

# Using biological indices to classify schizophrenia and other psychotic patients

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## Abstract

Although classification of mental disorders using more than clinical description would be desirable, there is scant evidence that available laboratory tests (i.e. biological indices) would provide more valid classifications than current diagnostic systems (e.g. DSM-IV). We used cluster analysis of four biological variables to classify 163 psychotic patients and 83 nonpsychiatric comparison subjects. Analyses revealed a three-cluster solution with the first cluster reflecting electrodermal deviance, the second cluster representing nondeviant biological function, and the third cluster reflecting increased nailfold plexus visibility and ocular motor dysfunction. To assess the construct validity of proband clusters we examined ocular motor performance in 156 first-degree relatives as a function of proband cluster membership. First-degree relatives of third cluster probands exhibited worse ocular motor performance than relatives of other cluster probands. Additionally, better classification sensitivity and specificity were obtained for the relatives when they were grouped by proband cluster than by proband DSM-IV diagnosis. When a single proband characteristic (i.e. eyetracking performance) was used to group relatives, classification sensitivity and specificity failed to significantly increase over grouping by proband DSM-IV diagnosis. Multivariate biologically defined clusters may offer an advantage over DSM-IV classification when examining nosology and etiology of psychotic disorders. © 2001 Elsevier Science B.V. All rights reserved.

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## 1. Introduction

The diagnostic validity of many mental disorders is questionable. Robins and Guze (1970) proposed that diagnostic validity and homogeneity of mental disorders would improve if researchers pursued (1)

clinical description, (2) laboratory measures (mainly biological) that are reliable and precise, (3) delimitation of one disorder from other disorders using clinical description or laboratory measures, (4) follow-up studies to determine the stability of diagnoses over time, and (5) family studies examining the heritability of clinically described disorders or promising laboratory tests. Although investigators have aspired to classify mental disorders using laboratory-based methods rather than clinical description (Murray et al., 1992), there is scant evidence that classification based on

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laboratory procedures would be more valid than present day diagnostic systems (e.g. DSM-IV; American Psychiatric Association, 1994).

Researchers and clinicians alike dispute the validity of current systems for classifying psychotic patients. For instance, many investigators have questioned whether schizophrenia is a single disorder or better conceptualized as a group of related disorders (for a review see Cloninger, 1994; Tsuang and Faraone, 1995). Based in part on the wide variety of biological anomalies found in subgroups of schizophrenia patients, some investigators have proposed more than one distinct mental disorder within schizophrenia (Carpenter et al., 1988; Crow, 1980). Although researchers have examined biological anomalies associated with subgroups of psychotic patients (e.g. Malaspina et al., 1998; Ross et al., 1998; Sponheim et al., 1997; Tamminga et al., 1992; Thaker et al., 1989) and identified subgroups of psychotic patients through statistical analyses of symptomatology and course (Castle et al., 1992; Dollfus et al., 1996; Farmer et al., 1983; Goldstein et al., 1990; Kendler et al., 1998; Manton et al., 1994), to our knowledge no published studies have directly examined whether multiple biological indices (i.e. laboratory measures) identify meaningful and unique subgroups of psychotic patients.

To determine whether psychotic patients can be usefully classified with multiple laboratory procedures, it is best to choose measures that tap distinct biological systems and are deviant in individuals with psychosis. In this investigation we considered four such measures: ocular motor functioning, electroencephalogram frequency characteristics, nailfold plexus visibility, and electrodermal activation. All four measures have been shown to be abnormal in psychotic patients generally (Iacono, 1985) and more importantly, all four have been shown to be deviant in the psychotic participants included in the current investigation, all of whom have been included in the Markers and Predictors (MAP) of psychosis study of Iacono and Beiser (1989). Research from the MAP project has shown that psychotic patients have smooth-pursuit ocular motor dysfunction (Iacono et al., 1992), augmented low frequency and diminished alpha band power in the electroencephalogram (Sponheim et al., 1994), increased nailfold plexus visibility (Clementz et al., 1992b), and deviant

electrodermal activation (Iacono et al., 1999). These measures have been found to be related to various features associated with psychosis including brain structural features (e.g. Curtis et al., 1999; Sponheim et al., 2000; Takeuchi et al., 1994), negative symptoms (e.g. Curtis et al., 1999; Katsanis and Iacono, 1991; Sponheim et al., 2000), impaired neuropsychological performance (e.g. Curtis et al., 1999; Katsanis and Iacono, 1991), obstetrical complications (Ohman and Hultman, 1998), and poor prognosis (e.g. Beiser et al., 1994; Curtis et al., 1999; Ohman et al., 1989).

