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Premorbid Multivariate Prediction of Adult Psychosis-Spectrum Disorder: A High-Risk Prospective Investigation

Jason Schiffman, Ph.D.^a, Emily Kline, Ph.D.^b, Nicole Jameson, B.S.^a, Holger J. Sorensen, M.D., Ph.D.^{c,d}, Shana Dodge, Ph.D.^e, Thomas Tsuji, M.A.^a, Erik L. Mortensen, Cand. Psych.^{d,f}, and Sarnoff Mednick, Ph.D., Dr.Med.^{f,g}

^aDepartment of Psychology, University of Maryland, Baltimore County

^bDepartment of Psychiatry, Harvard Medical School at Beth Israel, Deaconess Medical Center

^cDepartment of Psychiatry, Amager Hospital, Capital Region of Denmark, Copenhagen University Hospital, Denmark

^dInstitute of Public Health and Center for Healthy Aging, University of Copenhagen

^eUniversity of Hawaii (currently works for Engility Corporation)

^fInstitute of Preventive Medicine, Copenhagen University Hospital, Denmark

^gUniversity of Southern California

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

Correspondence concerning this article should be addressed to Jason Schiffman, Department of Psychology, University Of Maryland, Baltimore County, Baltimore, MD 21250., schiffma@umbc.edu, Telephone: (410) 455-1535, Fax: (410) 455-1055.

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Contributors

Dr. Schiffman oversaw the study design, data analysis, data interpretation, write-up, and manuscript preparation. Dr. Kline and Ms. Jameson contributed to analysis and write-up. Drs. Sorensen, Dodge, Mortensen, and Mr. Tsuji contributed to manuscript conceptualization, data-analysis consultation, and write-up. Dr. Sorensen also contributed to data collection. Dr. Mednick was the founder of this project, contributing to every aspect of the study.

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The authors have no actual or potential conflicts of interest to disclose.

complementary approach to identifying individuals at risk for developing psychosis-spectrum disorders.

Keywords

psychosis; premorbid; high-risk; neurological; social; prediction

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., 2015). 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 & 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).

Materials and Methods

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 “highrisk” participants (having a biological parent identified with schizophrenia) from the larger cohort were recruited for a more detailed evaluation. Matched controls were also recruited.

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).

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 were 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.

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., 2012). Table 1 provides a more detailed description of the neurodevelopmental and social variables.

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).

Statistical Analyses

Missing data for the neurological measures were rare, however, 19% of the items completed by teachers were missing (see Tsuji et al., 2013). Data were missing completely at random (MCAR; $\chi^2=29.17$, $df=19$, $p=.06$) (Little, 1988). To maximize statistical power and address missing values, multiple imputations were implemented for the social variable (5 iterations, 50 case draws, 2 parameter draws, resulting in 5 imputations) (Rubin, 1987). Pooled estimates are reported.

The primary analysis was a multinomial logistic regression used to assess the predictive relation of neurological and social function variables collected premorbidly, and genetic risk, to diagnostic outcome. A secondary multinomial logistic regression with step-wise forward entry was performed to test the incremental contribution of the social function

variable to the original neurodevelopmental model presented in Golembo-Smith et al. (2012). Utilizing the outcome from the primary regression model, a receiver operating characteristic (ROC) analysis was performed to determine a statistically derived “optimal” cut-off score using predictive probability of a psychosis-spectrum outcome. Analyses were conducted using SPSS 22.

Results

Table 3 reports ANOVAs between outcome groups. Significance and effect sizes (d) of between-group differences were examined using Bonferroni post-hoc comparison analysis (Table 4). A multinomial logistic regression predicting adult diagnostic outcomes from premorbid neurodevelopmental variables (sex, parental risk status, laterality, MPAs, ocular alignment, IQ scores, and coordination), as well as the social function variable, indicated that the model significantly predicted outcome diagnoses (spectrum, other diagnosis, or no mental illness; overall model $\chi^2(18,244) = 83.46, p < .01$). Significant predictors in the full model included: parent diagnosis [$\chi^2 = (2, 244) 12.48, p < .01$]; MPAs [$\chi^2 = (2, 244) 11.55, p < .01$]; social function [$\chi^2 = (2, 244) 29.76, p < .01$]; and significance reaching trend status from IQ [$\chi^2 = (2, 244) 5.72, p < .06$].

