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Resolving the Latent Structure of Schizophrenia Endophenotypes Using Expectation-Maximization-Based Finite Mixture Modeling

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Prior research has focused on the latent structure of endophenotypic markers of schizophrenia liability, or schizotypy. The work supports the existence of 2 relatively distinct latent classes and derives largely from the taxometric analysis of psychometric values. The present study used finite mixture modeling as a technique for discerning latent structure and the laboratory-measured endophenotypes of sustained attention deficits and eye-tracking dysfunction as endophenotype indexes. In a large adult community sample ($N = 311$), finite mixture analysis of the sustained attention index d' and 2 eye-tracking indexes (gain and catch-up saccade rate) revealed evidence for 2 latent components. A putative schizotypy class accounted for 27% of the sample. A supplementary maximum covariance taxometric analysis yielded highly consistent results. Subjects in the schizotypy component displayed higher rates of schizotypal personality features and an increased rate of treated schizophrenia in their 1st-degree biological relatives compared with subjects in the other component. Implications of these results are examined in light of major theories of schizophrenia liability, and methodological advantages of finite mixture modeling for psychopathology research, with particular emphasis on genomic issues, are discussed.

Keywords: finite mixture modeling, schizotypy, schizophrenia, endophenotype, latent structure

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Endophenotypic (Gottesman & Gould, 2003) indicators of the liability for schizophrenia have been the focus of extensive laboratory research for several decades. This research has sought to illuminate those neurocognitive or psychological processes that can be measured objectively using either laboratory or psychometric techniques with demonstrated validity. The emerging corpus of data supports several putative endophenotypes as particularly promising for inclusion in genomic research and the rational expansion of the phenotype for schizophrenia (Holzman, 1994; Lenzenweger, 1998; Matthysse & Parnas, 1992). Two endophenotypic indicators that are particularly well established are deficits in sustained attention (Cornblatt & Keilp, 1994; Cornblatt & Malhotra, 2001) and impairments in smooth pursuit eye movements (Levy, Holzman, Matthysse, & Mendell, 1993; O'Driscoll et al., 1998, 1999; Sponheim, Iacono, Thuras, Nugent, & Beiser, 2003). Subtle deficits in each of these neurocognitive processes are thought to tap into the latent liability for schizophrenia, or what Meehl (1962, 1990) termed *schizotypy*. Prior research has established the relations between deficits in sustained attention (Cornblatt & Keilp, 1994) as well as eye-tracking dysfunction (Levy et al., 1993) and criteria of validity for schizophrenia liability. However, the underlying nature of these two prominent endophenotypes has not been explored despite strong assumptions regarding the latent structure of schizophrenia liability in the major theoretical models (Gottesman, 1991; Gottesman & Shields, 1972; Holzman et al., 1988; Meehl, 1962, 1990). We, therefore, sought to approach the substantive question of latent structure for these endophenotypes as a mixture problem (McLachlan & Peel, 2000; Titterington, Smith, & Makov, 1985).

Both sustained attention and smooth pursuit eye movements are measured using objective laboratory technologies, and there are

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considerable methodological benefits in using such laboratory-based measures to tap endophenotypes (Gottesman & Gould, 2003). Many of these benefits accrue from the incorporation of the methods of the experimental psychology laboratory into studies designed to uncover disturbances in basic psychological processes in psychopathology (Lenzenweger & Hooley, 2003; Maher, 1966, 2003), and the scientific yield from the use of such methods in schizophrenia research has been considerable (Lenzenweger & Dworkin, 1998; Lenzenweger & Hooley, 2003). There are two major advantages to the use of endophenotypes that are assessed with objective laboratory methods. First, there is the increase in measurement precision that comes with quantitative laboratory measures that exceeds what is obtainable with rating scales. The net effect of such precision is to reduce noise in the dependent variables and thereby increase measured effect sizes. Second, endophenotypes assessed with objective laboratory measures are not subject to various measurement artifacts such as rater bias, halo effects, and response biases (e.g., social desirability effects, dissimulation tendencies). The adverse and potentially misleading impact of such artifacts (e.g., rater effects) in psychological data that are, for example, subjected to latent structure analyses has been demonstrated by Beauchaine and Waters (2003).

Given the benefits of objective measurement and assuming deficits in sustained attention and smooth pursuit eye movements are valid endophenotypes for schizotypy, then two questions arise. The first concerns the nature of the latent structure of such continuous performance metrics, and the other, necessarily, concerns methods for the exploration of that latent structure. Several prominent models of the genetic diathesis for schizophrenia make strong assumptions regarding the nature of the structure of schizophrenia liability. Meehl (1962, 1990) argued for a "mixed model" in which the presence of a single major locus for schizophrenia operates a background of polygenic effects. For Meehl, all persons can be classified into either a schizotypy (i.e., potentially schizophrenia prone) taxon (natural subgroup) or a nonschizotypy complement. Holzman and colleagues posited the presence of a *latent trait* that was indicative of either schizophrenia or eye-tracking dysfunction in an autosomal dominant gene model that assumed pleiotropy (Holzman et al., 1988). The Holzman–Matthysse model, as well, suggests that one is either at risk for schizophrenia by virtue of possessing a schizophrenia-specific "latent trait" or not at risk (i.e., the latent trait is absent). Finally, Gottesman (1991; Gottesman & Shields, 1972) proposed a multifactorial polygenic threshold model that contained a pronounced *threshold* effect in an underlying continuum of schizophrenia liability. Thus, for Gottesman (1991), despite a quantitative conceptualization of latent liability for schizophrenia, the threshold (much like a step function or inflection on a steep ogive) demarcates those at risk for schizotypic pathology (including schizophrenia) versus those not at risk.

What is common to all of these models is the proposition that the latent liability for schizophrenia is most likely distributed in a discontinuous (or quasi-discontinuous) manner, such that one either is at risk for the disease or is not. Given these substantive assumptions and the endophenotype framework, it then follows that the indicator space defined by an array of data gleaned from laboratory measures of schizophrenia liability should consist of at least two classes of persons: those carrying the liability and those not carrying it. Indeed, contemporary genetic investigations suggest the presence or absence of specific risk-conferring alleles for schizophrenia (e.g., catechol-*O*-methyltransferase [COMT] val/val genotype; Egan et al., 2001; Law et al., 2006; see also Harrison & Owen, 2003).

The second question concerns the manner for investigating the latent structure of an array of continuous (quantitative) data that emerges from laboratory measures that tap putative endophenotypes. The problem concerns the statistical resolution of latent structure such that the presence of meaningful classes, natural subgroups, or taxa can be detected. Prior research conducted using taxometric methods (Waller & Meehl, 1998) applied to values obtained from psychometric measures of schizotypy has supported the existence of a latent class of individuals demarcated from other individuals (i.e., two latent classes; Korfine & Lenzenweger, 1995; Lenzenweger, 1999; Lenzenweger & Korfine, 1992). Such findings are consistent with the theoretical conjectures reviewed above. However, taxometric methods remain in the early stages of statistical development; moreover, they only enable an investigator to assess whether a dimension versus two classes are present (i.e., more than two classes cannot be resolved). A viable alternative methodological approach to the resolution of latent structure that is statistically well principled and in advanced development can be found in *finite mixture modeling* (McLachlan & Peel, 2000; Titterington et al., 1985). Finite mixture modeling has grown in application in recent years owing to the fact that statistical basis for the approach was made more tractable with the introduction of the expectation-maximization (EM) algorithm (Dempster, Laird, & Rubin, 1977). Despite its utility and potential (cf. Gibbons et al., 1984), mixture modeling has seen only modest application in psychopathology research, and frequently such admixture analyses have focused on just one index of interest (i.e., univariate mixture analysis), for example, psychosis proneness (Lenzenweger & Moldin, 1990), ventricular size (Daniel, Goldberg, Gibbons, & Weinberger, 1991), age at admission (Welham, McLachlan, Davies, & McGrath, 2000), and eye movements (Ross et al., 2002). Mixture modeling has been used to parse the dynamic processes involved in smooth pursuit eye movements in schizophrenia using reaction times (Belin & Rubin, 1995; Matthysse, Levy, Wu, Rubin, & Holzman, 1999; Rubin & Wu, 1997). Mixture model-based methods are also emerging that allow one to estimate latent growth trajectory classes in developmental/longitudinal data and to explore associations with both predictor and outcome variables (e.g., Nagin, 1999; see also Bauer & Curran, 2003). However, multivariate finite mixture modeling, in which three or more variables of interest are modeled simultaneously, has gone essentially unused in psychopathology research. There have been two recent applications of multivariate normal mixture analysis: one focused on psychiatric ratings of schizotypal personality disorder (Fossati et al., 2005) and the other used a mixture modeling approach to model heterogeneity in laboratory data (Lenzenweger, Jensen, & Rubin, 2003).