Just as the validity of DSM categories remains subject to debate, a problem that arises in using biological measures to classify psychiatric patients concerns how to evaluate the construct validity of the resulting laboratory-based classification. Ideally, we would like to demonstrate that our clusters differ on some psychopathology-relevant etiologic factor. Of the four biological measures in this investigation, only smooth pursuit ocular motor dysfunction has been found to be deviant in the biological relatives of MAP probands (Iacono et al., 1992), a finding consistent with literature indicating that deviant ocular motor function may index genetic vulnerability for a subset of those with schizophrenia (see Iacono, 1998a,b, for recent reviews). Although psychotic probands were found to be abnormal on the other three laboratory assessments, their first-degree relatives were not (Clementz et al., 1992b, 1994; Iacono et al., 1999). This apparent difference in the ability of these measures to identify genetic risk in MAP psychotic probands coupled with the notion that ocular motor dysfunction may tap a specific etiologic factor led us to use the ocular motor performance of biological relatives to evaluate the construct validity of cluster classification.

We argue that the degree to which the relatives, classified by biologically defined proband clusters, differ in their ocular motor function attests to the construct validity of the proband cluster divisions. To support the contention that biologically based classification may have an advantage over the DSM, we would expect the association between deviant ocular motor function in relatives and membership in a certain cluster to be stronger than the association between deviant ocular motor function in the relatives and a diagnosis of schizophrenia. Also, to demonstrate that a multivariate approach to classification is an

Table 1  
Characteristics of subjects

DSM-IV diagnostic group <sup>a</sup>	Probands				First-degree relatives			
	N	Age		Percent female	N	Age		Percent female
		Mean	SD			Mean	SD	
<i>Schizophrenia</i>								
First-episode	51	22.7	5.1	22	50	43.2	15.4	58
Chronic	50	28.9	4.3	12	NA	NA	NA	NA
<i>First episode nonschizophrenic psychosis</i>								
Unipolar psychotic	23	24.3	5.3	30	23	41.7	15.8	61
Bipolar psychotic	31	24.7	6.6	39	34	37.5	13.8	50
Schizoaffective	1	22.0	NA	100	1	54.0	NA	100
Schizophreniform	7	21.3	5.0	57	12	41.8	15.9	66
<i>Nonpsychiatric comparison</i>	83	27.3	9.2	41	36	37.5	15.6	61

(NA = not assessed)

<sup>a</sup> DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th ed.

improvement over one based on a single biological measure, we would expect the association between membership in a cluster and relatives' deviant tracking to be stronger than the association between a proband having deviant tracking and his or her relatives having poor tracking. These results would be consistent with the expectation that important biological information is lost when only one variable (e.g. deviant ocular motor function) is used to identify proband group membership. In sum, our analyses addressed the following questions: (1) Do biological variables characterize groups of psychotic probands differently than the DSM-IV system? (2) Do first-degree relatives of probands in different biologically defined clusters exhibit different ocular motor performance? (3) Is there evidence that the construct validity of biological cluster classification may be better than traditional DSM classification?

## 2. Methods

### 2.1. Subjects

#### 2.1.1. Probands

Table 1 summarizes the characteristics of probands and first-degree relatives who participated in the study. All patients were subject to a diagnostic assess-

ment that included administration of a semi-structured interview (the Present State Examination or PSE, 9th edition; Wing et al., 1974) by a trained psychiatrist or clinical psychologist, and a review of clinical chart and hospital information. First-episode patients were part of a longitudinal study that led to their receiving additional diagnostic interviews at nine and 18 months after study intake. Diagnoses were originally assigned according to DSM-III (American Psychiatric Association, 1980) criteria after a consensus diagnosis was reached by at least two clinicians who had reviewed a patient's data across all points in time (first-episode patients) and from all sources, including hospital records (both first-episode and chronic patients). For this report, DSM-IV consensus diagnoses were made by reviewing all interview, symptom checklist, course, and functioning data from which original diagnoses were made.

First-episode schizophrenic and nonschizophrenic psychosis probands were referred through a community-wide network comprising all psychiatric hospitals and community mental health centers in Vancouver, Canada, and referrals from private practice psychiatrists and general practice physicians who agreed to assist in the study. An attempt was made to recruit all persons, between the ages of 16 and 54, who experienced their first episode of psychosis during a two and a half-year period. To be included

as a first-episode proband, subjects had to be experiencing their first episode of disorder and have hallucinations, delusions, or grossly disorganized behavior (i.e. be psychotic). Chronic schizophrenic probands were recruited from an extended-care mental institution and affiliated board-and-care homes in the Vancouver area. All patients were considered to be clinically stable, operationally defined as no prescribed change in medication status during the two weeks preceding assessment.

One hundred sixty three first-episode and sixty-five chronic patients both received a consensus DSM-IV diagnosis and successfully completed the assessment on all four biological measures. Almost all patients were on medications at intake. Previous analyses involving the first-episode and chronic probands have shown no significant effects of medications, or recent alcohol or drug abuse, on the variables used in the cluster analyses (Clementz et al., 1992b; Ficken, 1991; Gooding et al., 1993; Iacono et al., 1999; Sponheim et al., 1994).

