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Sensitivity and specificity of select biological indices in characterizing psychotic patients and their relatives

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Abstract

Background: Although studies have detailed biological abnormalities in schizophrenia patients and their first-degree biological relatives, few studies have directly compared the utility of biological indices in these individuals. *Methods*: Measures of global smooth-pursuit ocular motor (OM) function, low frequency and alpha band electroencephalogram (EEG) power, and nonspecific fluctuations (NSF) in electrodermal activity and visibility of the plexus in the nailfold were collected from 136 schizophrenia patients and 67 of their first-degree biological relatives, 71 affective disorder psychotic patients and 68 of their first-degree biological relatives, and 169 nonpsychiatric comparison subjects. We conducted receiver operator characteristic (ROC) analyses to determine how well each index differentiated the patient groups and the groups of first-degree relatives. *Results*: Smooth-pursuit ocular motor function, low frequency and alpha band EEG power, and nailfold plexus visibility differentiated schizophrenia patients from nonpsychiatric comparison subjects. Nailfold plexus visibility was the only measure that significantly differentiated schizophrenia patients from both nonpsychiatric controls and affective patients. Smooth-pursuit ocular motor function and the number of electrodermal nonspecific fluctuations differentiated relatives of schizophrenia patients from nonpsychiatric comparison subjects. *Conclusion*: Increased nailfold plexus visibility may mark a process associated with abnormal brain development leading to schizophrenia. Smooth-pursuit dysfunction may mark genetic vulnerability that is relatively specific to schizophrenia.

Keywords: Schizophrenia; Psychosis; Classification; Genetic vulnerability; Sensitivity; Specificity

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1. Introduction

Researchers have used biological indices in attempts to precisely characterize abnormalities in schizophrenia patients (e.g., Malaspina et al., 1998; Murray et al., 1992). In addition to detailing aberrant physical phenomena, biological indices may reveal

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abnormalities that are nearer the level of gene products than behavioral indices, are readily quantifiable, and carry substantial statistical power (e.g., Almasy and Blangero, 2001; Calkins and Iacono, 2000; Cannon et al., 2001). Consequently, biological variables may hold more potential than behavioral indices in characterizing groups of schizophrenia patients in ways relevant to etiology. Although identifying a biological abnormality in schizophrenia is a first step to appraise the meaning and utility of the anomaly, one must examine how specific it is to schizophrenia, its severity with respect to the many other anomalies in the disorder, and whether people who share genes with affected individuals show a similar deviation. A large body of work examines biological abnormalities in schizophrenia patients (for a review, see Heinrichs, 2001); however, few studies have made direct comparisons of the utility of various biological indices in characterizing schizophrenia patients and their first-degree relatives (e.g., Faraone et al., 1995).

Statistically, utility is defined in terms of sensitivity and specificity. In psychopathology research, the sensitivity of an index usually reflects the likelihood that an individual in a particular diagnostic group (e.g., schizophrenia) will be identified as having the abnormality of interest. Sensitive indices are important to epidemiological and family studies where accurate prevalence and incidence estimates are a priority. The specificity of an index reflects the likelihood that an individual belonging to a comparison group (e.g., nonpsychiatric comparison subjects) is identified as not abnormal on the index. In linkage and biological marker studies where low false-positive rates are critical, researchers emphasize specificity. The sensitivity and specificity of an index for differentiating a diagnostic group from a comparison group are dependent on the index's cut point for classifying cases as normal or abnormal. If one resists selecting a cut point, receiver operator characteristic (ROC) analyses may be used to characterize sensitivity and specificity across the full range of index values. Consequently, ROC analyses provide a measure of the index utility independent of a selected cut point (Hanley and McNeil, 1982).