The manner in which finite mixture modeling is similar to or different from other latent structure analysis techniques is likely to be of interest to psychopathology researchers. Given the emerging popularity of taxometric (Lenzenweger, 2004; Meehl, 1995) analytic techniques in psychological science research as a technique for examining latent structure, we note here, briefly, some similarities and differences between taxometric and finite mixture modeling techniques. To begin, for the two-class situation, taxometric methods (like latent profile analysis) and finite mixture

modeling share a comparable analytic model (Bauer & Curran, 2004), but they are methods designed to answer different substantive questions. Taxometric methods (Meehl, 1995; Meehl & Yonce, 1996; Waller & Meehl, 1998) are typically used to determine whether or not a single quantitative dimension or a two-class qualitative latent structure best characterizes the structure underlying observed quantitative data. In contrast, finite mixture modeling is used to determine how many latent normal components best characterize observed quantitative data (McLachlan & Peel, 2000; Titterington et al., 1985). Important differences between the two families of methods are worth noting. Taxometric methods do not yield a data partition if there are no discrete groups embedded in a multivariate distribution, whereas finite mixture modeling yields partitions in the underlying data, and fit measures as well as comparison statistics (e.g., resampling-based likelihood ratio tests [LRTs]) are used to discern the number of latent components. Finite mixture modeling directly reproduces the covariance structure of the data, whereas taxometric methods do not. Furthermore, finite mixture modeling does not assume local independence of indicators within groups but does explicitly assume normality within groups, an assumption that is used in the estimation of model parameters. Taxometric methods do assume local independence of indicators within groups, and the methods do not explicitly assume multivariate normality, even though the latter typically receives little attention in applications. Finally, as presently developed, taxometric methods are really only capable of detecting two latent classes if they exist, whereas finite mixture modeling can detect any number of latent components (i.e., one, two, three, or more). Beauchaine (2003) provided additional useful discussion of the differences between these two families of statistical methods.

One might also ponder a comparison of a popular cluster analysis method, K-means clustering, and finite mixture modeling.[1] The use of K-means clustering is essentially equivalent to fitting mixtures of normal distributions using method-of-moments arguments with a common spherical covariance matrix. That is, it produces spherical clusters of common size. But often in practice the clusters are elliptical in shape and may have different scales or orientations. The latter clusters are allowed under a normal mixture model with component distributions having unrestricted covariance matrices. With the normal mixture model, the clusters are invariant under change in location, scale, and rotation, of which the first two (i.e., invariance under location and scale) are highly desirable. Hierarchical agglomerative methods are considerably dependent on the metric adopted. A further advantage of finite mixture modeling over K-means and hierarchical clustering methods is that it provides a statistical framework (i.e., a likelihood) to evaluate how many clusters there are in the data. Although regularity conditions do not hold for the LRT statistic for tests on the number of components to have its usual null distribution of chi-squares in finite normal mixture models, it can be bootstrapped to provide *p* values. Also, there is much empirical evidence to suggest that the Bayesian information criterion (BIC) provides a good guide as to the number of components in a normal mixture modeling approach (McLachlan & Peel, 2000). In addition to the bootstrapped LRT and BIC approach, there is also the method of posterior predictive checks and *p* values, which does not rely on asymptotic approximations, for assessing model fit (Gelman, Carlin, Stern, & Rubin, 2003; Gelman, Meng, & Stern, 1996; Rubin, 1984). This approach, however, is computationally intensive but may be more appropriate in certain circumstances.

Our study, therefore, had two primary goals. First, it sought to advance our knowledge of the latent structure of laboratory-assessed endophenotypic measures of schizophrenia liability that were not psychometric in nature. Second, it approached the current theoretical question as a mixture problem and applied finite mixture modeling to investigate it. The present study, therefore, sought to examine the underlying structure of sustained attention and smooth pursuit eye movement performance measures in a large, relatively unselected adult community sample, with no prior history of psychosis, using finite mixture modeling applied to multiple measures simultaneously. We emphasize that the use of quantitative measures of attention and eye-tracking performance, which have ratio scaling characteristics, allows one to use data that circumvent the difficulties associated with "rating" (as opposed to "count") data as well as other potential artifacts (e.g., item difficulty levels in psychometric measures; cf. Coleman et al., 2002; Cook et al., 2002). In short, we address substantive issues related to the latent structure of schizophrenia liability and provide an illustration of the application of a statistical approach that should prove useful in psychopathology research.

Method

Subjects

This study was conducted at Harvard University (Cambridge, MA). A total of 311 individuals were enrolled from multiple communities in eastern Massachusetts. Subjects were recruited with posted flyers in public places and by advertisements in community newspapers. The content of the flyers neutrally described a generic psychological study that involved the completion of questionnaires as well as various other psychological tasks. The flyer content in no way addressed schizophrenia, schizotypy, or behavioral features associated with psychopathology. The goal of the recruitment flyers was to solicit a broad range of individuals from the general adult community population interested in completing the study. Potential subjects were screened via phone by trained research assistants for information regarding their age (limited to 18–45 years to avoid age-related artifacts in tracking performance), current illicit drug use (e.g., barbiturates, crack, heroin, and others) and alcohol use/abuse history, history of psychotic illness, antipsychotic medication use (e.g., haloperidol, chlorpromazine, fluphenazine, risperidone, clozapine), antimania medication use (e.g., lithium), and head injury associated with loss of consciousness. Research assistants inquired about all of these exclusionary criteria in a systematic fashion using a structured schedule developed for this study. Antipsychotic medication use, antimania (lithium) medication use, and use of barbiturates were used as exclusion criteria as they suggested the presence of a possible psychotic illness or represented substances known to erode eye-tracking performance (potentially yielding false-positive deviance on the eye-tracking measures). Any subject with a definite or equivocal history for one of the exclusion signs was not considered further. Eligible study subjects entered the protocol and were screened again for any evidence of prior psychosis. Potential study subjects were not excluded from possible participation on the basis of family history of psychosis, as this would serve to artifactually diminish unexpressed schizophrenia liability in the sample.

Features of the resulting study sample largely resemble those of the general population included in the Boston–Lawrence metropolitan statis-

[1] We note that taxometric analysis and K-means clustering have been compared expertly by Beauchaine and Beauchaine (2002).

tical area as described in the 1990 United States census data, which was used to guide sample recruitment consistent with the time this study was conducted (i.e., 1999 through early 2001). One exception to this is that women were somewhat overrepresented, possibly because of their tendency to volunteer for research at a higher rate than men (e.g., Beer, 1986; Miller, Kobayashi, Caldwell, Thurston, & Collett, 2002; Senn & Desmarais, 2001).

Subjects were instructed to avoid any alcohol use for 24 hr before their testing session because alcohol can degrade smooth pursuit eye movement (Levy, Lipton, & Holzman, 1981) and sustained attention (Dougherty et al., 1999) performance. Subjects had the study procedures explained to them, and then they read and signed an informed-consent form. They were then administered a breathalyzer test with the Alco-Sensor IV (Intoximeters, St. Louis, MO) instrument to ensure that there was no prior alcohol ingestion. All of the subjects were screened for any prior history of psychosis (schizophrenia, schizophreniform illness, bipolar disorder, unipolar depression with psychosis) by using an established computerized screening instrument (see below). Subjects were individually tested on the eye movement and sustained attention tasks, and afterward they completed a psychometric measure of schizotypal personality disorder features. Subjects' eye movement performance, sustained attention performance, and schizotypal feature information remained unknown throughout the data collection and data reduction. Subjects received an honorarium of $50.