Follow-up multinomial logistic regression using step-wise forward entry methods in which neurological scales were included prior to adding the social function scale indicated that the addition of the social scale significantly improved the predicted fit of the model [χ^2 change = $(2, 244) 29.76, p < .01$], and increased overall variance predicted [Cox and Snell R^2 change = .092; Nagelkerke R^2 change = .108]. Table 5 provides individual predictor information when predicting different outcomes.

Probabilistic diagnostic categorizations were predicted from the model, yielding 48.5% accuracy for those with a spectrum outcome and a total correct classification rate of 60.2% (Table 6). A ROC curve was plotted to predict spectrum versus non-spectrum outcomes (as ROC curves do not allow consideration of three outcomes, other disorders and no mental illness groups were combined). Using predicted probabilities as the ROC curve predictor variable, the AUC was .86 [95% C.I. = .78–.93, $p < .01$], in the “excellent” range (Hosmer & Lemeshow, 2000) (Fig 1).

The “optimal” statistically derived cut-off was identified [see Golembo-Smith et al. (2012) for description on cut-off point calculations], yielding a sensitivity of .82, specificity of .76, positive predictive value of .35, and negative predictive value of .96. Overall, the inclusive model was able to correctly classify 77% of participants into spectrum vs. not-spectrum outcome groups (Table 7).

Discussion

Extending our prior work predicting spectrum outcomes from premorbid neurological variables by including a measure of social function, the current study provides evidence for the complementary role of both factors. Results suggest social function is a unique and significant predictor, contributing independently to predicting diagnostic outcomes above and beyond that of the neurodevelopmental findings alone.

The pattern of findings remained for individual neurological predictors despite the inclusion of the social function variable. The multinomial logistic regression generated in the prior work yielded a correct classification rate of 33% for those with a psychosis outcome; in the current study, this increases to 48%. Although this increase is promising, it is also important to note that in both studies, the overall correct classification rate across the three outcome groups remained more or less constant at around 60%. This might imply that social functioning has special pertinence to psychosis-spectrum diagnoses as opposed to other outcomes. When examining the results from the ROC curve that maximized prediction between two groups (psychosis-spectrum versus all other participants), the correct classification rate of the updated model was 77%, with sensitivity of .76, and specificity of .82¹. Including the social function variable, the model correctly classified an additional three spectrum cases (now 27 out of 33), and two non-spectrum cases (now 161 out of 211), yielding a positive predictive value of .35.¹

Recent efforts to predict psychosis have gravitated away from the more time intensive (nearly 50 year follow-up in this case) genetic dependent (parent with schizophrenia) high-risk model as employed in the current study, to a “clinical high-risk model” (CHR) that focuses more on identifying attenuated psychotic symptoms that tend to emerge one to two years prior to diagnosable psychosis. Clinical high-risk studies have shown promise in prediction of conversion to psychosis over two to three years (average two year conversion from risk to psychosis is 29%) (Fusar-Poli et al., 2012). Further, recent studies employing measures of biological (e.g., MRI, blood assays; Koutsouleris et al., 2009; Perkins et al., 2014) and social/environmental factors (e.g., urbanicity, social impairment; Dragt et al. 2011; Cannon et al., 2008) demonstrate the potential of using a variety of factors to improve overall accuracy of psychosis prediction models. Although there are many differences between CHR studies and the present study, the predictive ability of this nearly 50 year prospective study compares reasonably well with the more proximal CHR approach. The possibility of integrating early social and biological markers as seen in the present study, with other CHR factors currently emphasized in the field, has the potential to enhance the accuracy of early identification.