In order to draw comparisons of the utility of four biological variables in characterizing schizophrenia patients and their relatives, this report describes the results of receiver operator characteristic (ROC) analyses contrasting the sensitivity and specificity of biological indices in an epidemiological sample of psychotic patients and their first-degree relatives. In this report, we focus on four biological variables on which schizophrenia patients have exhibited abnormalities (see Iacono, 1985 for a review): global smooth-pursuit ocular motor (OM) function, low frequency and alpha band electroencephalogram (EEG) power, nonspecific fluctuations (NSF) in electrodermal activity, and the visibility of the plexus in the nailfold (PVS). These four variables represent different, and apparently independent, biological systems for characterizing abnormalities in schizophrenia subjects. Like other samples of schizophrenia patients, the current sample of schizophrenia patients (from the Markers and Predictors [MAP] of psychosis study of Iacono and Beiser (1989)) exhibits smooth-pursuit ocular motor dysfunction (Iacono et al., 1992), augmented low frequency and diminished alpha band EEG power (Sponheim et al., 1994), increased PVS (Clementz et al., 1992), and elevated NSF rates in electrodermal responders (Iacono et al., 1999).

Of the four biological measures in this investigation, smooth-pursuit ocular motor function and NSF rate have been found to be deviant in the biological relatives of MAP probands (Iacono et al., 1992, 1999). Many studies, in addition to the MAP study, provide evidence that smooth-pursuit ocular motor dysfunction may reflect genetic vulnerability for schizophrenia (see Iacono, 1998 for a recent review). Similarly, children of parents with schizophrenia produce a greater rate of NSFs than children of parents without a mental disorder, and those children who later develop schizophrenia exhibit elevated NSF rates during childhood (Hollister et al., 1994). However, high-risk individuals who later develop nonschizophrenic Axis-I disorders also show high rates of NSFs (Hollister et al., 1994). Some investigations have found that individuals purported to be at risk for schizophrenia and schizophrenia-spectrum disorders exhibit elevated PVS (cf. Poole et al., 1995; Gooding and Miller, 1998).

In the current investigation, we conducted a set of ROC analyses focused on answering the following questions: Which biological indices have the greatest utility in (1) characterizing schizophrenia patients and

(2) capturing physical abnormalities in the first-degree relatives of schizophrenia patients? Unlike our previous work (Sponheim et al., 2001), biological indices were used to characterize conventional Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic groups rather than abandon DSM-IV classification and employ cluster analysis.

2. Methods and materials

2.1. Subjects

2.1.1. Probands

Table 1 summarizes the characteristics of probands and their first-degree biological relatives who participated in the study. Patients completed a diagnostic assessment consisting of a semi-structured interview (the Present State Examination (PSE), 9th edition; Wing et al., 1974) and a review of clinical chart and hospital information. Diagnoses were originally assigned according to DSM-III (American Psychiatric Association, 1980) criteria according to consensus diagnosis. DSM-IV (American Psychiatric Association, 1994) diagnoses were made for this report after a review of all interview, symptom checklist, course, and functioning data used in making the original diagnoses (see Sponheim et al., 2001 for a full description of diagnostic procedures and subjects).

Table 1
Characteristics of subjects

DSM-IV diagnostic group	Probands				First-degree relatives			
	N	Age		Percent female	*N*	Age		Percent female
		Mean	SD			Mean	SD	
Schizophrenia patients	136	25.5	5.6	17	67	42.7	15.1	56
Affective disorder patients	71	25.8	7.2	38	68	39.4	14.7	51
Nonpsychiatric comparison	123	31.1	14.0	47	46	36.8	15.8	70

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Schizophrenia subjects consisted of 68 first-episode (mean age = 22.8) and 68 chronic (mean age = 28.3) patients. No relatives of chronic schizophrenia patients were included in the sample. All affective disorder patients were experiencing their first episode of disorder involving psychotic symptoms. For the purpose of this report, nonpsychiatric comparison probands and their first-degree relatives were collapsed into a single nonpsychiatric comparison sample.