Clinical Measures

Schizotypal Personality Questionnaire. The Schizotypal Personality Questionnaire (SPQ; Raine, 1991) is a 74-item true/false self-report questionnaire that assesses cognitive, perceptual, affective, and interpersonal features consistent with the symptoms for *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed., rev.; *DSM–III–R;* American Psychiatric Association, 1987) schizotypal personality disorder. It generates nine separate dimensional scores, one for each of the nine *DSM–III–R* schizotypal personality disorder criteria. These separate dimensions are combined to create three factors that correspond conceptually to the well-known reality distortion, disorganization, and negative symptom components in schizophrenia (Lenzenweger & Dworkin, 1996).[2] Internal consistency for total SPQ scores is .91, subscale alpha values have a mean of .74, and test–retest reliability is high ($r = .82$; Raine, 1991). Deviance on the SPQ has been shown to identify schizotypal personality disorder (Kremen, Faraone, Toomey, Seidman, & Tsuang, 1998).

Diagnostic Interview Schedule Screening Interview (DISSI). The DISSI (Robins, Helzer, Croughan, & Ratcliffe, 1981) is a computerized, self-administered assessment Axis I disorder screener. The DISSI possesses good to excellent sensitivity and specificity rates for the detection of schizophrenia/schizophreniform illness, mania, and depression/dysthymia (Bucholz et al., 1991). No subject was psychotic at the time of testing, and no subject was classified as having a definite psychotic disorder.

Sustained Attention Measurement and Analysis

Sustained attention was measured using the Continuous Performance Test—Identical Pairs Version (CPT–IP) developed by Cornblatt and colleagues (Cornblatt, Lenzenweger, & Erlenmeyer-Kimling, 1989; Cornblatt, Risch, Faris, Friedman, & Erlenmeyer-Kimling, 1988). The CPT–IP is a high momentary processing load, low a priori signal probability attention task that taps effortful or controlled information processing (see Parasuraman, 1984; Parasuraman, Warm, & See, 1988) and is described elsewhere in great technical detail (Cornblatt et al., 1988, 1989; Lenzenweger, 2001; Lenzenweger, Cornblatt, & Putnick, 1991). Prior research has not found a ceiling effect for the CPT–IP when used with relatively high-functioning normal control subjects (Cornblatt et al., 1988, 1989; Lenzenweger, 2001; Lenzenweger et al., 1991). This study used a 300-trial CPT–IP administration presenting only four-digit numeric stimuli (Bergida & Lenzenweger, 2006).

CPT–IP performance has been typically analyzed by using the methodology of signal detection theory (Green & Swets, 1966; Macmillan & Creelman, 1991). The d' index, which measures discriminability, and the $ln\beta$ index, which measures response bias or decision criterion, were computed with the hit rate and false-alarm (commission error) rate data. These indexes provide a measure of overall performance accuracy on the CPT–IP, and this focus on an overall level of performance on the CPT–IP (i.e., overall signal-noise discrimination) is consistent with the existing schizophrenia research literature on sustained attention (Nuechterlein et al., 1998) as well as with Parasuraman's (1984, p. 63) distinction between level of performance and vigilance decrement on a sustained attention task. Thus, each subject received two CPT performance scores, d' and $ln\beta$, and only the d' score was used in this mixture analysis as it is argued to represent the endophenotype for schizophrenia liability (e.g., Cornblatt & Keilp, 1994).

Eye Movement Recording and Analysis

Oculomotor data were collected in a darkened room with subjects seated 57 cm from a 17-in. computer monitor (Model PS775 Professional Series, Viewsonic, Walnut, CA) running at 135 Hz. A 250-Hz infrared video-based pupil tracker (Eyelink, SR Research, Mississauga, Ontario, Canada) was used to record the movements of the subject's dominant eye. This system has a spatial resolution of about 0.25°. Before testing, subjects completed a three-point calibration across 24° of visual angle. The system automatically computes a drift correction prior to the start of each trial.

The pursuit stimulus consisted of a 0.5° × 0.5° red square presented against a dark background. Subjects were asked to keep their gaze on the target as it moved horizontally at 0.4 Hz across 20° of visual angle with a sinusoidal velocity profile. At the center of the target an "X" changed to an "O" and back at random intervals, and subjects were asked to press a response button whenever they detected a change. Such manipulations are known to increase attention and improve pursuit equally in patients and controls (Sweeney, Haas, Li, & Weiden, 1994). Subjects first performed a 10-s practice trial, then three 30-s trials of pursuit during which they were required to monitor target changes during pursuit in two of the three trials (Trial 3 was a "no-monitoring" trial). As the gain indexes for Trials 1 and 2 were highly correlated with the gain index for Trial 3 (Trial 1 × Trial 3 $r = .70$, Trial 2 × Trial 3 $r = .71$, both $ps < .0001$), the mean of these three trials was computed for subsequent analyses. Also, both the catch-up saccade rate indexes for Trials 1 and 2 were correlated with the catch-up saccade rate for Trial 3 (Trial 1 × Trial 3 $r = .84$, Trial 2 × Trial 3 $r = .98$, both $ps < .0001$), and therefore the mean of these three trials was computed for subsequent analyses.

Eye movements were parsed quantitatively using a semiautomated custom analysis software package (Eyelink, SR Research, Mississauga, Ontario, Canada). Pursuit gain (eye velocity/target velocity) was the measure of the smooth component of the pursuit task. The calculation was based on the portion of the pursuit in a 651-ms window centered on the peak velocity in each half cycle (O'Driscoll et al., 1998). Saccades and blinks were excluded from the eye trace for gain analysis. The first half cycle of each trial was also excluded from the analyses along with the portion of pursuit 200 ms before and after each blink.

Saccades were identified in the same analysis window using criteria of peak velocity equal to or greater than 22°/s above the ongoing pursuit eye

[2] For this study, the Reality Distortion factor contained odd beliefs/magical thinking, unusual perceptual experiences, suspiciousness, and ideas of reference; the Disorganization factor contained odd behavior and odd speech; and the Negative factor contained constricted affect, social anxiety, and no close friends. The composition of the Disorganization factor here differs slightly from that described by Raine (1991) as it does not include suspiciousness, which loaded on both Positive Feature factors in Raine's study but was assigned to the Reality Distortion factor for this study.

speed and average acceleration greater than 3,500°/s^2. The saccade variable of interest was the rate of catch-up saccades defined according to the criteria of Friedman, Jesberger, and Meltzer (1992). Number of catch-up saccades was divided by time in seconds minus the duration of any blinks or artifact.

Intellectual Functioning and Family History of Psychopathology

General intellectual level was estimated using years of education and the Digit Symbol Substitution Test (DSST) from the Wechsler Adult Intelligence Scale—Revised (Wechsler, 1981). Years of education is highly correlated ($r = .62$) with estimated full scale IQ (Matarazzo & Herman, 1984). DSST scores correlate .57 with IQ in the general population (Wechsler, 1981).

Finally, for exploratory purposes, we used the family history method (Andreasen, Endicott, Spitzer, & Winokur, 1977) to collect information regarding presence of treated schizophrenia as well as other forms of treated psychopathology (i.e., depression, bipolar disorder, anxiety disorders, alcohol/drug abuse, obsessive–compulsive disorder, eating disorders, autism, attention deficit hyperactivity disorder) in the subjects' first-degree biological family members. Each subject completed a listing of each of his or her first-degree biological relatives. The subject then provided mental health information for each of these relatives to the best of his or her knowledge. Only cases of psychopathology in which treatment had been received were noted for the purposes of this exploratory analysis. Use of the treatment criterion ensured a higher threshold for evidence of familial psychopathology (see Andreasen et al., 1977; Lenzenweger & Loranger, 1989).