Nonpsychiatric comparison subjects were volunteers recruited from family practice clinics in low-income neighborhoods, employment centers, community centers and vocational colleges. Comparison subjects were excluded if they reported a history of mental health treatment in either themselves or their first-degree relatives. The 83 nonpsychiatric comparison subjects were free of drug or alcohol dependence and any chronic physical illnesses.

### 2.1.2. First-degree relatives

An attempt was made to recruit all biological first-degree relatives of the first-episode probands living within 80 km of Vancouver, who were between the ages of 16 and 65, provided that consent was obtained from the probands to contact them. Those with organic cerebral or chronic physical illness, ocular motor or visual disorders, severe mental retardation, or a history of substance dependence were excluded from study. The main purpose of the epidemiological investigation in which these patients were participants was to identify all cases of first-episode psychosis and to recruit a comparison sample of young, chronic schizophrenia patients. Thus, to be included in the study, it was not necessary to have an available relative (no attempt was made to recruit relatives of chronic patients). Overall, 60% of the first-episode probands

contributed at least one family member to the study. The average size of a family was 2.6 individuals; 56% of the relatives who participated were parents. These rates varied little across diagnostic groups. For the probands whose family members did participate, we were able to successfully recruit 57% of all available first-degree relatives. Of the probands who had no relatives participating, 60% had no available first-degree relatives (e.g. the proband was adopted or the relatives lived far away).

### 2.2. Apparatus and procedures

For the ocular motor assessment, participants tracked a moving dot with their eyes while their head was immobilized. The dot was driven by a sine wave generator, traversing 20° of visual arc, at a frequency of 0.4 Hz for 20 cycles. Both eye tracking and target signals were digitized, and corrected for phase differences. The root-mean-square difference between the signals was calculated for the best 16 consecutive cycles of eye tracking. The log base 10 of median root-mean-square (RMS) error of the 16 cycles was used as the dependent measures (for more details, see Iacono et al., 1992).

Three minutes of EEG were recorded while subjects were in a resting state. The EEG was recorded from Cz, C3, and C4 referenced to linked ears with a 35-Hz, half-amplitude, low-pass filter and a 1-s time constant. EEG data were digitized, segmented, filtered, screened for high frequency and blink artifact, and corrected for ocular contamination using the electrooculogram (Gratton et al., 1983). The square root of EEG power values was computed, divided into delta (1–3 Hz), theta (3.125–8 Hz), alpha (8.125–13 Hz), beta1 (13.125–20 Hz), beta2 (20.125–25 Hz), and beta3 (25.125–30 Hz) power bands, divided by total spectrum power (i.e. power from 0 to 30 Hz), and corrected for age. Factor analyses of probands' and relatives' EEG power bands for all subjects revealed a beta factor and an augmented-low-frequencies-diminished-alpha factor with eigenvalues greater than 1. The augmented-low-frequencies-diminished-alpha factor was chosen for inclusion in cluster analyses because psychotic patients exhibited significantly higher scores on this factor than nonpsychiatric comparison subjects, while

there were no group differences on the beta factor (see Sponheim et al., 1994).

Maricq's Scale for Plexus Visualization was used to quantify the visibility of the capillary plexus at the base of the nailfolds (for detailed overview of this assessment, see Clementz et al., 1992b). Plexus visibility refers to the degree to which the capillaries at the base of the nailfold can be visualized on each finger with the aid of a low-power stereo microscope. Visualization scores were assigned without knowledge of diagnosis and according to a nine-point scale anchored by reference photographs; 0 represented no visible plexus, 4 was extensive plexus visibility, and halfpoints were given for intermediate visibilities. The log base 10 of ratings summed across all fingers was used to compute the plexus visibility score. The intraclass test–retest reliability of nailfold plexus visibility ratings on a subset of these subjects was greater than 0.95 over an interval of 9 months (Clementz et al., 1992b).

The electrodermal activity of subjects was assessed during the presentation of two sound effects and two series of 0.5 s, 1000 Hz tones with 40 ms rise and fall times (see Iacono et al., 1999 for details). One tone series consisted of eight tones at 85 dB, the other series contained 12 tones at 105 dB. Scores were calculated for each subject on a single factor identified through a principal components analysis (varimax rotation) of number of skin conductance responses, log-transformed skin conductance response amplitude to the first stimulus, log-transformed mean skin conductance level calculated as the average of the individual levels measured at the onset of each stimulus, log-transformed frequency of nonspecific fluctuations during the tone series, and a categorical index of response status (responder = responded to at least one tone; nonresponder = responded to none of the tones). To achieve an overall index of electrodermal activation deviance, the absolute value of factor scores minus the nonpsychiatric control group mean was computed (Ficken, 1991). The use of such a score is consistent with findings indicating that psychotic patients tend to be either electrodermally hypo- or hyper-responsive in habituation studies. For instance, Iacono et al. (1999) have noted that elevated rates of electrodermal nonresponding have been consistently observed in schizophrenia and mood disorder, and psychotic patients who are electrodermal responders

appear to be hyperaroused. This hyperarousal is evidenced by elevated skin conductance levels, high rates of skin conductance responding, and frequent nonspecific electrodermal fluctuations.