First-episode schizophrenia patients and affective disorder psychotic patients (hereafter referred to as affective disorder patients) had to be experiencing their first episode of disorder and have hallucinations, delusions, or grossly disorganized behavior (i.e., had to be psychotic). The MAP study attempted to recruit all persons, between the ages of 16 and 54, who experienced their first episode of psychosis during a 2.5-year period in the Vancouver, British Columbia area. Chronic schizophrenia patients were recruited from an extended-care mental institution and affiliated board-and-care homes in the Vancouver area. Patients were considered clinically stable and had received no prescribed change in medication during the 2 weeks preceding assessment. Although almost all patients were on medications at intake, analyses involving the first-episode and chronic patients revealed no significant effects of medications or recent alcohol or drug abuse on the variables used in analyses (Clementz et al., 1992; Ficken, 1991; Iacono et al., 1999; Gooding et al., 1993; Sponheim et al., 1994). First-episode and chronic schizophrenia groups failed to differ in global smooth-pursuit ocular motor function, low frequency and alpha band EEG power, NSF, and PVS. Similarly, first-episode major depressive and bipolar groups failed to differ on the four dependent variables. 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 that they themselves or any first-degree relative had received mental health treatment in the past. The nonpsychiatric comparison subjects were free from 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 schizophrenia and affective disorder patients living within 80 km of Vancouver, who were between the ages of 16 and 65. First-degree relatives with ocular motor or visual disorders, organic cerebral or chronic physical illness, a history of substance dependence, or severe mental retardation were excluded. Sixty percent of first-episode patients contributed at least one family member to the study; 56% of the relatives who participated were parents. The average proband family was 2.6 individuals. Fifty-seven percent of all available first-degree relatives were recruited from families with participating first-degree relatives. First-degree relatives of nonpsychiatric comparison subjects were also recruited for participation. For the purpose of this report, nonpsychiatric comparison probands and their first-degree relatives were combined to form a single group of comparison subjects.

2.1.3. Apparatus and procedures

For the ocular motor assessment, participants tracked a moving dot with their eyes while their heads were 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. Horizontal electrooculogram (EOG), vertical EOG (blinks), and target signal were recorded on a Sensor Medics R-612 Dynograph polygraph and a Vetter Model A FM tape recorder. Both eye tracking and target signals were digitized and corrected for phase differences. The root mean square (RMS) difference between the signals was calculated for the 16 best 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 measure (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. Data were collected 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 frequency diminished alpha (LFA) factor with eigenvalues greater than 1. The LFA factor was selected for ROC analyses because psychotic patients exhibited significantly higher scores on this factor than nonpsychiatric comparison subjects. There were no group differences on the beta factor (see Sponheim et al., 2000).

Maricq's scale for plexus visualization was used to quantify the visibility of the capillary plexus at the base of the nailfolds (for a detailed overview of this assessment, see Clementz et al., 1992). 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 stereomicroscope. 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 for extensive plexus visibility; and half values (e.g., 2.5) were given for intermediate visibilities. The log base 10 of ratings summed across all fingers was used to compute the plexus visibility score (PVS). 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., 1992).

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). For the purpose of this report, we examined only electrodermal nonspecific fluctuations (NSFs) to a 12-tone series presented at 105 dB. The interval between tones was pseudorandomized, ranging from 25 to 70 s and averaging 50 s. NSFs were defined as skin conductance response-shaped increase in electrodermal activity of 0.05 μS or larger that occurred at least 10 s after a tone, but before the next tone. Because the NSF data distribution markedly deviated from normality, the variable was transformed adding one to the frequency tally and computing the log base 10 of the value.

2.1.4. ROC analyses

Receiver operator characteristics (ROC) were used to examine the sensitivity and specificity of biological indices in patients, first-degree relatives, and comparison subjects. Sensitivity in ROC analyses identifies subjects of a particular group member-

Table 2
Comparisons of patients, relatives, and nonpsychiatric comparison subjects on biological measures

Index	Group					Statistic	Probability
	Schizophrenia patients	Relatives of schizophrenia patients	Affective disorder patients	Relatives of affective disorder patients	Nonpsychiatric comparison sample		
Smooth-pursuit ocular motor function (RMS error)	2.21 (0.24)	2.22 (0.28)	2.18 (0.24)	2.14 (0.25)	2.09 (0.22)	$F_{4496} = 5.84^{a,b}$	$p < 0.0005$
Nailfold plexus visibility (PVS)	0.65 (0.43)	0.35 (0.33)	0.41 (0.40)	0.42 (0.41)	0.40 (0.38)	$F_{4490} = 9.69^{a,c}$	$p < 0.0005$
EEG abnormality (LFA factor score)	0.16 (1.04)	0.02 (1.01)	0.22 (0.97)	0.01 (0.96)	− 0.20 (1.02)	$F_{4441} = 2.94$	$p = 0.020$
Electrodermal nonspecific fluctuations (NSF)	0.48 (0.59)	0.47 (0.43)	0.28 (0.44)	0.37 (0.42)	0.32 (0.45)	$F_{4447} = 2.82$	$p = 0.029$

Numbers represent group means with standard deviations in parentheses. RMS error = root mean square error; PVS = plexus visibility score; EEG = electroencephalogram; LFA factor score = augmented low frequency diminished alpha factor score; NSF = number of nonspecific fluctuations. RMS error, PVS, and NSF values were subject to log base 10 transformations.