Data Reduction and Statistical Analysis

Six cases were dropped from the original sample of 311 because of failure to complete the CPT–IP properly. An additional 11 subjects were dropped from the sample because of technical difficulties during the eye-tracking measurements. The sample available for the mixture modeling was 294.

The three variables derived from the attention and eye-tracking laboratory measures for the finite mixture analysis were d', average gain, and average catch-up saccade rate. The d' and gain variables were scored so higher scores indicated worse performance. Each of these variables was then standardized (z scores) separately by sex, and the distribution of the z scores was examined for skewness. The d' and catch-up saccade rate variables were relatively normally distributed. The gain variable revealed some positive skew. Given that skewness can affect the results of mixture model analyses (extreme skewness can lead to overestimation of components; Gutierrez, Carroll, Wang, Lee, & Taylor, 1995; MacLean, Morton, Elston, & Yee, 1976; McLachlan & Peel, 2000), we sought to reduce the skewness for the gain variable by using a conventional transformation (natural log) as in prior studies (e.g., Matthysse et al., 1999; Rubin & Wu, 1997). Doing so helped to reduce skew in gain, thus making it more comparable with that observed for d' and catch-up saccade rate. We did not use an exceptionally severe transformation for the gain variable (e.g., an optimal Box-Cox transformation to reduce skew). Thus, we struck a balance with respect to how we handled skewness for the gain measure.

Finite Mixture Modeling Analysis

Finite mixture analysis (Dempster et al., 1977; McLachlan & Peel, 2000; Titterington et al., 1985) was conducted using the UNIX-based program EMMIX (Version 1.3; Peel & McLachlan, 1999), which utilizes the EM algorithm (Dempster, Laird, & Rubin, 1977). The statistical formalism underlying finite mixture modeling is given briefly in the online Technical Appendix. The goal of finite mixture analysis is to resolve the most likely number of normal components underlying a multivariate array of continuous data. We evaluated the number of components underlying d', gain, and catch-up saccade rate and tested one, two, and three component models. Evaluation of model fit was done by comparisons of the bootstrapped likelihood ratio associated with each model (McLachlan & Peel, 2000). We also used the BIC (Schwarz, 1978) to assess fit.[3] The BIC takes the complexity of a model into account and penalizes models with a larger number of parameters. Smaller values of BIC indicate a better model fit. We used the bootstrapped LRTs as well as the BIC to assess fit because these two approaches have been shown to perform well across many simulated and empirical investigations (McLachlan & Peel, 2000). Finally, we note that a mixture of normal distributions does not necessarily have to reveal the latent mixture via bimodality or multimodality in the observed distribution (Beauchaine, 2003; Murphy, 1964), because even if an observed distribution is unimodal, it can harbor an underlying mixture of normals and therefore not reveal an obvious clue to the latent organization. Thus, use of finite mixture modeling provides important leverage on discerning the latent structure of data, especially when the observed data provide only subtle clues as to latent structure.

After resolving the number of components underlying the three variables with finite mixture modeling, we obtained posterior probabilities for component membership for each subject. These probabilities were then used to assign individuals on a case-by-case basis to the component in which they most likely belonged. The component membership was then used as a grouping variable in subsequent comparisons using other criteria of validity, such as schizotypal personality features (compared with t tests) and family history of treated schizophrenia and other psychopathology (proportions compared with continuity corrected chi-square test and Fisher's exact test). We used Cohen's d to determine effect sizes. We evaluated the normality of distributions by using the one-sample Kolmogorov–Smirnov Z test.

Supplementary Maximum Covariance Taxometric Analysis

Although the primary focus of the present study was on the application of finite mixture modeling for the illumination of the latent structure of these laboratory task performance data, we also conducted a supplementary taxometric analysis, using maximum covariance analysis (MAXCOV), of these same data.[4] This supplementary analysis was conducted to see whether a taxometric analysis also yielded evidence of a two-class latent structure for these data. The technique of MAXCOV is well known, and technical details can be found in Waller and Meehl (1998; see also Meehl, 1995; Meehl & Yonce, 1996). We used the R-code of Grove (2004) to conduct the MAXCOV analyses. The covariance curves generated by the MAXCOV analysis were examined for evidence of taxonicity, or the existence of a latent taxon (i.e., class).

Results

The descriptive demographic data for the sample ($N = 294$) are contained in Table 1. The sample was made up largely of Caucasian subjects (61% female) with an average age of about 30 years. The subjects had completed, on average, 16 years of education, and the mean IQ equivalent for the sample was 110.

[3] As noted previously, an alternative, albeit more computationally intensive, approach to assessing model fit is the method of posterior predictive checks and p values developed by Rubin and colleagues (for technical discussions and illustrations, see Gelman et al., 1996; Gelman et al., 2003; Rubin, 1984). This approach does not rely on asymptotic approximations as other approaches do.

[4] The supplementary taxometric analysis was requested by a reviewer.

Table 1
Demographic Features of Sample (N = 294)

Variable	%	*M*	*SD*
Sex			
Female	60.9		
Male	39.1		
Age (years)		30.01	7.44
Race			
African American	4.8		
Latino/Hispanic	3.4		
White Caucasian	75.8		
Asian/Pacific Islander	10.9		
Other	5.1		
Education (years)		16.12	2.13
DSST (scaled score)		11.98	2.55
Mother's education (years)		14.88	2.97
Father's education (years)		16.07	3.78

Note. DSST = Digit Symbol Substitution Test from the Wechsler Adult Intelligence Scale—Revised.

Finite Mixture Modeling Analysis

The distributions for the three variables of interest (d', gain, and catch-up saccade rate) are shown in Figure 1 (higher score values indicate worse performance). The EM-based finite mixture analyses were done for one, two, and three normal component models with unrestricted covariance matrices. The results for these model fits are contained in Table 2 based on 100 bootstrap replications. The analyses were also conducted for 200, 300, and 1,000 bootstrap replications, which yielded similar results across all estimations. The results contained in Table 2 indicate that a model consisting of two normal components provided the best fit to these data according to both the bootstrapped LRT and the BIC. Thus, it appears that two discernible groups are commingled within the overall distribution of sustained attention and eye-tracking performance scores. The estimates of the mixing proportions for each of the two components were .73 and .27, respectively (these proportions take into account fractional weighting of the cases). The distribution of the posterior probabilities can be seen in Figure 2. The posterior probabilities cluster largely at the two ends of the distribution with a fraction of the cases falling at intermediate values. Such a pattern is consistent with the existence of two components generating these data. These posterior probabilities provide a basis for the outright assignment of individual cases to either of the resolved components. Doing so placed 232 individuals in the first component and 62 in the second component, assuming a posterior probability of .50 or higher indicates likely membership in the second component. We designated the second component the putative *schizotypic* component.

An important assumption in finite mixture modeling with normal components is that the underlying components indeed have relatively normal distributions. We tested the normality of the distributions of d', gain, and catch-up saccade rate for each of the components. In the first component ($n = 232$), the scores for all three variables were approximately normally distributed: d' ($z = .758$, $p < .62$), gain ($z = .566$, $p < .91$), and catch-up saccade rate ($z = .612$, $p < .85$). The same variables were also approximately normally distributed in the second component ($n = 62$), d' ($z = .616$, $p < .85$), gain ($z = .924$, $p < .37$), and catch-up saccade rate ($z = .888$, $p < .41$).