### 2.3. Statistical analyses

Cluster analysis was used to determine the grouping of probands. Cluster analysis is a method of classification in which individuals are grouped or "clustered" according to the degree to which they are similar on various attributes. The goal of cluster analysis is to create the most similarity within groups and the most difference between groups. In the present study two cluster analysis methods were used. To determine the number of clusters, we used a hierarchical agglomerative method incorporating squared Euclidean distance as the metric for determining distance between cluster centroids and Ward's method for clustering. Ward's method (Ward, 1963) optimizes the minimum variance (error sum of squares) within clusters. Each subsequent cluster is that which produces the smallest error sum of squares. The hierarchical agglomerative method starts each case defined as a cluster. At each subsequent step, as determined by the measurement metric and the clustering algorithm, the most similar clusters are combined. We used visual inspection of the dendrogram generated by the clustering procedure and Mojena's "Stopping rule #1" to estimate the optimal number of clusters (Mojena, 1977). At each stage of clustering, a coefficient is generated. The entire clustering process yields a distribution of clustering coefficients. Mojena's "Stopping rule #1" stipulates that clustering should stop when the change in clustering coefficients is significantly different from one clustering stage to the next, or if significance is not achieved, when the largest standard deviate is generated.

There are two difficulties with hierarchical clustering. First, there are no widely accepted single criteria for determining the optimal stopping point in this process (Aldenderfer and Blashfield, 1984). The second difficulty with hierarchical clustering is that the single-pass nature of the method may lead to unstable clusters. Consequently, we used an iterative clustering method (*k*-means clustering) to determine cluster membership and increase the stability of clusters. Iterative clustering methods start with a set

Table 2  
Weights of cluster variables for three-cluster solution

Variable	Cluster 1 (EDD) <sup>a</sup>	Cluster 2 (nondeviant)	Cluster 3 (NPV/OMD) <sup>b</sup>
RMS error of smooth pursuit eye tracking	−0.13	−0.52	0.95
Electroencephalogram factor score	0.43	−0.53	0.43
Nailfold plexus visibility score	−0.14	−0.43	1.05
Electrodermal factor score	0.92	−0.56	−0.18

<sup>a</sup> EDD = electrodermal deviance.

<sup>b</sup> NPV = nailfold plexus visibility; OMD = ocular motor dysfunction.

number of clusters as the target and begin with arbitrarily partitioning the cases into the target number of clusters. Then, through successive iterations, membership of cases to clusters is changed until the most homogeneous clusters have been created.

Response operating characteristics (ROC) were used to examine the sensitivity and specificity of ocular motor indices in the probands and their relatives. Sensitivity in ROC analyses identifies subjects of a particular group membership (e.g. cluster 1) who have been accurately classified as a member of that group because their score is above the chosen cutoff point. Specificity is represented by the proportion of subjects from another comparison group (e.g. cluster 2) that are accurately classified as a member of the comparison group because their scores fall below the chosen cutoff point. ROC analyses plot the sensitivity and specificity of every possible cutoff score to obtain a curve which represents the distributional overlap between two groups on a given measure. By calculating the area under the curve (AUC) of the ROC, one can derive an index of the performance of a given measure. Potential AUC values range from 0.5 to 1.0. An index that is perfectly able to distinguish between two groups has an AUC value of 1.0, while an index on which groups overlap completely has an AUC of 0.5 (represented by a diagonal line on the ROC plot). The AUC value can then be interpreted as an estimate of the probability that a randomly chosen patient from one group will have a higher score on the measure than a randomly chosen patient from the other group. ROC analyses were performed using the LABROC program (Metz et al., 1988). LABROC provides maximum likelihood estimates of a binormal

ROC curve and its associated parameters from a set of continuously distributed data.

### 3. Results

#### 3.1. Clustering of probands with biological variables

To identify groups of probands who exhibited similar covariation on biological measures, cluster analyses were carried out on RMS error of smooth-pursuit eye tracking, the electroencephalogram abnormality factor, plexus visibility score, and the electrodermal deviance factor for all probands. In patients, control subjects, and relatives the correlations between the four cluster variables were minimal. The highest Pearson correlation was 0.14 and the lowest was −0.16, with all other correlations ranging from 0.097 to −0.092, indicating that these four measures tap relatively unrelated constructs. Results of cluster analyses supported a three-cluster solution. Table 2 presents loadings of the four biological variables on the three proband clusters. Cluster one [EDD (electrodermal deviance) cluster] was associated with electrodermal and electroencephalogram abnormalities. Cluster two [nondeviant cluster] was associated with a lack of biological abnormalities. Cluster three [NPV/OMD (increased nailfold plexus visibility/ocular motor dysfunction)] was associated with increased nailfold plexus visibility, ocular motor dysfunction, and electroencephalogram abnormalities. In order to confirm cluster stability, cluster analyses were run on 10 samples composed of 60% of the subjects, randomly selected from the data set. The identified cluster pattern emerged in nine of the