Multiple comparisons using Tukey B: [a]schizophrenia patients>nonpsychiatric comparison; [b]relatives of schizophrenia patients>nonpsychiatric comparison; [c]schizophrenia patients>affective disorder patients.

ship who have been accurately classified as members of that group because their scores are above the chosen cutoff point. Specificity is the proportion of subjects from another comparison group that are accurately classified as members 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 that 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 0.0 to 1.0. An index that is perfectly able to distinguish between two groups has an AUC value of 1.0, while an index in 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 individual from one group will have a higher score on the measure than a randomly chosen individual from the other group. ROC analyses were performed using SPSS (SPSS, 1999). SPSS provides maximum likely estimates of a binormal ROC curve and its associated parameters from a set of continuously distributed data. Because AUC is a summary index of classification computations from each point in a pair of distributions, results may differ from inferential statistical methods comparing means of distributions.

3. Results

Preliminary analyses were carried out to determine independence of ocular motor, EEG, nailfold plexus, and electrodermal measures. Pearson's product–moment correlations within the total sample of patients, relatives, and nonpsychiatric comparison subjects

Table 3
Area under the curve (AUC) values for comparisons involving patient groups on biological indices

Variable	Group comparison		
	SZ vs. NP	SZ vs. AFF	AFF vs. NP
RMS error	0.65 *	0.53	0.61 *
PVS	0.66 *	0.65 *	0.50
LFA factor score	0.60 *	0.48	0.62 *
NSF	0.55	0.58	0.47

SZ = schizophrenia patients; NP = nonpsychiatric comparison sample; AFF = affective disorder patients.

RMS error = root mean square error during smooth-pursuit ocular motor task; PVS = nailfold plexus visibility score; LFA factor score = augmented low frequency diminished alpha electroencephalogram factor score; NSF = number of nonspecific electrodermal fluctuations.

* AUC is significantly above 0.5.