This study suffers from several notable limitations. Given the longitudinal nature of the study design, exact replication of these findings would be difficult. Nonetheless, the findings represent a “proof of concept,” suggesting that other prospective high-risk studies might be able to use both neurological and social premorbid measures to predict future onset of psychosis-spectrum disorders. It should also be noted that ROC analyses do not afford the opportunity to predict three groups, so our use of this analysis combined the “no mental illness” and “other disorder” groups together. Despite a loss of sensitivity to the distinctions between no mental illness and other non-psychotic illness, the ROC analysis does have real-world applicability for those interested in differentiating psychosis-spectrum from any other condition. Additionally, the social function scale had a large portion of missing data, and therefore we used multiple imputation to increase statistical power. It is relevant to note that

¹Golembo-Smith et al. (2012) correct classification was 75%, with sensitivity of .73 and specificity of .75.

the MCAR pattern suggested that the imputed values yielded unbiased statistical estimates, and unreported analyses using the raw data were very consistent with the imputed data.

Findings from this 50 year high-risk project could be considered within the context of a neurodevelopmental-social model, suggesting the inclusion of social risk factors as important, incrementally valid elements in a developmental trajectory towards psychosis (Howes & Murray, 2014). It is possible that early social difficulties and possible isolation from others, as measured here, may induce a stress response contributing to a cascade of exposure that leads to maladaptive biological responses (e.g., increased cortisol levels leading to dysregulation of dopaminergic pathways) that eventually contribute to psychosis (Mizrahi et al. 2012; Corcoran et al., 2003). This process, in conjunction with other neurologic pathways, may provide a more comprehensive account of a developmental course toward psychosis. These findings are in keeping with emerging evidence that there may be some, but not completely, overlapping underlying circuit dysfunction contributing to both neurological and social deficits (e.g., Gard et al., 2009; Wynn et al., 2010; Waltz and Gold, 2007). Additionally, a comprehensive premorbid screening evaluation that considers neurologically identified markers and social factors provides a useful illustration of the gradual unfolding of both physical and social signs of neurodevelopmental illness, and holds the potential to contribute to clinically useful prediction among people at genetic risk for psychosis.

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This manuscript is dedicated to the memory of Sarnoff A. Mednick, a mentor of the highest quality, and a true visionary in this, and other, fields.

