smith et al. (2012).

2.2. Assessment of genetic risk

Hospital record reviews and face-to-face interviews assessed parents' psychiatric status in order to determine participant level of genetic risk. Three genetic risk groups were ascertained: children whose mother or father 1) had a psychiatric hospital diagnosis of schizophrenia ("high-risk"), 2) had a psychiatric hospitalization for a non-psychotic disorder ("other-risk"), and 3) had no record of psychiatric hospitalization ("low-risk"). Further validation of parental diagnoses was conducted in 1992 and 2007 (see Golembo-Smith et al., 2012). After attrition, the final risk groups were: high-risk, $n = 94$; other-risk, $n = 84$; and low-risk, $n = 66$. Final risk groups were relatively equivalent on demographic characteristics.

2.3. Measurements of neurological and social function

When participants were 10–13 years old, they were assessed by a pediatric neurologist on a variety of neurological tasks. Neurological variables included laterality, minor physical anomalies (MPAs), IQ, and coordination (Golembo-Smith et al., 2012). Concurrently, research participants' teachers were asked to complete a five-item questionnaire assessing participants' degree of social function within the school context (Tsuji et al., 2013). Table 1 provides a more detailed description of the neurodevelopmental and social variables.

2.4. Diagnostic outcome

In 1992, when participants were between the ages of 31 to 33, a psychiatrist administered the SCID (Spitzer et al., 1990) and the psychosis section of the Present State Examination (Wing et al., 1974). Participant psychiatric hospital records were also examined. In 2007, an additional diagnostic update was completed through a scan of the Danish Psychiatric Central Registry for psychiatric admissions between the years of 1994 to 2007. Adult diagnostic outcome data from the interviews and/or hospital records were available for 244 of the 265 initial subjects; 33 participants were diagnosed with a psychosis-spectrum disorder ("spectrum"), 78 were identified as having a non-psychotic disorder ("other disorder"), and 133 had no identified mental health diagnosis ("no mental illness") (Table 2).

Table 2
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*