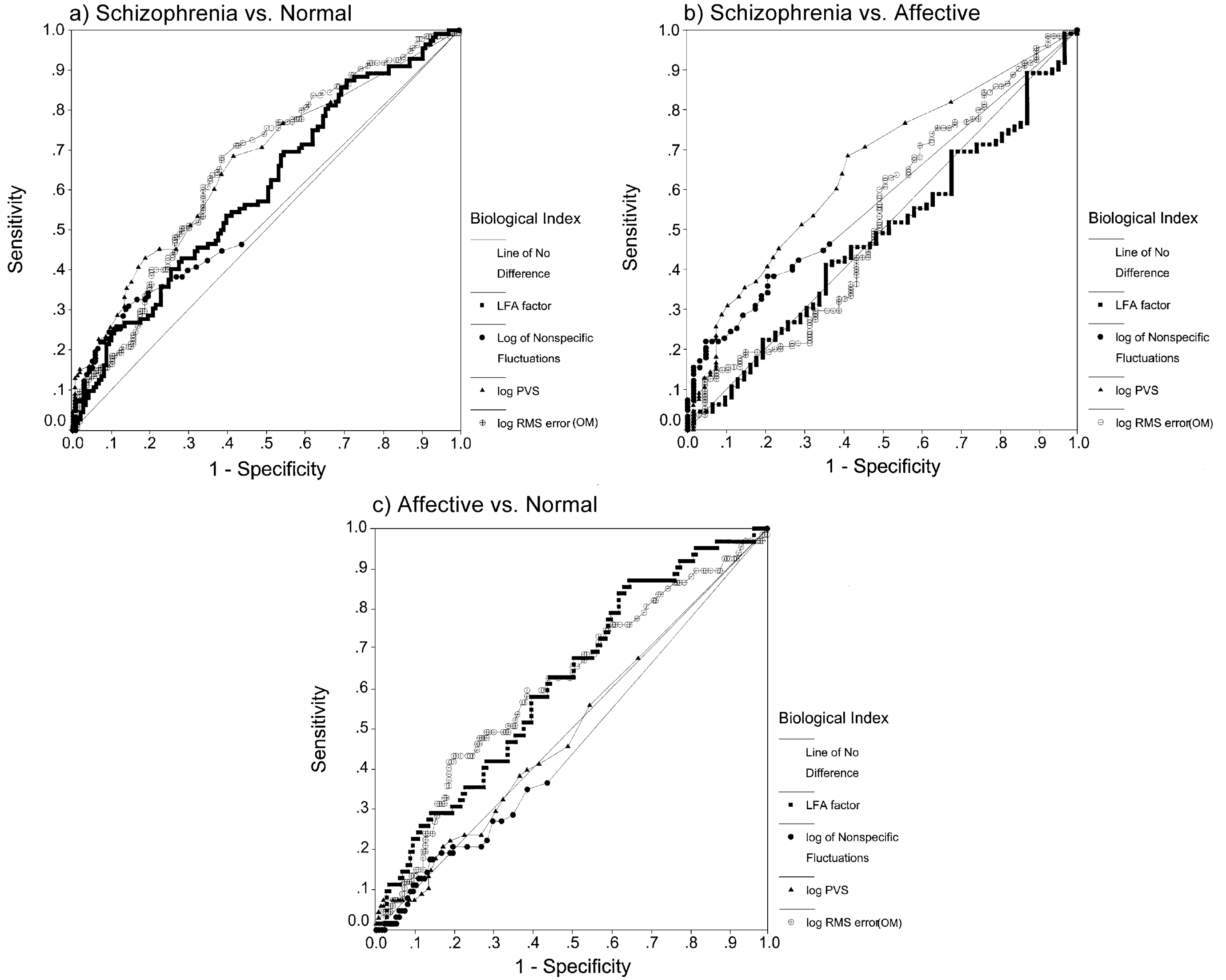

Fig. 1. Receiver operator characteristic (ROC) plots from comparisons of schizophrenia patients, affective disorder psychotic patients, and nonpsychiatric comparison subjects on four biological measures: RMS = root mean square, OM = ocular motor, PVS = plexus visibility score, and LFA factor score = augmented low frequency diminished alpha factor score.

ranged from − 0.06 to 0.09. The 24 correlations within specific groups ranged from − 0.15 to 0.14, with the exception of a correlation of − 0.23 between LFA factor score and PVS in relatives of probands. The low correlations suggested that the indices tapped distinct biological abnormalities in the subject sample.

We conducted group comparisons to determine whether subject groups exhibited predicted differences on ocular motor (RMS error), EEG (LFA factor), nailfold plexus visibility (PVS), and electrodermal (NSF) measures. Table 2 presents means, standard deviations, and results of statistical tests. For each biological variable, a one-way analysis of variance (ANOVA) was carried out with group (schizophrenia, relatives of schizophrenia, affective disorder patients, relatives of affective disorder patients, and nonpsychiatric comparison subjects) as the between-subjects factor and the biological index of interest as the dependent variable. Analyses revealed that the five subject groups differ on all four biological measures, indicating that group differences were present and the utility of measures for group differentiation could be tested through ROC analyses.