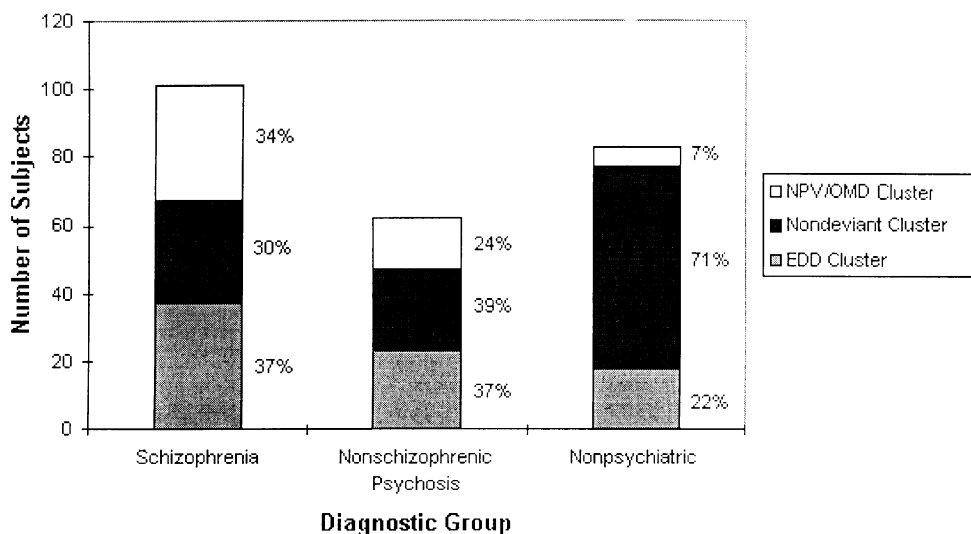


Fig. 1. Cluster membership of schizophrenia, nonschizophrenic psychosis, and nonpsychiatric comparison probands.

10 analyses run, indicating that the three-cluster solution was relatively stable and replicable within this data set.

We examined the distribution of proband diagnostic groups across the three clusters of subjects. Fig. 1 depicts the percentage of probands from each diagnostic group that were placed into each of the three clusters of subjects. Cluster membership failed to align with clinically defined categories with the exception of 71% of the nonpsychiatric comparison probands belonging to the biologically nondeviant cluster.

To evaluate the construct validity of proband clusters, we examined ocular motor functioning in first-degree relatives of probands. An analysis of variance (ANOVA) of RMS error in first-degree relatives revealed ocular motor performance varied as a function of proband cluster membership,  $F_{2,151} = 9.74$ ,  $p < 0.0005$ . The ocular motor performance of relatives of NPV/OMD cluster probands ( $M = 2.29$ ,  $SD = 0.26$ ) was worse than the ocular motor functioning of relatives of nondeviant cluster probands ( $M = 2.08$ ,  $SD = 0.23$ ),  $t = 4.26$ ,  $p < 0.0005$ , and relatives of EDD cluster probands ( $M = 2.11$ ,  $SD = 2.11$ )  $t = 3.50$ ,  $p = 0.001$ . Relatives of EDD cluster probands failed to show ocular motor deficits compared to relatives of nondeviant cluster probands,  $t = 0.64$   $p > 0.05$ , indicating that ocular motor

dysfunction was specific to first-degree relatives of NPV/OMD cluster probands.

To determine whether relatives of a particular proband diagnostic group accounted for ocular motor dysfunction in relatives of NPV/OMD cluster probands, we examined RMS error scores of each diagnostic group's relatives as a function of proband cluster membership. Fig. 2 depicts relatives' RMS error values and means as a function of diagnostic group and cluster. Because data for first-degree relatives of chronic schizophrenia patients were unavailable, only relatives of first-episode schizophrenia patients contributed data to the relatives of schizophrenia patients group. An ANOVA for relatives of schizophrenia probands in the three clusters revealed significant differences in RMS error,  $F_{2,46} = 7.46$ ,  $p = 0.002$ . RMS error scores for relatives of schizophrenia probands in the NPV/OMD cluster (mean = 2.36,  $SD = 0.25$ ) were significantly higher than those of relatives of schizophrenia probands in the nondeviant cluster (mean = 2.00,  $SD = 0.14$ ;  $p = 0.002$ ) and tended to be higher than those in the EDD cluster (mean = 2.17,  $SD = 2.17$ ,  $p = 0.056$ ). There was a trend for relatives of nonschizophrenic psychosis probands in the NPV/OMD cluster to exhibit higher RMS error values (mean = 2.22,  $SD = 0.27$ ) than relatives of nonschizophrenic psychosis probands in the other clusters (nondeviant

