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Testing Liddle's three-syndrome model in families with schizophrenia

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Abstract

While the symptoms of schizophrenia can be grouped into positive and negative syndromes, increasing evidence suggests that three clusters of symptoms are present. Liddle (1987a) described a three-syndrome model comprised of reality distortion, psychomotor poverty and disorganization symptom clusters. This model was assessed in the present study using a sample of 72 members of five families segregating schizophrenia. A wide range of psychopathology was present across a spectrum of diagnoses. Data on symptoms used in Liddle's model were derived from the Positive and Negative Syndrome Scale (PANSS) and a mental status examination. Factor analysis of the data indicated the presence of three clusters of symptoms. The psychomotor poverty or negative symptom cluster was confirmed in the familial sample. However, the other two factors differed somewhat from the Liddle model. Hallucinations, delusions, disorganized thinking and inappropriate affect formed one factor; suspiciousness and stereotyped thinking formed the other. These three symptom clusters may be comparable to the catatonic, hebephrenic and paranoid classical subtypes of schizophrenia. The implications of Liddle's model for genetic studies of schizophrenia require further investigation.

Keywords

Negative symptom; Familial; Genetics; Syndrome; Spectrum; (Schizophrenia)

1. Introduction

Grouping the clinical features of schizophrenia into positive and negative symptom clusters has a long history, and evidence of both reliability and validity (reviewed by Barnes and Liddle, 1990; Andreasen and Flaum, 1991; McGlashan and Fenton, 1992). However, factor analysis studies have demonstrated three clusters of symptoms, suggesting that the two-syndrome model is inadequate (Bilder et al., 1985; Liddle, 1987a). Many groups have now

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replicated a three-syndrome model (Kulhara and Chandiramani, 1990; Mortimer et al., 1990; Arndt et al., 1991; Cleghorn et al., 1992; Minas et al., 1992; Peralta et al., 1992). Similar to positive and negative symptoms (Strauss et al., 1974; Crow, 1980), the three 'syndromes' or clusters of symptoms appear to represent independent or semi-independent dimensions of psychopathology that frequently coexist in individuals with schizophrenia (Liddle, 1987b).

The most consistently replicated of the three symptom clusters, termed psychomotor poverty by Liddle (1987a), is similar to a core negative symptom grouping and includes features such as blunted affect and poverty of speech. Another cluster contains core positive symptoms such as delusions and hallucinations which Liddle named reality distortion. The third symptom group includes thought form disorders, inappropriate affect and/or bizarre behavior. This has been characterized as both a disorganization cluster, independent of the positive–negative symptom construct (Bilder et al., 1985; Liddle, 1987a), and alternatively as a second group of positive symptoms (Arndt et al., 1991; Minas et al., 1992). A recent review of factor analysis studies of schizophrenia (Peralta et al., 1992) showed there was overall fair consistency with the model proposed by Liddle. However, the clustering of positive symptoms into syndrome groups showed some variability. Others have reached similar conclusions (Arndt et al., 1991; Minas et al., 1992).

Recent genetic studies have supported the validity of positive and negative symptom dimensions (McGuffin et al., 1991; Tsuang et al., 1991; Bassett et al., 1993), but have not assessed a three-syndrome model. Disorders occurring in elevated levels in biological relatives of schizophrenic patients (Lowing et al., 1983; Kendler et al., 1984, 1985; Torgersen, 1985) are composed of symptoms that may fall into one of the proposed three syndromes. For example, Dworkin et al. (1991) found that thought disorder, flat affect, poverty of speech and decreased social competence (the latter three of which could be considered negative symptoms) were increased in adolescents who had a parent with schizophrenia. From the same high risk study of offspring of schizophrenic parents, Squires-Wheeler et al. (1989) found that the features of DSM-III-R schizotypal personality disorder were significantly increased in young adulthood, particularly the disorganization syndrome-like symptoms of odd speech and inappropriate affect, and the positive syndrome-like items of odd behavior and recurrent illusions. Although few of these studies have used standardized assessments of symptoms in direct interviews of relatives, the results suggest similar symptoms may be detected in family members who do not have schizophrenia. Such subthreshold phenomenology, proposed to be caused by variable expression of a faulty gene in non-schizophrenic relatives, may be aligned into positive and negative symptom groupings (reviewed by Tsuang et al., 1991) or regrouped according to a three-syndrome model. In either case the goal is to demarcate symptom clusters relevant for genetic studies.