Table 3 presents area under the curve (AUC) values for ROC analyses involving patients. Fig. 1 depicts the ROC curves for the four biological variables used in the patient group comparisons. With the exception of NSF, the AUCs for schizophrenia–nonpsychiatric group comparisons were significantly above chance, indicating that smooth-pursuit ocular motor function, low frequency and alpha band abnormalities, and nailfold plexus visibility carried significant utility in differentiating schizophrenia patients from control subjects. Inspection of the ROC curves in Fig. 1a and b revealed that a subgroup of schizophrenia patients had higher NSF values than nonpsychiatric comparison subjects and affective patients, but many schizophrenia patients exhibited NSF of near zero. Fifty-eight of the sixty-six schizophrenia patients (88%) with zero NSF values were electrodermal nonresponders, meaning they exhibited no electrodermal responses for the first two 105-dB tones. It is not surprising that a person failing to respond to loud stimuli will also fail to produce NSFs in the absence of any stimulus. Studies have consistently identified about 40% of schizophrenia patients as electrodermal nonresponders (see Iacono et al., 1993 for a review). The only biological variable to differentiate schizophrenia and affective disorder patients was PVS (see Fig. 1b). RMS error and LFA factor score significantly differentiated affective disorder patients from nonpsychiatric comparison subjects, while PVS and NSF failed to differentiate these groups (see Fig. 1c). These results indicate that select biological variables are useful in differentiating both schizophrenia and affective patients from nonpsychiatric comparison subjects; however, only plexus visibility carries significant utility in differentiating schizophrenia patients from affective patients.

In order to examine the utility of the biological indices in differentiating relatives of schizophrenia patients from relatives of affective disorder patients and individuals without a family history of mental disorder, we carried out ROC analyses contrasting groups of first-degree relatives and the nonpsychiatric comparison group. Table 4 presents area under the curve (AUC) values for ROC analyses involving relatives. Fig. 2 depicts the ROC curves for the four biological variables used in the group comparisons for relatives. RMS error and NSF carried significant utility in differentiating relatives of schizophrenia patients from individuals who have no history of mental disorder in their first-degree relatives. None of the biological indices differentiated relatives of schizophrenia patients from relatives of affective patients, or relatives of affective disorder patients from individuals without a family history of mental disorder.

Table 4
Area under the curve (AUC) values for comparisons involving relatives of patient groups on biological indices

Variable	Group comparison		
	Rel SZ vs. NP	Rel SZ vs. Rel AFF	Rel AFF vs. NP
RMS error	0.63 *	0.57	0.56
PVS	0.48	0.47	0.50
LFA factor score	0.56	0.51	0.57
NSF	0.60 *	0.57	0.55

Rel SZ = first-degree relatives of schizophrenia patients; NP = nonpsychiatric comparison sample; Rel AFF = first-degree relatives of affective disorder patients.

RMS error = root mean square error during smooth-pursuit ocular motor task; PVS = nailfold plexus visibility score; LFA factor score = augmented low frequency diminished alpha electroencephalogram factor score; NSF = number of nonspecific electrodermal fluctuations.

* AUC is significantly above 0.5.