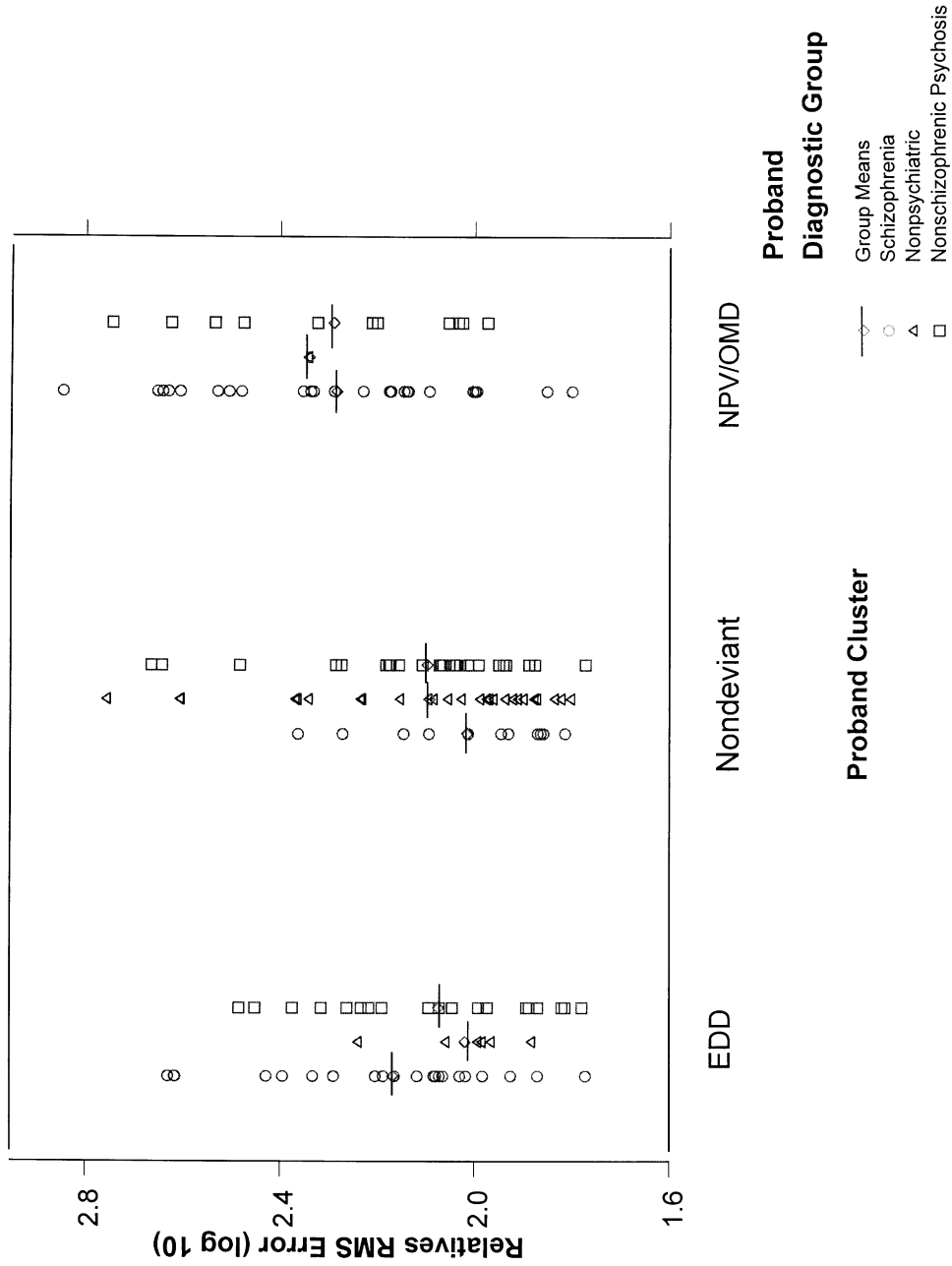


Fig. 2. Distribution of RMS error during a smooth-pursuit eye-tracking task for first-degree relatives as a function of proband cluster and proband diagnostic group.

cluster: mean = 2.10, SD = 0.23; EDD cluster: mean = 2.08, SD = 0.21),  $F_{2,66} = 2.14$ ,  $p = 0.126$ , suggesting ocular motor dysfunction in relatives of NPV/OMD cluster probands was not solely due to relatives of schizophrenia patients. Because there was only one relative of nonpsychiatric comparison probands in the NPV/OMD cluster, comparable analyses based on relatives of nonpsychiatric comparison probands could not be conducted.