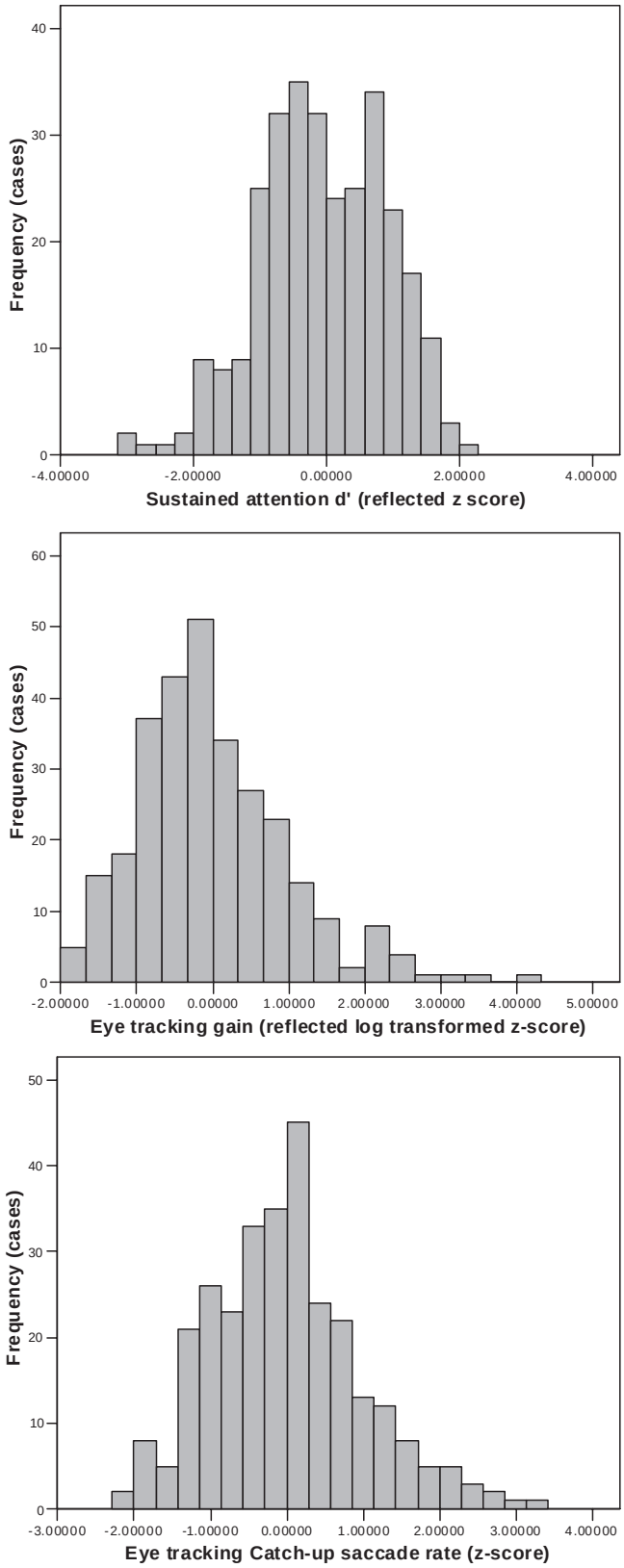

Figure 1. Distributions for sustained attention (d'; top), gain (middle), and catch-up saccade rate (bottom) measures in the sample ($N = 294$). Higher values reflect poorer performance.

Table 2
Summary of Finite Mixture Modeling Fits for Sustained Attention and Smooth Pursuit Eye-Tracking Mesures (N = 294)

g	Log likelihood	−2 log λ	*p*	BIC
1	−1.134.11			2,319.37
2	−1.083.39	101.45	.01	2,274.76
3	−1.063.12	44.53	.11	2,291.07

Note. *g* = number of components (groups); BIC = Bayesian information criterion (smallest value indicates best fit).

Criterial Associations Analyses

After assigning the study subjects to their respective components, this membership provided a basis for group comparison of the subjects on other variables of interest. In this case, we were particularly interested to see if subjects in the second component (the putative schizotypic component) had higher scores on an objective measure of schizotypal personality disorder features, as well as a greater rate of treated schizophrenia in their first-degree biological relatives, as would be predicted on a theoretical basis. As shown in Table 3, the schizotypic group (i.e., second component) displayed significantly higher levels of schizotypal features across all SPQ dimensions and total score.[5]

Regarding a positive family history for treated schizophrenia among first-degree biological relatives, data were available for 284 subjects (10 subjects were either adopted or did not provide family history information). Within the first component, 1 of 224 subjects had a positive family history for treated schizophrenia, whereas 3 of 60 subjects in the second component had a positive family history. These rates differed significantly: continuity corrected $\chi^2(1, N = 284) = 4.17$, $p < .04$ (two-tailed); Fisher's exact test, $p < .031$. Being a member of the schizotypic component was associated with a higher rate of treated schizophrenia among biological first-degree relatives.

Although the subjects in the second component revealed higher levels of schizotypal personality features, as well as an increased rate of treated schizophrenia in their first-degree biological relatives, it was equally important to see whether these subjects were not generally deficient on other measures across a variety of domains. The two-component solution we found might be of diminished theoretical interest if the members of the second component were simply more impaired across other broad domains such as intellectual level, socioeconomic factors, and general psychopathology in relatives (beyond just schizophrenia). Therefore, we compared the subjects in Component 2 with those in Component 1 on age, education, DSST performance, and mother and father education levels (i.e., social class). The subjects in the schizotypic component did not differ significantly from those in Component 1 in terms of age, $t(292) = 0.002$, $p = .998$; year of education, $t(292) = 0.378$, $p = .706$; DSST performance, $t(292) = 1.46$, $p = .14$; mother's education level, $t(286) = 0.289$, $p = .773$; or father's education level, $t(282) = 0.12$, $p = .903$.

It is possible that those persons in the schizotypic component revealed positive family histories for a wide variety of treated psychopathology, suggesting that they were simply at greater risk for general psychopathology. We compared the rates of treated psychopathology in the first-degree biological relatives, assessed via the family history method noted above, for those subjects in the two components. For the all the disorders we assessed (i.e., depression, bipolar disorder, anxiety disorders, alcohol/drug abuse, obsessive–compulsive disorder, eating disorders, autism, attention deficit hyperactivity disorder), the rates of the disorders in the first-degree relatives did not differ significantly across the members in the two components. In fact, for bipolar disorder, alcohol/drug abuse, obsessive–compulsive disorder, eating disorders, autism, and attention deficit hyperactivity disorder, these disorders were found only among the first-degree relatives of those subjects in the *nonschizotypic* (i.e., first) component. It is particularly noteworthy that all cases ($n = 5$) of bipolar illness (a psychotic illness) were found among the relatives of persons in the first component (i.e., none were found in the schizotypic [i.e., second] component). Thus, it appears that on the basis of the family history data, the schizotypic component was not merely tapping general psychosis-related liability in the subjects.[6]

Supplementary Taxometric (MAXCOV) Analysis

We conducted a MAXCOV (Meehl & Yonce, 1996) analysis on the same three endophenotypic indicators that were used in the finite mixture modeling analysis. The intention of this analysis was to determine if a different analytic method would also yield evidence of a partition in these data similar to the finite mixture modeling analysis. The raw MAXCOV plots for the three combinations of variables, in which each variable served once as the input variable (Figure 3). All covariance curves departed substantially from a uniformly flat line (i.e., what is expected for dimensional data) and revealed a pattern associated with a latent taxon (or latent class). The covariance curves for Catch-Up Saccade Rate × Gain with d' as the input (Panel A) and d' × Gain with catch-up saccade rate (Panel B) as the input both reveal a maximum covariance shifted toward the right end of the respective curves, and the curve for d' × Catch-Up Saccade Rate with gain (Panel C) as the input reveals a cusp in the rightmost interval. Each of these curves is suggestive of a latent discontinuity as per interpretive principles of Meehl (Meehl & Yonce, 1996; Waller & Meehl, 1998). The goodness-of-fit index for this analysis was .84, suggestive of a reasonable fit (diminished, in part, by nuisance covariance). The nuisance covariance among the indicators for the total sample was .313; the within taxon average correlation = .28, and the within complement average correlation = .21.

The plot of the posterior probabilities (Figure 4) is also consistent with a latent discontinuity underlying these quantitative data.