The current study was designed to test Liddle's (1987a) three-syndrome model using a factor analysis of symptoms in a familial sample with a broad spectrum of psychopathology, including schizophrenia and genetically related conditions. Liddle's model was selected as it has been fairly widely replicated in schizophrenic samples and has the most supporting external validation, including neuropsychological and cerebral blood flow correlates (Liddle, 1987b; Liddle and Morris, 1991; Liddle et al., 1992). The sample available for the current study ($n = 72$) was believed likely to generate a meaningful factor solution since Liddle

(1987a) was able to successfully identify three symptom clusters using a small sample size and a limited number of items. The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used to measure positive and negative symptoms because it has a broader range per item than most instruments and its psychometric properties were found to be robust in this familial sample (Bassett et al., 1993). The main assumption of the study was that the PANSS is sufficiently sensitive to detect subtle clinical features that could be manifestations of a putative schizophrenia genotype. Factor analysis using a familial sample could identify symptom clusters which may have applications in genetic studies of schizophrenia, particularly those examining quantitative traits.

2. Materials and methods

Subjects were members of five families of Celtic origin from a rural Canadian region who were participating in a genetic linkage study of schizophrenia and had a completed Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) assessment and mental status examination (MSE) ($n = 75$). A detailed description of the sample and methodology may be found in Bassett et al. (1993). In brief, after obtaining written informed consent, subjects had diagnostic assessments using modified Structured Clinical Interviews for DSM-III-R: the Patient Edition (SCID-P) for Axis I disorders and Personality Disorders (SCID-II) for Axis II disorders (Spitzer et al., 1990a; 1990b). A comprehensive mental status examination including assessment of inappropriate affect was also completed on each subject. One of us (A.S.B.) participated in all diagnostic and mental status assessments and, immediately following, rated each subject using the PANSS. MSE and PANSS assessments were completed when subjects were in remission from acute psychiatric illnesses or were in stable chronic states. Interview information and all collateral data were used to determine a consensus lifetime DSM-III-R diagnosis using the Best Estimate Clinical Evaluation and Diagnosis (BECED) method (Endicott, 1988).

Seventy-five subjects had a completed PANSS and MSE. Excluded from the analyses were data from three male subjects with the following diagnoses: dementia, pervasive developmental disorder, and chronic schizophrenia with evidence on CT scan of an old infarction in the left parietal region that could be the cause of a neglect syndrome difficult to distinguish from severe negative symptoms. The sample for the current study therefore consisted of 72 subjects.

Individual items (see Table 1) were selected from the positive, negative and general psychopathology subscales of the PANSS, representing the closest equivalents to the symptoms derived from the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen, 1983) which were used in Liddle's (1987a) factor solution. (The 1983 CASH incorporated the Scale for the Assessment of Negative Symptoms (SANS) and a forerunner to the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1982; 1984)). There was no corresponding item on the PANSS for the disorganization symptom, inappropriate affect. Although there were existing measures of this clinical symptom, such as in the SANS/SAPS, these would not have had a structure parallel to the other PANSS items. A standardized item on a seven-point rating scale, (absent (1), questionable, mild, moderate, moderate-severe, severe, and extreme (7)) consistent with other PANSS items,

was therefore created and rated using detailed descriptive data from the MSE. A Cronbach's coefficient alpha was calculated using the existing seven items from the PANSS positive scale and the new inappropriate affect item. The resulting value of 0.82 gave strong support for the consistency of the new item with the existing PANSS structure.

Principal components extraction with promax rotation (Statistical Analysis System (SAS)) was performed on the nine symptoms selected. Promax first provides an orthogonal solution and then rotates to an oblique solution. A minimum eigen-value of 1 was used as the criterion for retaining factors, and all variables with loadings of more than 0.45 were retained on a factor. Variables were reordered and grouped by the size of loading to facilitate interpretation.

3. Results

Demographic and clinical information for subjects in the study are reported in Table 2. Means and standard deviations for the nine symptoms selected for the factor analysis are shown in Table 3. These data showed a positive skew, with most subjects having low ratings for symptoms. There was sufficient range of ratings for all items to allow for acceptable correlations, but the skew may have attenuated the importance of major factors by reducing the magnitude of correlations. Three factors were retained in the factor analysis. Examination of the oblique solution suggested that these factors were only moderately correlated with each other, as follows: 0.16 (factors 1 and 2), 0.23 (factors 2 and 3) and 0.22 (factors 1 and 3), representing 2.6%, 5.3% and 4.8%, respectively, in overlap of variance between factors. Therefore, the orthogonal (varimax) solution was reported because of its greater conceptual simplicity and ease of interpretation.