To investigate whether clustering of probands with biological indices resulted in improved differentiation between their relatives, ROCs for relatives classified by proband cluster (i.e. EDD cluster, nondeviant cluster, NPV/OMD cluster) were compared to ROCs for relatives classified by proband diagnostic groups (i.e. schizophrenia, nonschizophrenic psychosis, nonpsychiatric comparison; see Fig. 3a and b). Better classification sensitivity and specificity were obtained for relatives of probands grouped by proband cluster than grouped by proband DSM diagnosis. The AUC for relatives of NPV/OMD cluster probands and relatives of nondeviant cluster probands was 0.74 [standard error (SE) = 0.048], while AUC for relatives of schizophrenia probands and relatives of nonpsychiatric comparison probands was 0.60 (SE = 0.049),  $t(187) = 1.98$ ,  $p < 0.05$  (see Fig. 3a). The AUC for relatives of NPV/OMD cluster probands and relatives of EDD cluster probands was 0.70 (SE = 0.055), while AUC for relatives of schizophrenia probands and relatives of nonschizophrenic psychosis probands was 0.55 (SE = 0.045),  $t(206) = 2.12$ ,  $p < 0.05$  (see Fig. 3b). The greater AUCs observed for relatives classified by proband cluster than by proband DSM diagnosis suggests that proband groups identified with biological indices have greater etiologic homogeneity (as indicated by ocular motor function in their biological relatives) than proband groups identified through clinical description.

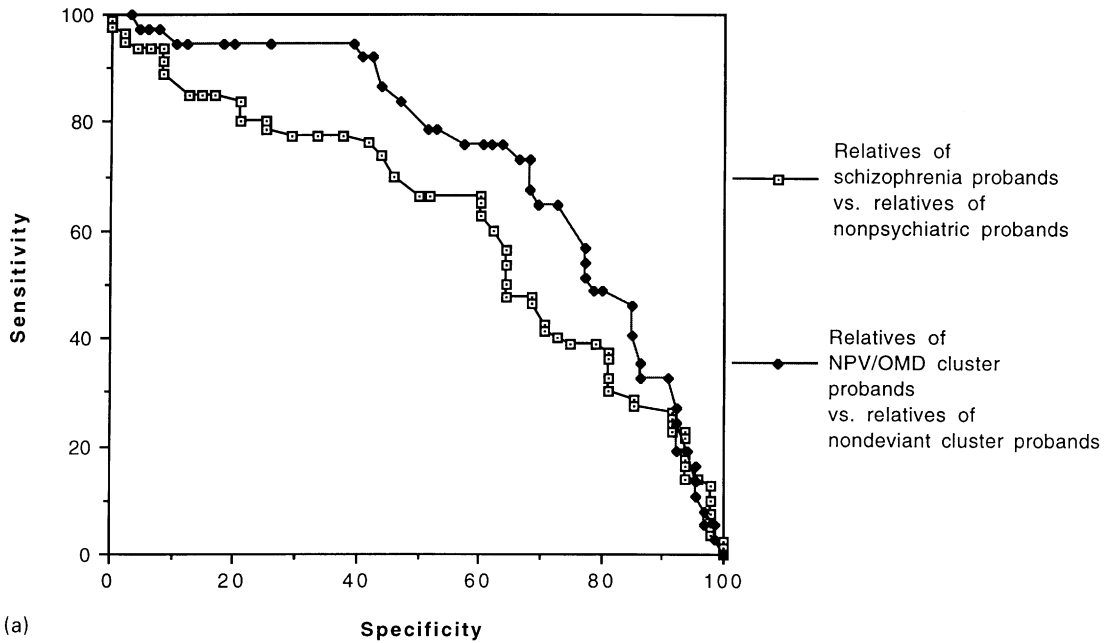
To examine whether using several biological variables to define clusters of psychotic probands offered an advantage over using a single biological measure, we carried out ROC analyses for relatives classified solely on the basis of the proband's ocular motor functioning. Because previously reported RMS error distributions of smooth-pursuit eye tracking reveal a score of 300 (2.48 in log-transformed units) to be a point of rarity (Clementz et al., 1992a; Iacono et al., 1992), relatives were divided based on whether the

family proband had RMS error scores above or below 300. The relatives of the "good" and "poor" eye tracking probands were then compared on their ocular motor functioning. Differentiation of groups of relatives classified by a single proband index (i.e. RMS error of smooth pursuit eye tracking) [AUC = 0.68 (SE = 0.055)] failed to significantly improve differentiation between relatives of DSM diagnosed schizophrenia probands and relatives of nonpsychiatric control probands [AUC = 0.60 (SE = 0.049)],  $t(325) = 0.96$ , *ns*.