[5] We also parsed the subjects into first- or second-component membership using a more conservative approach to classification based on the posterior probabilities. In this supplementary analysis we retained only those cases with a posterior probability of .25 or less for the first component, and those cases with a posterior probability of .75 or higher were assigned to the second component. We held aside those cases with posterior probabilities intermediate between .25 and .75. Analysis of the schizotypal personality data using this parsing method yielded a highly similar pattern of findings for all three SPQ factors and total SPQ score, namely the subjects in the second component had significantly more schizotypic features than those in the first component.

[6] Detailed results of these statistical analyses may be requested from Mark F. Lenzenweger. They were omitted to conserve space.

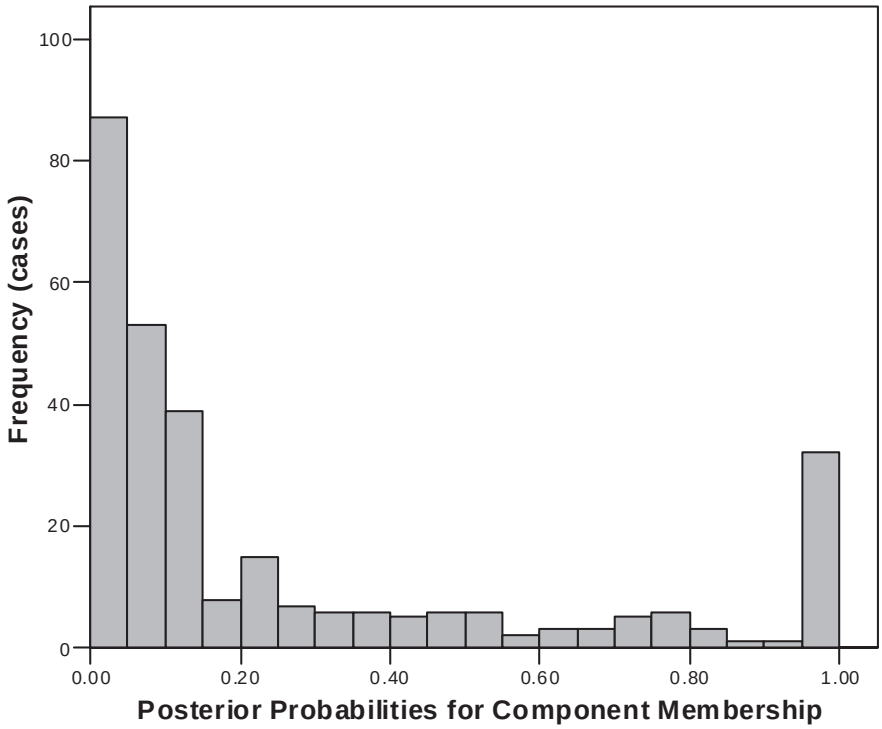

Figure 2. Posterior probabilities for component membership for the two-component finite mixture model.

Most cases are arrayed at either of the extremes of the range of posterior probabilities (i.e., 0 and 1.00), with some intermediate values. This distribution is roughly comparable with that found in Figure 2 from the mixture analysis. The average separation of the latent means was 1.035. The estimated base rate (from the Bayesian [posterior] membership probabilities) was .27, a figure that accords well with the mixing proportion of .27 for the schizotypy component derived from the finite mixture modeling analysis. Using a base rate estimated from the Bayesian (posterior) probabilities, which are based on all three indicators considered simultaneously, for the MAXCOV analysis is comparable with the approach taken in the finite mixture modeling for estimating mixing proportions, which are based on all three indicators considered simultaneously. Finally, the correlation of the posterior probabilities for Component 2 membership from the finite mixture modeling analysis with the posterior probabilities for taxon membership from the MAXCOV analysis was .60 ($p < .0004$), suggesting comparable rank orderings of the posterior probabilities across the two methods.

Discussion

We sought to illuminate the nature of the underlying structure of multiple endophenotypes for schizophrenia using finite mixture modeling. We selected two well-validated major endophenotypic indicators of schizophrenia liability—sustained attention and smooth pursuit eye movement performance—and assessed these performance constructs in a large, quasi-randomly ascertained adult community sample. Using EM-algorithm-based multivariate finite mixture modeling, we were able to directly address the issue of the nature of the underlying structure of sustained attention and smooth pursuit eye movement. Our results revealed that two components could be resolved within the joint distribution of d' (sustained attention), gain (eye tracking), and catch-up saccade rate (eye tracking), and the two-component solution provided the best fit to the data. The two components that were resolved within this multivariate space were themselves approximately normal in shape in the three variables. The distribution of posterior probabilities for component membership was also consistent with the existence of

Table 3
Schizotypal Personality Disorder Features in Two Participant Groups (N = 294)

	Normal (n = 232)		Schizotypic (n = 62)				
SPQ dimension	*M*	*SD*	*M*	*SD*	*t*	*p*	*d*
Reality distortion	6.28	5.78	8.16	6.69	2.21	.03	0.32
Disorganization	4.19	3.75	5.44	3.79	2.32	.02	0.33
Negative	5.50	4.71	6.76	4.37	1.98	.05	0.27
Total	15.97	11.62	20.35	12.09	2.62	.009	0.37

Note. SPQ = Schizotypal Personality Questionnaire. The p values are based on two-tailed test of statistical significance; d = Cohen's measure of effect size (i.e., standardized difference between two groups).

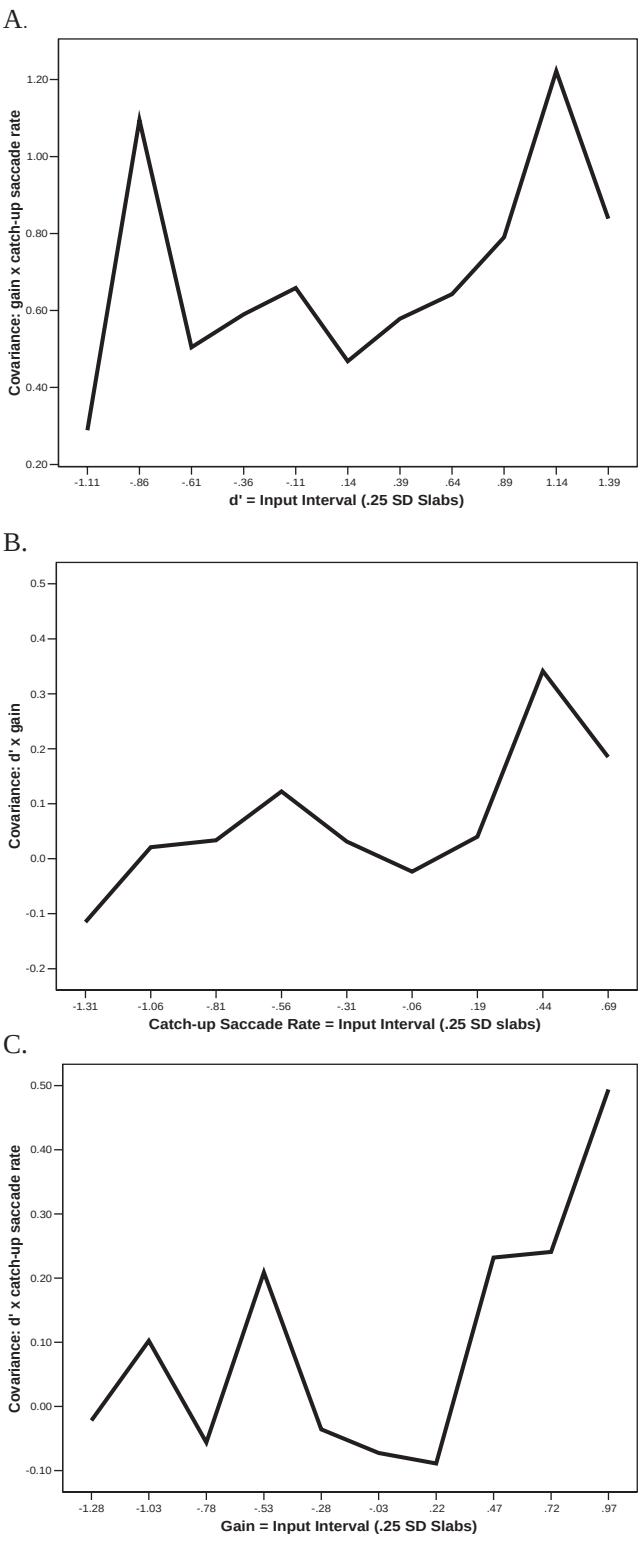

Figure 3. Raw maximum covariance (MAXCOV) curves for the three indicators d', eye-tracking gain, and eye-tracking catch-up saccade rate. A: Catch-Up Saccade Rate × Gain (input = d'). B: d' × Gain (input = catch-up saccade rate). C: d' × Catch-Up Saccade Rate (input = gain).