The loadings of the variables on factors and variance accounted for are shown in Table 3. The variables which loaded on the first factor were delusions, hallucinations, conceptual disorganization (thought form disorder) and inappropriate affect, features which could broadly be considered positive symptoms. However, stereotyped thinking, a measure of inflexibility of thought and poverty of thought content, also had a relatively high loading. The second factor appeared to represent a negative symptom dimension, with loadings of 0.716 and greater for the three items and no item loading significantly on other factors. Three variables, suspiciousness, stereotyped thinking and delusions, loaded significantly on the third factor. However, the substantially higher loading of delusions on factor 1 suggested that this symptom should be considered part of that factor and not factor 3. Internal reliability (Cronbach's alpha coefficient) for factors 1 and 2 were 0.73 and 0.70 respectively. The two items on factor 3 showed an internal consistency (Pearson r) of 0.59 ($p = 0.001$). The three factors together accounted for 71.5% of the total variance.

4. Discussion

4.1. Replication of the negative syndrome

Similar to many other recent results using factor analysis of positive and negative symptoms (Peralta et al., 1992), the familial sample used in the current study produced a three factor solution which explained 71.5% of the total variance among the items and contained a

negative symptom cluster with factor-specific loadings. The presence in a familial sample of a cluster of negative symptoms is additional evidence of the importance of these symptoms in schizophrenia. In addition, an important feature of studies which use relatives, including the current investigation, is that since few or no relatives are depressed, institutionalized or on neuroleptics, the issue of secondary negative symptoms is minimized (Tsuang et al., 1991). The current study added to the growing body of literature which has consistently found a negative symptom grouping, using a variety of assessment instruments, in samples of schizophrenia alone and in samples including relatives (McGuffin et al., 1991; Tsuang et al., 1991; Bassett et al., 1993).

4.2. Positive and disorganization syndromes: differences to Liddle's model

In contrast, the grouping of positive symptoms across studies is less consistent (Peralta et al., 1992). Strauss et al.'s (1974) initial proposal for three categories of schizophrenic symptoms included a positive symptom grouping with 'positive' thought form disorder, delusions and hallucinations. However, results obtained from factor analyses (Bilder et al., 1985; Liddle, 1987a) have delineated a positive symptom factor (delusions–hallucinations) and a separate thought disorder (disorganization) factor for chronic schizophrenia. In the present study, delusions and hallucinations clustered together with two disorganization items (thought disorder and inappropriate affect). The items suspiciousness and stereotyped thinking, which were considered as positive and disorganization symptoms respectively (Table 1), formed their own factor. There are several possible reasons for these differences from the Liddle (1987a) model.

4.3. Sample considerations

There may be features specific to the present study that produced the results. The sample comprised individuals with a broad range of lifetime diagnoses, some of whom had no history of psychiatric illness. If a putative schizophrenia gene segregates in an autosomal dominant-like manner, one would expect that approximately half of the individuals in these families would carry such a gene. However, due to reduced penetrance some family members may not express even mild clinical features. The presence of multiple 'normals' in the factor analysis could alter the solution by attenuating correlations and thereby reducing the chance of replicating the findings of previous studies. The relatively small sample size could also contribute to this outcome. Alternatively, data from this diagnostically heterogeneous familial sample could result in a different but fruitful factor solution. The latter possibility appears to be more likely because the factor analysis did delineate three factors, each containing items that may be considered to be on a continuum with normal behavior. These could therefore indicate underlying quantitative traits of genetic interest.

The presence of what could broadly be considered as two positive symptom factors (1 and 3) in the current sample may also reflect convergence of items related to diagnosis. The items delusions and hallucinations imply the presence of a psychotic illness, and both loaded on one of the positive factors. The other seven items used in the factor analysis are not specific to psychotic illness, and are more continuous with everyday experiences and behavior. There may be an effect of diagnostic distribution within the sample on the factor solution. This would not, however, explain the presence of the additional two items on the same factor as

delusions and hallucinations, nor would it explain the separation of suspiciousness and stereotyped thinking from the first positive symptom factor. Unfortunately, the number of subjects with schizophrenia in the current study was insufficient to test separately from other family members whether Liddle's particular three factors would be replicated using the PANSS items selected.

Another possibility is that the familial form of schizophrenia under study could be different from schizophrenia in other clinical samples. The families in the current study may be representative of familial schizophrenia but the precise prevalence of genetic forms of schizophrenia in the general population is unknown. The severity of positive and negative symptoms however was similar between the familial schizophrenia being studied and general schizophrenia in the literature (Bassett et al., 1993). The fact that the differences between the findings in the current study and those in the literature for schizophrenia are relatively minor is further evidence of clinical similarities between familial and general schizophrenia.