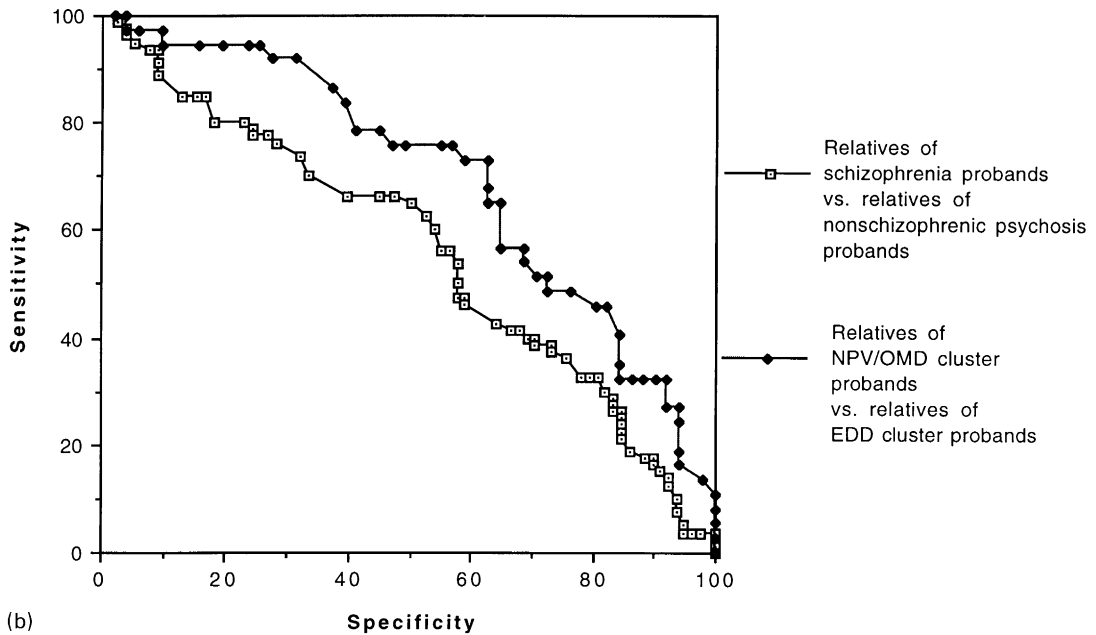
#### 4. Discussion

Results of this study have several implications for research regarding the nosology of psychosis. First, analyses of four biological variables revealed three clusters of psychotic and nonpsychiatric comparison probands that did not align with the clinical diagnoses of probands. Second, this study supports the notion that biological variables used to characterize psychotic patients can yield patient groups with greater supposed etiologic homogeneity than traditional diagnostic categories. We found greater differentiation in the ocular motor performance of relatives classified by proband biological cluster than by proband DSM-IV diagnosis. Lastly, the results lend credence to the approach of using laboratory tests in family studies to improve the diagnostic validity of mental disorders (Robins and Guze, 1970).

Our analyses suggest that a cluster of relatively homogenous individuals whose first-degree relatives exhibit ocular motor dysfunction consists of about a third of schizophrenia probands, a quarter of nonschizophrenic psychosis probands, and a low percentage of nonpsychiatric comparison subjects. Given the ocular motor dysfunction in their relatives, the psychotic patients in the NPV/OMD cluster may carry genetic vulnerability for psychosis marked by poor global ocular motor performance. The third of schizophrenia and nonschizophrenic psychosis probands categorized as biologically nondeviant, and the other third of psychosis probands classified as electrodermally abnormal, may represent other psychotic subtypes with etiologies not marked by ocular motor dysfunction. Resting state brain electrical abnormalities as assessed by EEG are present in



(a)



(b)

Fig. 3. Response operator characteristics (ROC) plots for relatives' RMS error as a function of proband cluster membership and diagnosis: (a) first-degree relatives of NPV/OMD cluster probands vs. first-degree relatives of nondeviant cluster probands, and first-degree relatives of schizophrenia patients vs. first-degree relatives nonpsychiatric comparison probands; (b) first-degree relatives of NPV/OMD cluster probands vs. first-degree relatives of EDD cluster probands, and first-degree relatives of schizophrenia patients vs. first-degree relatives of nonschizophrenic psychosis patients.

both clusters of psychotic patients. Nonspecificity of EEG abnormalities is consistent with previous reports indicating that both schizophrenia patients and nonschizophrenic psychosis patients exhibit augmented low frequency and diminished alpha band EEG power (Sponheim et al., 2000).

Although many researchers have attempted to study nosology of psychotic disorders through statistical methods, they have uniformly based the identification of groups of psychotic patients on analyses of symptoms, course, or history (Castle et al., 1994; Dollfus et al., 1996; Farmer et al., 1983; Goldstein et al., 1990; Manton et al., 1994). In some cases these studies assess validity of clinically described clusters by examining the rates of mental disorders in probands' first-degree relatives (Kendler et al., 1998). The present study extends this line of research by providing evidence that eventually biological variables may prove useful as a basis for classifying psychosis. We found psychotic probands classified through analyses of ocular motor function, electroencephalogram frequency characteristics, nailfold plexus visibility, and electrodermal deviance to have first-degree relatives with greater differences in ocular motor performance than relatives classified by proband DSM diagnosis. This study provides some of the first evidence supporting the Robins and Guze (1970) assertion that laboratory tests may permit a more refined classification of mental disorders characterized by improved homogeneity and greater etiologic validity. Whether the particular four measures we used in the present investigation would ultimately prove satisfactory for this purpose requires replication in another sample. Until then, we interpret our findings more as encouraging the use of the approach we have outlined here than as evidence that the measures we used should be adopted in the DSM classification of psychotic disorders.

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