two components generating these data. A supplementary taxometric analysis revealed a pattern suggestive of a latent discontinuity, or the presence of a latent taxon. This pattern of results in the MAXCOV analysis was seen as supportive of the finite mixture modeling results, namely, the existence of two putative classes underlying these data. Furthermore, the MAXCOV results yielded a base rate estimate highly consistent with that found in the finite mixture modeling analysis, a base rate of .27 (the mixture modeling analysis yielded a mixing proportion of .27). Thus, two different analytic methods, based on somewhat different assumptions (e.g., local independence, presence vs. absence of assumed data partitions), yielded comparable results. Therefore, we view the primary results of the finite mixture modeling analysis—the presence of two latent components—as relatively robust and of considerable theoretical interest.

An important additional aspect of this investigation concerned what we viewed as set of criterion or validation analyses. We wanted to assess whether those in the second (or schizotypic) component really revealed evidence consistent with a greater likelihood of possessing schizophrenia-related liability. This could be evaluated by considering symptoms in the subjects themselves and the presence or absence of schizophrenia in their first-degree biological relatives. Thus, in the first analysis, we evaluated whether individuals in the second component were phenomenologically more schizotypic than those residing within the larger component by virtue of displaying greater numbers of schizotypal personality disorder features, which are known to be reflective of an increased liability for schizophrenia (Battaglia et al., 1991; Kendler et al., 1993; Lenzenweger & Loranger, 1989). Indeed, as assessed by the SPQ, those subjects found within the second component displayed higher rates of disorganized, negative, and reality distortion schizotypal personality features, as well as more schizotypal features overall (total score), compared with the subjects in the first component. Also, we found that subjects in the second component were significantly more likely to have a positive family history for treated schizophrenia among their biological first-degree relatives compared with the subjects in the first component. In this context, we also highlight that the results from our control analyses, which examined age, education, DSST scores, and parental educational levels across the two components, were not consistent with an interpretation that members of the second component could be characterized as generally deviant with respect to these variables. Moreover, in our additional analyses of treated psychopathology among the biological first-degree relatives of our subjects, we found that the vast majority of general psychopathology, accounting for a wide array of disorders, was found among the relatives of the cases in the first component. It is important to note that all cases of bipolar illness were found among the relatives of cases residing in the first component.

The meaning of these results is relatively clear, namely, the second component did not merely identify persons who performed poorly on the sustained attention and smooth pursuit eye movement tasks and who were also given to having a great deal of nonspecific psychopathology in their families. Quite to the contrary, our results support the view that those persons found to reside in the second component were more schizotypic, as well as more likely to have a schizophrenia-affected relative, than the other subjects in the study; the subjects in the second component

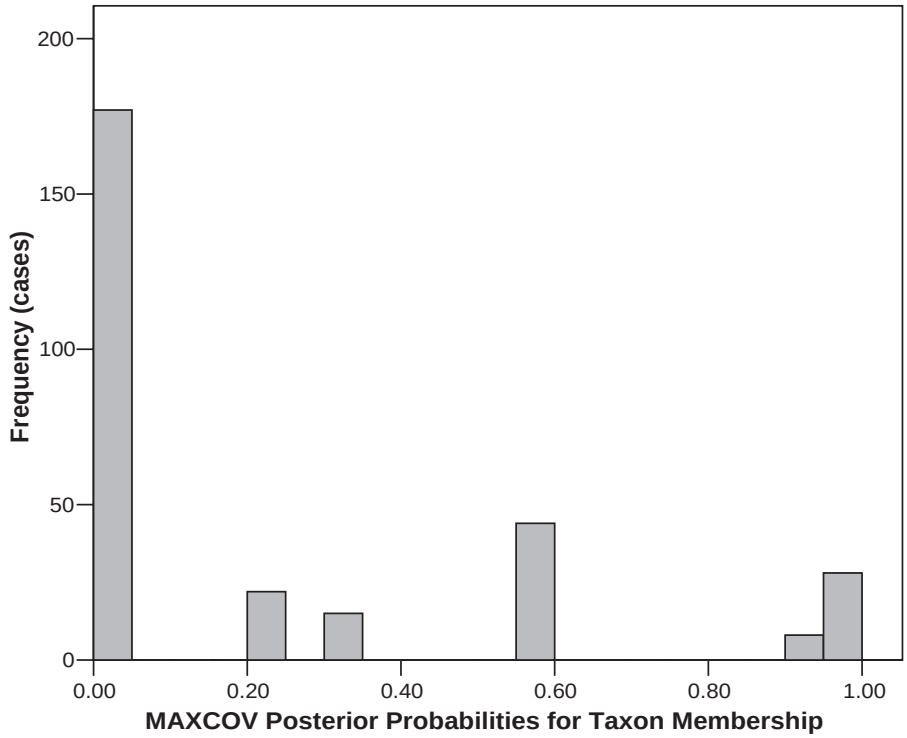

Figure 4. Posterior probabilities for taxon membership for the maximum covariance (MAXCOV) taxometric analysis.

did not reveal evidence of generalized impairment or deviance on a host of comparison variables.

Distributions, Mixtures, and Statistical Considerations

Our mixture modeling results clearly supported the existence of two components residing within the overall sample as defined by the three indicators we analyzed; however, we stress that we see these results as heuristic in value and suggestive of further exploration rather than as being definitive. It is important to consider statistical issues relevant to our conclusions regarding the underlying structure of these data. Are there aspects of our data or analytic strategy that could have impacted the number of components that we extracted from the data? There are two issues of relevance: one concerns the potential impact of skewness on our results and the other concerns the statistical tools that we used to guide our conclusions regarding the number of components resolved.

First, considering the issue of skewness, nonnormal data can impact finite mixture modeling analyses as we noted earlier, and this issue has received extensive empirical study and substantive discussion in the mixture modeling literature (e.g., Gutierrez et al., 1995; MacLean et al., 1976; McLachlan & Peel, 2000). In short, extreme skewness can lead to overestimation of the number of components in a mixture modeling analysis, and this is why we attended to the relative normality of the distributions for our data prior to analysis and why we used a modest transformation of one variable to enhance normality (i.e., log transformation for the gain variable). It is also the case that mixture modeling assumes that the *latent* components themselves are relatively normal in shape, so skewness in the latent components can also affect the results of a mixture analysis. Therefore, we evaluated the degree of skewness of the distributions of d', catch-up saccade rate, and gain in each the two components. None of the six distributions revealed statistically significant skew (according to the one-sample Kolmogorov–Smirnov tests of normality). We argue, therefore, that our approach to skewness reflected a balanced and informed approach that helped to protect against false inferences regarding the structure of our data.

A second issue impacting our conclusions concerns the principles governing the determination of the proper/optimal number of components in a finite mixture modeling analysis. We used two well-developed methods for determining the number of components underlying our three indicators: the bootstrapped LRT and the BIC. Both of these methods supported our two-component solution. In this manner, finite mixture modeling differs from other latent structure methods that have often relied on more subjective methods for the determination of an optimal number of clusters (e.g., dendrograms or icicle plots) or factors (e.g., scree plots) or even taxometric analysis (i.e., visual inspection of covariance curves). A related question, which occasionally arises in the discussion of mixture modeling results, concerns whether the method always generates evidence for two components, and the answer to this question is no. In short, if one fits a mixture of $g = 2$ components, then a mixture analysis will necessarily produce two clusters. Thus, one needs to test the significance of the components by testing for the smallest number of components compatible with

the data using, say, resampling, BIC, or posterior predictive *p* values.