4.4. Assessment and methodological considerations

The choice of the instrument used to measure positive and negative symptoms, the PANSS, was different from those used in the other studies which have replicated and validated Liddle's three-syndrome model. Most have used the SANS and SAPS, or derivatives thereof, with variable use of individual items (Liddle, 1987a), subscale totals (e.g. Arndt et al., 1991) or both (Peralta et al., 1992). The PANSS items selected may not have measured the same clinical features as the SANS and SAPS items or subscale scores. However, the PANSS does have significant cross-correlations to the SANS and SAPS (Kay et al., 1988; Fenton and McGlashan, 1992) and the negative symptom cluster was replicated in the current study. Alternatively, the PANSS may not be sensitive enough to detect mild pathology in the relatives of schizophrenia. This does not appear likely, however, given the instrument's broad range in each item and previously documented differences between subjects with schizophrenia spectrum disorders and those not having such a disorder (Bassett et al., 1993). There is however evidence that different measurement instruments have an impact on the factor solution. When Liddle (1987a) used the Present State Examination (PSE) (Wing et al., 1974) instead of the SANS/SAPS-related CASH, a four rather than a three factor structure was found in the same sample of chronic schizophrenic subjects. In the four factor solution, bizarre delusions and auditory hallucinations loaded on a separate factor from delusions of reference and persecution. This four factor solution with the PSE may be more consistent with the solution derived using the current sample than the previously described three factor result.

The results in the current study do not, however, appear solely to be due to the instrument used to measure symptoms since they have both similarities and differences to Kay and Sevy's (1990) principal component analysis using all 30 items of the PANSS. The latter study of chronic schizophrenic subjects showed a seven-component solution, including four major symptom complexes: positive symptoms, negative symptoms, depression and excitation. Consistent with most other studies, Kay and Sevy (1990) found a negative symptom component which included the three negative symptoms selected for the current

study. Positive symptoms, as others have found, separated into several clusters. Consistent with Liddle's model, conceptual disorganization loaded on a separate component. However, this item also had a significant loading on the positive symptom (delusions–hallucinations) component, which is similar to the present results. Interestingly, suspiciousness segregated in a different component from other positive symptoms in Kay and Sevy's (1990) analysis, consistent with Liddle's (1987a) PSE analysis and the present results. In fact, Kay and Sevy (1990) found that suspiciousness and stereotyped thinking each formed their own component. The present findings are also consistent with those of Minas et al. (1992) who suggested that delusions of persecution may represent a fourth independent dimension of psychopathology underrepresented in the SAPS. Minas et al. (1992) found the negative symptom and disorganization clusters using the SANS and SAPS, as have many others. The considerable heterogeneity in the hallucination–delusion symptom group and separation of persecutory delusions these researchers found may be due to their larger sample and/or the fact the sample contained a mix of psychotic disorders of varying severity.

4.5. Other limitations

A possible limitation of all cross-sectional studies is the degree to which the findings represent stable traits. Symptom clusters detectable at one time may change during the course of illness (Liddle, 1987a). While this is likely to have occurred in the subjects participating in the current study, the assessment of subjects in a non-acute, and/or chronic stable state may at least favor persistent symptoms. Since the mean duration of psychotic illness in the current sample was over 16 years, a stable pattern of symptoms was likely, though not certainly, established for these subjects.

4.6. Classical subtypes of schizophrenia

The symptom clusters identified in the current study may be conceptualized as being consistent with the symptom groupings found in three classical diagnostic subtypes of schizophrenia–paranoid: suspiciousness and rigid thinking; hebephrenic: delusions, hallucinations, thought disorder and inappropriate affect; catatonic: blunted affect, poverty of speech and psychomotor retardation. Others have also found different symptom clusters compatible with these classical subtypes of schizophrenia. Peralta et al. (1992) suggested the classical subtypes may each be reflected in Liddle's three syndromes. Kay and Sevy (1990) proposed a different model where each classical subtype could be a composite of two concurrently occurring symptom clusters. For example, positive and depressive components could account for the paranoid subtype. These factor analytic studies have shown that statistically derived symptom clusters and clinically observed diagnostic subtypes may be reconciled at a phenomenological level. A hypothesis can also be put forward to link symptom clusters, etiology and mechanism.