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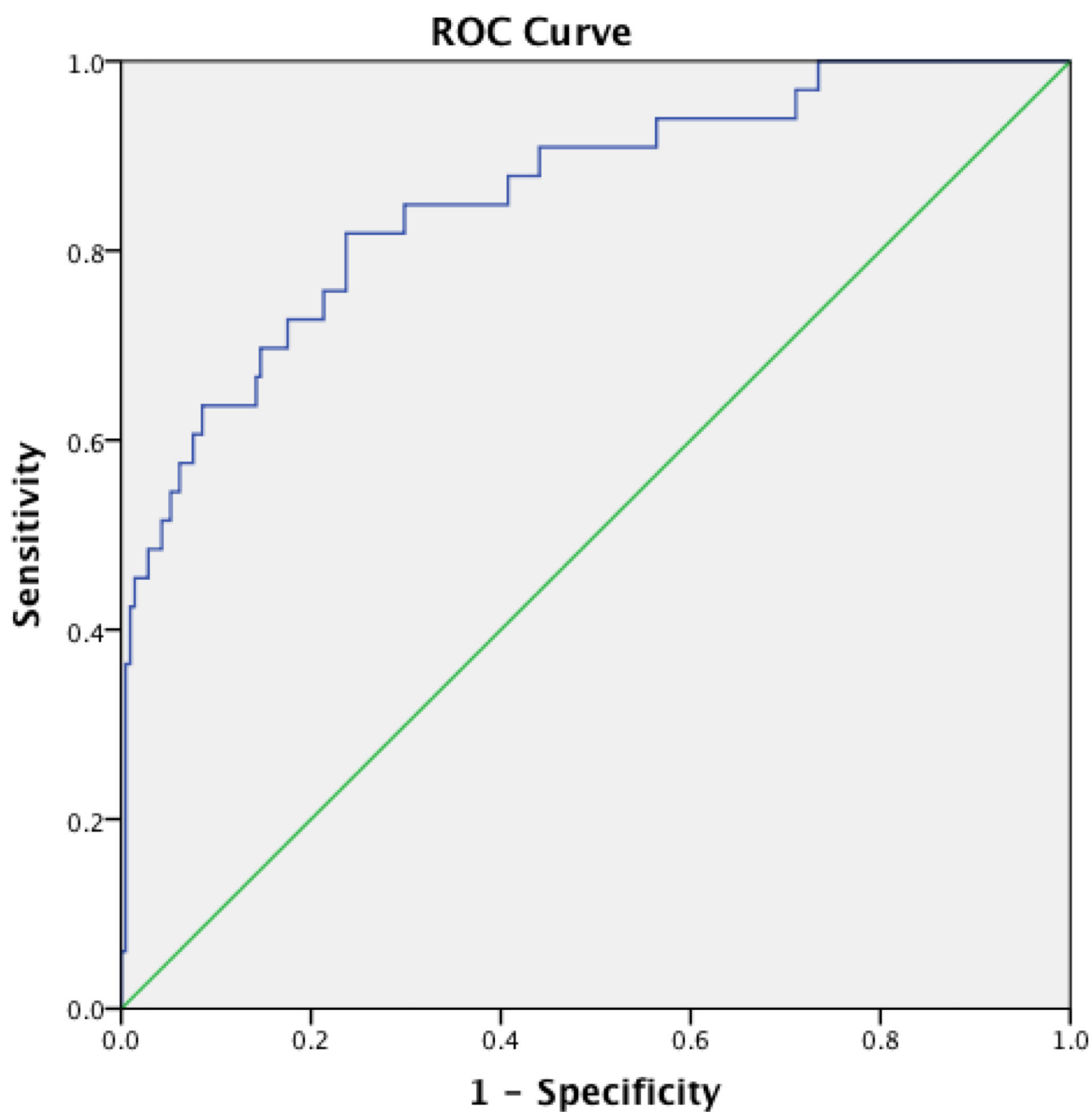


Figure 1.
ROC Curve predicting schizophrenia-spectrum vs. other outcomes

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, hypertelorism, adherent ear lobes, low-seated ears, malformed ears, asymmetrical ears, soft pliable ears, single transverse palmar crease, high-steeped 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 and 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, 1949). 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, and 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. 2012).

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	
<u>Schizophrenia-spectrum</u>										
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
<u>Other Disorders</u>										
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.	.68	24.8	5.9	40	38	28	34	16	78
<u>No mental illness</u>										
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 3

Means, standard deviations, and F values of predictor variables

Variable	Spectrum Outcome Mean (SD) (Range) N = 33	OD Outcome Mean (SD) (Range) N = 78	NMI Outcome Mean (SD) (Range) N = 133	F	p
Laterality	61 (1.63) (-1.55 – 3.57)	.01 (1.53) (-1.55 – 3.57)	-.16 (1.44) (-1.55 – 3.57)	3.50	.03
MPA	3.50 (1.58) (1 – 8)	2.73 (1.44) (0 – 5)	2.57 (1.59) (0 – 8)	4.79	.01
IQ	102.55 (17.96) (45 – 130)	104.27 (15.11) (69 – 147)	109.39 (13.85) (66 – 151)	4.50	.01
Coordination	3.84 (8.35) (-7.73 – 22.17)	.15 (6.07) (-8.19 – 16.93)	-1.04 (6.02) (-7.96 – 19.51)	7.73	<.01
Social function	17.54 (4.92) (6 – 25)	20.67 (3.36) (9 – 25)	21.74 (2.96) (8.10 – 25)	20.18	<.01

Note: OD=Other Disorders, NMI=No Mental Illness; higher scores indicate more dysfunction with the exception of the social function scale where lower scores indicates more dysfunction.