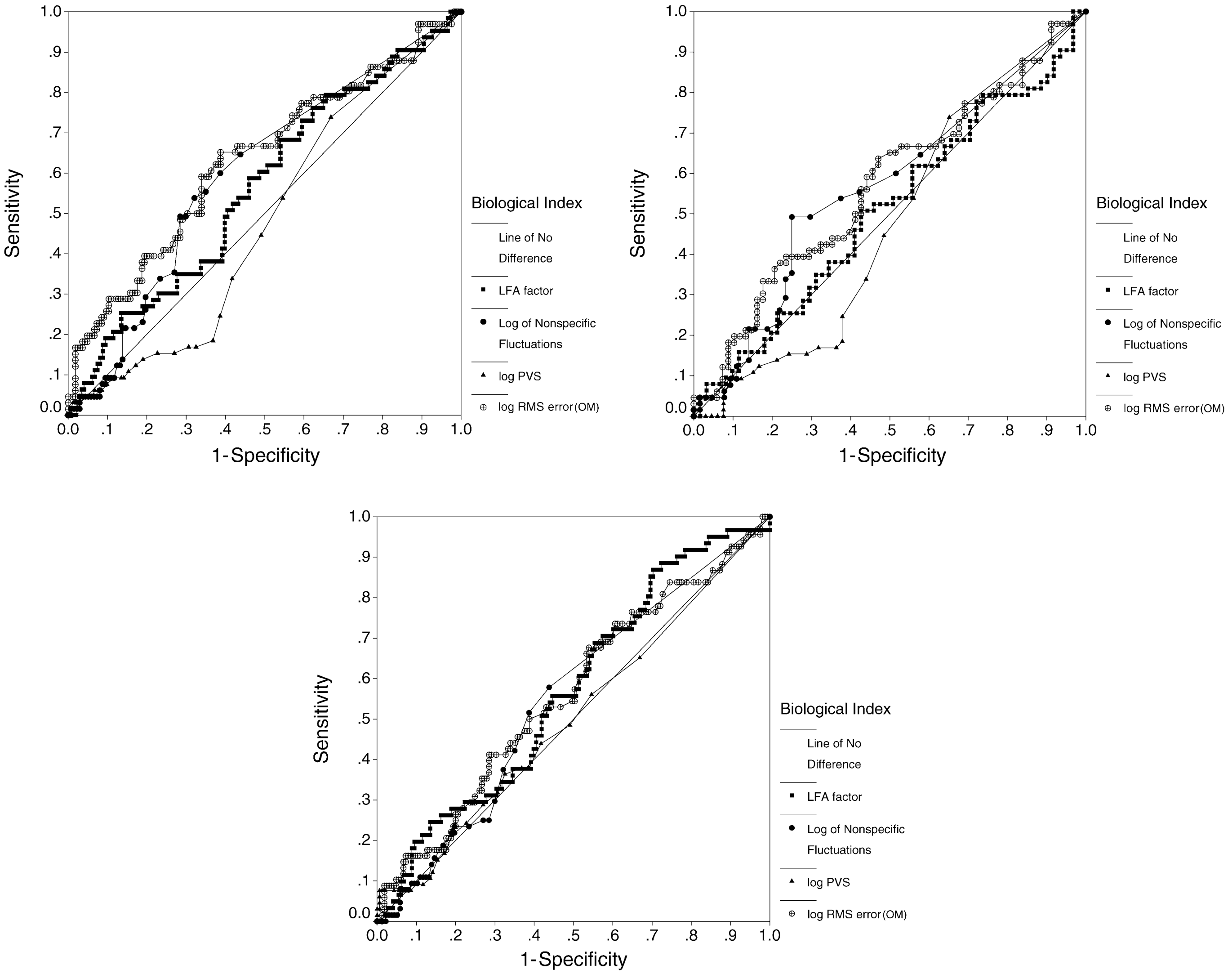

Fig. 2. Receiver operator characteristic (ROC) plots from comparisons of first-degree relatives of schizophrenia patients, first-degree relatives of affective disorder psychotic patients, and nonpsychiatric comparison subjects on four biological measures: RMS = root mean square, OM = ocular motor, PVS = plexus visibility score, and LFA factor score = augmented low frequency diminished alpha factor score.

4. Discussion

Results suggest that smooth-pursuit ocular motor function (RMS error), low frequency and alpha band EEG power (LFA factor score), and nailfold plexus visibility (PVS) differentiate schizophrenia patients from nonpsychiatric comparison subjects. Nailfold plexus visibility was the only measure that significantly differentiated schizophrenia patients from both nonpsychiatric controls and affective disorder psychotic patients (i.e., affective patients), with schizophrenia patients exhibiting greater plexus visibility than affective disorder psychotic patients. Smooth-pursuit ocular motor function and the number of electrodermal nonspecific fluctuations (NSF) differentiated relatives of schizophrenia patients from nonpsychiatric comparison subjects. Smooth-pursuit ocular motor function and nonspecific fluctuations failed to differentiate relatives of affective disorder psychotic patients from nonpsychiatric comparison subjects.

Of the biological measures used in this investigation, increased nailfold plexus visibility was most specific to schizophrenia patients. The mechanism by which plexus visibility is increased remains unknown but may have something to do with skin transparency. The brain and skin develop from the same ectodermal tissue (Hoving et al., 1990), and the plexus is most visible during childhood becoming less visible during adolescence and early adulthood (Maricq, 1965; Whitson and Jones, 1971). Consequently, plexus visibility may mark a developmental process, possibly associated with brain development. This argument is bolstered by findings of increased plexus visibility in other neurodevelopmental disorders such as mental retardation (Jones and Whitson, 1971; Maricq, 1964). Because schizophrenia patients with high plexus visibility exhibit more negative symptoms and cognitive impairment than low plexus visibility schizophrenia patients (Curtis et al., 1999; Poole et al., 1991), highly visible plexus may characterize a subgroup of patients unique to schizophrenia that has neurodevelopmental pathology. Although NSF failed to differentiate patient and comparison groups, inspection of ROC plots (see Fig. 1a and b) suggests that high NSF values are specific to schizophrenia. Because electrodermal nonresponding is common in schizophrenia subjects, inclusion of these individuals resulted in poor group differentiation at low NSF values. When only responders are included in the analyses, the NSF ROC plot for schizophrenia patients and nonpsychiatric controls had an AUC value of 0.76. AUC for the ROC plot of schizophrenia and affective patients was 0.73. Therefore, in psychotic patients who are electrodermal responders, a high number of NSF may be specifically associated with schizophrenia.