4.7. Pleiotropism

Liddle (1987b) has proposed that the observed clinical diversity of schizophrenia, even within one individual, arises from the differential dysfunction of several cerebral regions linked by a common fundamental abnormality. This would be compatible with the genetic concept of pleiotropism: a single etiology with multiple manifestations. Although speculative, a hypothesis could be developed from the mechanism of another genetic

syndrome. A neurological disorder showing the phenomenon of pleiotropism is myotonic dystrophy, which is characterized by myotonia (tonic muscle spasms), muscle wasting, cataracts, hypogonadism and sometimes intellectual deterioration. At different stages of the illness in individual patients different symptoms predominate, and the severity and type of symptoms vary in different members of a family, even within the same sibship (Howeler et al., 1989). In addition, the low correlation of age of onset for parent and offspring pairs in myotonic dystrophy has been reported to resemble that for mental illness (Bell, 1947). Recent advances in molecular genetics have identified the dynamic mutation mechanism that explains the clinical observations. Myotonic dystrophy is now known to be caused by a single autosomal dominant gene with an unusual, unstable mutation (Buxton et al., 1992; Harley et al., 1992). A comparable mechanism may be at work in familial schizophrenia.

4.8. Summary

Overall the results from the current study are consistent with Liddle's hypothesis that, rather than types of schizophrenia, there are concurrently occurring dimensional syndromes of psychopathology which could reflect involvement of different brain regions which are united by a single etiopathology. We propose that this would be a genetic etiology. However, the implications of the present study for Liddle's hypothesis require further evaluation in familial schizophrenia, using larger samples and methods such as longitudinal follow-up and correlative studies of cognition as well as structural and functional brain imaging abnormalities. An ultimate etiological proof would determine that three dimensions of clinical symptomatology are important traits in behavioral expression of a gene or genes predisposing to schizophrenia. Future research may eventually lead to this conclusive resolution of the complex clinical picture of schizophrenia.

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Table 1

PANSS items selected to test Liddle's three-syndrome model

Liddle (1987a) syndromes	Selected PANSS items[a]
Reality distortion	
Delusions of persecution	Suspiciousness
Delusions of reference	Delusions
Voices speak to patient	Hallucinatory behavior
Psychomotor poverty	
Unchanging facial expression	Blunted affect
Paucity of expressive gesture	
Affective non-responsivity	
Lack of vocal inflection	
Poverty of speech	Lack of spontaneity and flow of conversation
Decreased spontaneous movement	Motor retardation
Disorganization	
Tangentiality	Conceptual disorganization
Derailment	
Pressure of speech	
Distractibility	
Poverty of content of speech	Stereotyped thinking
Inappropriate affect	Inappropriate affect[a]

[a] Item created parallel to PANSS items (see text).

Table 2

Demographic and clinical characteristics of the sample ($n = 72$)

Lifetime diagnostic group	Male		Female		Age (years)		Married		Duration of illness (years)		Number of admissions	
	n	%	*n*	%	Mean	SD	*n*	%	Mean	SD	Mean	SD
Schizophrenia ($n = 15$)	7	46.7	8	53.3	43.7	17.1	2	13.3	16.8	15.2	9.5	10.1
Schizoaffective disorder ($n = 7$)	4	57.1	3	42.9	44.6	9.4	2	28.6	21.7	7.3	10.4	6.7
Psychosis not otherwise specified ($n = 5$)	1	20.0	4	80.0	50.2	16.7	2	40.0	26.3	23.7	7.2	13.0
Schizotypal and paranoid personality disorders ($n = 4$)	4	100	0	0	58.7	18.1	1	25.0	28.1	26.6	0	0
Alcoholism ($n = 5$)	5	100	0	0	48.4	19.7	3	60.0	15.3	12.1	0	0
Major depression ($n = 17$)	3	17.6	14	82.4	49.3	16.1	12	70.6	3.2	5.6	0.1	0.3
No major disorder ($n = 19$)	6	31.6	13	68.4	54.9	18.4	11	57.9	0	0	0	0

Table 3

Mean scores and factor loadings obtained by factor analysis of selected symptoms

Symptom	Mean (SD)	Factor 1	Factor 2	Factor 3
Conceptual disorganization	1.94 (1.26)	0.825	0.080	0.237
Delusions	1.72 (1.12)	0.747	0.151	0.458
Hallucinatory behavior	1.19 (0.72)	0.697	0.334	−0.124
Inappropriate affect	1.67 (1.55)	0.537	−0.237	0.335
Blunted affect	2.14 (1.21)	0.331	0.811	0.129
Motor retardation	1.68 (0.95)	0.147	0.797	−0.020
Lack of spontaneity and flow of conversation	1.81 (1.12)	−0.370	0.716	0.358
Suspiciousness	2.19 (1.24)	0.117	0.061	0.916
Stereotyped thinking	1.89 (0.94)	0.438	0.298	0.684
% Of total variance accounted for by each factor		27.6	23.3	20.6