Finally, in discussions of distributions and mixtures, one occasionally encounters the view that a mixture of normal distributions must always reveal itself distinctively in the shape of total distribution of scores for variables of interest. This view, however, is incorrect. A mixture of normal distributions does not necessarily reveal the latent mixture via nonnormality or bimodality/multimodality (Beauchaine, 2003, Figure 1, p. 505; Murphy, 1964). Moreover, even if a distribution is unimodal, it can harbor an underlying mixture of normals and not provide an obvious clue to the latent organization, depending in part on the degree of separation of the latent means.

Limitations

A number of caveats should be borne in mind for our study. First, schizotypal personality features were assessed using a self-report approach and, although reliable and valid, the data derived from this scale may not correspond exactly with those potentially available via an interview procedure. However, we note that both psychometric inventories and interviews are fundamentally self-report technologies. Second, our sample was a volunteer sample rather than one truly randomly ascertained using survey methods. However, it is well known that all forms of recruitment have some bias. It is possible that individuals who volunteered for our study differed in unknown ways from those who did not. Nonetheless, the sample acquired was quite similar demographically to the population in the region. Third, our study was conducted within a large, metropolitan area and therefore does not represent the potential range and diversity in sustained attention, eye tracking, and schizotypal personality features that might come from a more expansive study that included rural and semirural populations. Fourth, there could be other factors that might be associated with impaired sustained attention or decreased eye-tracking performance in this sample other than liability for schizophrenia. However, the methodological refinements in this protocol ensured that third-variable confounds such as alcohol use, extensive drug abuse histories, head injury, neurological illness, or history of psychosis were ruled out. Finally, we conducted our exploratory assessment of family history of schizophrenia using the family history method and, therefore, relied on the reports of the subjects' with respect to their family members. One could conceivably use the family interview method in which every relative is formally interviewed; however, such an approach is expensive, and the family history method is supported as a valid approach to assessing familial psychopathology (see Andreasen et al., 1977).

Implications and Conclusions

By using an EM-based finite mixture modeling approach to examining the latent organization of these prominent endophenotypes for schizophrenia, we were able to reveal evidence for two components underlying sustained attention and eye-tracking dysfunctions. Although prior taxometric research (e.g., Korfine & Lenzenweger, 1995; Lenzenweger, 1999; Lenzenweger & Korfine, 1992) found evidence for a latent discontinuity underlying psychometric measures of schizotypy, the taxometric method itself was limited in that it could only distinguish between essentially one versus two classes. Our mixture modeling approach allowed us to determine whether three or more components would fit the observed data. Therefore, we argue that finite mixture modeling, as a statistical approach, offers an important and useful alternative to other methods designed to illuminate the latent organization of continuous data. Another methodological advance of this study is the use of fully quantitative laboratory-assessed endophenotypes. Again, prior, largely taxometric, research concerning whether schizophrenia-related endophenotypes would be distributed discontinuously at the latent level has relied exclusively on psychometric measures. This study, however, used indexes that possessed ratio-scale measurement properties, thus psychometric artifact (e.g., difficulty level, item format) concerns are irrelevant. The variables we analyzed in the mixture analysis were themselves relatively normally distributed, thus skewness was also not a factor that could adversely impact our results.

We offer these data as provisional support for the theoretical conjecture that deficits in sustained attention and eye-tracking performance, which represent valid endophenotypes for schizophrenia, have a discontinuous latent organization. Meehl's (1990) and Holzman's (Holzman et al., 1988) models each posits the existence of a group that is at risk for schizophrenia and a complement group of those not at risk for the illness. Gottesman's (1991) model, by virtue of its pronounced threshold assumption, is also congenial with the existence of at-risk and not-at-risk subjects as well. Thus, in short, all three models argue for the existence of two latent classes in one form or another. Our results were highly consistent with these theoretical conjectures in that we found two classes fit these data well. That is, individuals fell into either one of two components, with approximately 27% (fractional weighting of mixing proportions) of the population residing within what we termed the schizotypic component. This mixing proportion of 27% itself raises interesting genetic questions regarding the frequency of the schizophrenia-related diathesis (i.e., possible recessivity). Our supplementary taxometric analysis of these data generated a highly similar base rate estimate for the latent taxon consistent with the mixing proportion figure from the mixture analysis. We stress that the 27% figure should not be taken to mean that 27% of the population is going to develop schizophrenia, as epidemiological data clearly do not support this. However, it is quite conceivable that the proportion of the population carrying the liability for schizophrenia is larger than the aggregate prevalence of expressed schizophrenia-related psychopathology (i.e., schizophrenia, delusional disorder, schizotypal personality disorder, paranoid personality disorder, psychosis not otherwise specified). Moving from a figure of 27% of the population residing within a putative liability component to accounting for observed rates of clinically expressed disease would obviously reflect the impact of many other factors (both protective and risk-increasing factors; see Gottesman, 1991; Meehl, 1990) and genetic assumptions (possible pleiotropy; Holzman et al., 1988).

We recognize that our estimate of the mixing proportion of 27%, based on these quantitative laboratory measures, for the second component is higher than the typical base rate estimates for the schizotypy taxon found in prior taxometric studies (usually 10%–15%; Korfine & Lenzenweger, 1995; Lenzenweger, 1999; Lenzenweger & Korfine, 1992). This discrepancy most likely reflects important differences between psychometric and laboratory measures of schizophrenia liability (i.e., schizotypy) and is worthy of

future study. It may not be reasonable to expect agreement across results obtained through the taxometric analysis of psychometric values, which may reflect the impact of item difficulty or, perhaps, skewness on ordinally scaled metrics, with results obtained from finite mixture analysis of nonskewed, fully quantitative data that are based on ratio-scaled metrics. Although the proportion of our sample deemed to be residing in the second (schizotypy) component is higher than the base rate estimates from prior taxometric studies of psychometric values, our subjects in the schizotypy component were clearly more schizotypic at the phenotypic level and revealed an increased rate of treated schizophrenia in their first-degree relatives as compared with the subjects in the larger (nonschizotypy) component. Thus, the subjects assigned to the second component are indeed schizotypic, and this is consistent with prior results from taxometric studies (Korfine & Lenzenweger, 1995; Lenzenweger, 1999).

We conclude by advocating the use of finite mixture modeling as a statistically well-principled method for the illumination of latent organization in continuous data in future psychopathology research. Furthermore, this statistical approach holds considerable value as an objective means for parsing observed heterogeneity in multiple phenotypic indicators, whether assessed clinically or measured with laboratory technologies, in schizophrenia research. Heterogeneity in laboratory data has hobbled progress in schizophrenia research for decades (Maher, 2003), and only recently have effective methods been developed for the resolution of heterogeneity beyond simplistic subtyping schemes (Lenzenweger et al., 2003). Through effective parsing of the phenotypic space associated with schizophrenia, meaningful subgroups of individuals can be identified, and these classifications then may aid efforts seeking to link specific polymorphisms to behavioral or neurocognitive phenotypes in genomic research (e.g., Egan et al., 2001; Harrison & Owen, 2003; cf. Law et al., 2006). Finally, we note that any statistical approach to understanding the latent structure of data will necessarily reveal only part of the story and cannot conclusively resolve a substantive issue. Not unlike the great debate regarding the latent structure of the distribution of blood pressure values in relation to essential hypertension (O'Shaughnessy, 2001; Pickering, 1959; Platt, 1947; Swales, 1985), we believe the substantive discussion regarding the fundamental nature of the latent structure of schizophrenia liability will be informed not only by statistical methods and results such as ours but also by reference to other data from other levels of analysis.

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