Table 4

Post-hoc paired group comparisons

Variable	Mean Difference Effect Size		
	Spectrum – NMI	Spectrum – OD	OD – NMI
Laterality	.77 ($p=.009$) $d=.50$.59 ($p=.057$) $d=.38$.17 ($p=.415$) $d=.12$
MPA	.93 ($p=.002$) $d=.58$.77 ($p=.017$) $d=.51$.16 ($p=.477$) $d=.10$
IQ	-6.85 ($p=.019$) $d=.43$	-1.72 ($p=.577$) $d=.10$	-5.12 ($p=.016$) $d=.35$
Coordination	4.88 ($p<.001$) $d=.67$	3.70 ($p=.006$) $d=.51$	1.19 ($p=.195$) $d=.20$
Social function	-4.20 ($p<.001$) $d=1.03$	-3.13 ($p<.001$) $d=.74$	-1.07 ($p=.029$) $d=.34$

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

Table 5

Summary of multinomial logistic regression analysis

Group and predictor	Wald χ^2	df	B	Odds Ratio	p	95% CI
<i>Spectrum vs. OD outcome</i>						
Intercept	1.49	1	3.27		.22	
Parent w/ spectrum vs. NMI	4.1	1	-1.80	0.17	.04	.03–0.94
Parent w/ spectrum vs. OD	2.83	1	-0.93	0.40	.09	.13–1.16
Sex	0.99	1	-0.55	0.58	.32	.20–1.71
Laterality	1.04	1	-0.16	0.85	.31	.63–1.16
MPAs	7.76	1	-0.47	0.63	<.01	.45–0.87
Ocular Alignment	3.70	1	-0.22	0.81	.06	.65–1.00
IQ	0.87	1	-0.02	0.98	.35	.95–1.02
Coordination	2.49	1	-0.06	0.94	.11	.88–1.01
Social function	11.67	1	0.21	1.23	<.01	1.09–1.39
<i>Spectrum vs. NMI outcome</i>						
Intercept	0.33	1	-1.58		.57	
Parent w/ spectrum vs. NMI	7.89	1	-2.46	0.09	<.01	.02–0.48
Parent w/ spectrum vs. OD	1.50	1	-0.68	0.51	.22	.17–1.50
Sex	0.10	1	-0.17	0.84	.75	.29–2.45
Laterality	2.22	1	-0.24	0.79	.14	.58–1.08
MPAs	10.31	1	-0.53	0.59	<.01	.42–.81
Ocular Alignment	1.28	1	-0.11	0.90	.26	.74–1.09
IQ	0.41	1	0.01	1.01	.52	.98–1.05
Coordination	2.75	1	-0.06	0.94	.10	.87–1.01
Social function	23.91	1	0.32	1.37	<.01	1.21–1.56

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

Model $R^2=.092$ (Cox & Snell), .108 (Nagelkerke); Model χ^2 (18,244)=83.46, $p<.001$

Table 6

Multinomial regression analysis classification summary

Observed	Predicted group membership			Σ
	Spectrum	OD	NMI	
Spectrum	16	2	15	33 (13.5%)
OD	7	18	53	78 (32.0%)
NMI	4	16	113	133 (54.5%)
Σ	27 (11.1%)	36 (14.8%)	181 (74.2%)	244 (100.0%)

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

Table 7

ROC analysis classification summary: spectrum vs. all others.

Observed	Predicted group membership		Σ
	Spectrum	Not Spectrum	
Spectrum	27	6	33 (13.50%)
Not Spectrum	50	161	211 (86.50%)
Σ	77 (31.5%)	167(68.4%)	244 (100.0%)

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