Schizophrenia patients exhibited smooth-pursuit ocular motor dysfunction and low frequency and alpha band abnormalities; however, affective disorder patients also exhibited these abnormalities. Smooth-pursuit ocular motor dysfunction is associated with prefrontal lobe impairment as measured by neuropsychological tests (Katsanis and Iacono, 1991; Park and Holzman, 1993; Snitz et al., 1999) and the failure to activate the frontal eye fields during ocular motion (O'Driscoll et al., 1999). Studies show that low-frequency band EEG power abnormalities are predominant over frontal brain regions (Knott et al., 2001; Sponheim and Kodalen, 1997; Wuebben and Winterer, 2001) and are associated with phenomena likely to be mediated by frontal brain regions (e.g., negative symptoms and ocular motor dysfunction: Sponheim et al., 2000). Therefore, it may be that ocular motor dysfunction and EEG abnormalities reflect frontal lobe brain anomalies that are shared with a subset of affective patients. Like schizophrenia patients, affective disorder patients have been shown to exhibit frontal lobe abnormalities (e.g., Ebert et al., 1993; Galynker et al., 1998). An alternative is that the smooth-pursuit ocular motion and EEG power findings are not specific to schizophrenia because there is a group of patients with shared etiology that spans clinically defined patient groups (see Sponheim et al., 2001). Because the affective patients in the present study were exhibiting psychotic symptoms, there may be increased probability of shared etiology with schizophrenia patients and decreased differentiation on biological indices.

Results suggest that of the measures in the present study, the most promising index for characterizing biological anomalies in first-degree relatives of schizophrenia patients is smooth-pursuit ocular motor dysfunction. Smooth-pursuit ocular motor dysfunction reflects the largest abnormality measured in this sample of relatives of schizophrenia patients and is on the order of the abnormality in schizophrenia patients themselves. Specific ocular motor abnormalities may reflect genetic vulnerability for the disorder; while indices reflecting developmental or general biological dysfunction (PVS and LFA factor score) may be an expression of the active disease process in patients. NSF is elevated in relatives of schizophrenia patients, but NSF rate for the relatives of schizophrenia patients was not different from the NSF rate of relatives of affective probands. Including only electrodermal-responding relatives failed to yield different findings. Although studies of the central nervous system determinants of electrodermal activity are few, frontal and temporal lobe involvement in electrodermal responding has been suggested through studies involving neurological patients with precisely described brain lesions (Tranel and Damasio, 1994), positron emission tomography (Hazlett et al., 1993), magnetic resonance imaging (Raine et al., 1991; Lencz et al., 1996), and neuropsychological tests (Katsanis and Iacono, 1992).

In conclusion, we tested the utility of four indices of biological abnormalities in schizophrenia. We found increased nailfold plexus visibility to be the only characteristic differentiating schizophrenia patients from both affective patients and nonpsychiatric comparison subjects. First-degree relatives of schizophrenia patients exhibited smooth-pursuit ocular motor dysfunction and an increased number of nonspecific electrodermal fluctuations. Relatives of affective disorder patients failed to exhibit biological abnormalities. Of the biological measures in this study, smooth-pursuit ocular motor dysfunction was the most pronounced abnormality in relatives of schizophrenia patients. Although these measures carry utility in separating the groups, they are not sufficiently powerful to carry clinical utility for identifying genetic vulnerability in an individual. Because the subject sample for this study was derived from an epidemiological study of psychosis, findings are likely to have greater generalizability than research undertaken at a single facility.

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