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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

modeling share a comparable analytic model (Bauer & Curran, 2004), but they are methods designed to answer different substan-

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.;

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 Intelli-

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

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 ($z = .888$, $p < .41$).

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

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

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 move-

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.,

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, iowever,

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

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