

# Relationship Between Positive and Negative Symptoms of Schizophrenia and Schizotypal Symptoms in Nonpsychotic Relatives

Ayman Fanous, MD; Charles Gardner, PhD; Dermot Walsh, MB, FRCPI; Kenneth S. Kendler, MD

**Background:** Continuous rather than categorical measures of psychopathology may provide greater statistical power to detect susceptibility loci for schizophrenia. However, it has not been established that the dimensions of schizophrenic symptomatology and personality traits in nonpsychotic individuals share etiological factors. We therefore sought to clarify the relationship between positive and negative symptoms of schizophrenic probands and dimensions of schizotypy in their first-degree relatives.

**Methods:** In the Roscommon Family Study, we examined the ability of positive and negative symptoms in probands to predict 7 factors of schizotypy in nonpsychotic relatives using regression analysis. These consisted of positive, negative, and avoidant symptoms; odd speech; suspicious behavior; social dysfunction; and symptoms of borderline personality disorder. We examined 3 proband groups: schizophrenia (n=127); schizophrenia, simple schizophrenia, and schizoaffective disorder (n=178); and all nonaffective psychoses (n=216), and their nonpsychotic relatives (n=309, 477, and 584, respectively).

**Results:** Positive symptoms in all nonaffective psychoses probands predicted positive schizotypy ( $\beta=0.1972$ ,  $P=.0004$ ), social dysfunction ( $\beta=0.0719$ ,  $P=.0489$ ), and borderline personality disorder symptoms ( $\beta=0.1327$ ,  $P=.0084$ ) in relatives, while negative symptoms predicted negative schizotypy ( $\beta=0.2069$ ,  $P=.0002$ ), odd speech ( $\beta=0.2592$ ,  $P=.0001$ ), suspicious behavior ( $\beta=0.2749$ ,  $P=.0001$ ), and social dysfunction ( $\beta=.2398$ ,  $P=.0002$ ). Proband negative symptoms and borderline personality disorder symptoms in relatives in the schizophrenia, simple schizophrenia, and schizoaffective disorder group were inversely related ( $\beta=-0.1185$ ,  $P=.05$ ).

**Conclusions:** Positive and negative symptoms in schizophrenia predict corresponding schizotypal symptoms in relatives. This provides evidence that these schizophrenic symptom factors (1) are etiologically distinct from each other and (2) occur on an etiological continuum with their personality-based counterparts.

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From the Departments of Psychiatry (Drs Fanous, Gardner, and Kendler) and Human Genetics (Dr Kendler), Medical College of Virginia of Virginia Commonwealth University, Virginia Institute for Psychiatric and Behavioral Genetics (Drs Fanous, Gardner, and Kendler); and St Loman's Hospital, Dublin, Ireland (Dr Walsh).

PSYCHIATRISTS from a variety of theoretical perspectives, including Kraepelin<sup>1</sup> and Bleuler,<sup>2</sup> have noted that family members of patients with schizophrenia often have odd personality features, including social isolation, poor interpersonal relationships, unusual thought content, and odd speech.<sup>3-9</sup> These traits were combined into our current concept of schizotypy by Spitzer et al in *DSM-III*.<sup>10</sup> Despite the familial relationship between schizophrenia and schizotypy and substantial evidence for a genetic basis to schizophrenia,<sup>11</sup> the extent to which the dimensions of schizophrenia and schizotypy share familial etiological factors is unknown.

Establishing that normal and disease states represent end points of a single continuum of liability has important implications for understanding the genetic

architecture of not only schizophrenia, but other complex disorders as well, such as hypertension and diabetes, where affection is defined quantitatively, not qualitatively. Establishing such a continuum of liability in schizophrenia will inform the methodology of molecular genetic studies, where it has been difficult to define an optimal phenotype.<sup>11</sup> Quantitative trait loci analysis may be statistically more powerful than traditional linkage methods in detecting susceptibility genes for complex disorders,<sup>12</sup> but its use assumes the genetic continuity of normal and disease states.

Schizophrenic psychopathology is multidimensional and heterogeneous.<sup>13,14</sup> Factor analytic studies often result in positive, negative, and disorganization factors.<sup>15-20</sup> Like schizophrenia, schizotypy is multidimensional and heterogeneous, and is composed of factors that resemble those

## SUBJECTS AND METHODS

### SUBJECTS

The Roscommon Family Study is an epidemiologically based family study of major mental illness in the west of Ireland. Two groups of index probands were examined: (1) schizophrenic—all cases with a diagnosis of schizophrenia from the population-based Roscommon County Case Register<sup>27</sup> (n=303), and (2) affective—a randomly chosen subsample of the cases from the Case Register with a diagnosis of major affective disorder. Because of budgetary restrictions, 75% of these cases were included (n=99). Of the schizophrenic probands, 18 had been ascertained through 2 private hospitals cooperating with the registry. We were unable to obtain access to these individuals, reducing the number of schizophrenic probands to 285. An average of 15 years after onset, we attempted to follow up all 384 index probands, of whom 37 were dead, 23 were untraceable, 50 refused interview, and 274 were personally interviewed by 1 of 2 Irish psychiatrists. Medical records were obtained for 359 probands. In cases of incomplete data, collateral histories, from either family members or community nurses, were obtained for an additional 52 index probands. In our judgment, sufficient clinical information was available to render a psychiatric diagnosis in 375 of these cases, of whom 126 individuals (123 from the original schizophrenic group and 3 from the original affective group) met *DSM-III-R*<sup>28</sup> criteria for schizophrenia. These diagnostic reviews were performed by one of us (K.S.K.) or Alan Gruenberg, MD, using a blind best-estimate procedure with demonstrated high interrater reliability.<sup>29</sup> Of these 126 subjects, 99 were personally interviewed, and 102 had 1 or more relatives with a personal interview or hospital record.

We attempted to personally interview, blind to proband status, all first-degree relatives, aged 16 years and older and residing in the island of Ireland or central and eastern England, of the index probands and a group of unscreened population controls matched for age and sex. We also attempted to obtain and abstract psychiatric hospital records for all hospitalized relatives. As several individuals and families were ascertained more than once, we used the general proband method, in which all individuals are counted once for each time they are independently ascertained.<sup>30</sup>

Personal interviews were completed in 86% of living traceable relatives (n=1753), including 342 relatives of probands meeting *DSM-III-R* criteria for schizophrenia. Their mean±SD age was 46±16 years and 49% were male. For an additional 12 relatives of the *DSM-III-R* schizophrenic probands, only hospital records were available. Herein, we present results on the relatives of probands with a personal interview and/or a hospital record.

### DIAGNOSES

The personal interview with probands and relatives was based on the Structured Clinical Interview for *DSM-III-R*<sup>31</sup> diagnoses for Axis I disorders and the Structured Interview for Schizotypy<sup>32</sup> for schizophrenia-related Axis II disorders. Blind, best-estimate diagnoses using all available information were also made for all relatives with personal interviews and/or hospital records using *DSM-III-R* criteria by 2 psychiatrists (K.S.K. or Alan M. Gruenberg, MD). In addition to coding diagnoses, these 2 psychiatrists completed the Major Symptoms of Schizophrenia Scale (MSSS).<sup>33</sup> This is an instrument designed for use in a best-estimate procedure that codes key

symptom and course features as assessed over the entire course of illness. It was designed to allow the experienced clinician to integrate the relative prominence of clinical features over the entire course of illness. The MSSS contains 9 key symptomatic dimensions: delusions (any), schneiderian delusions, hallucinations, positive thought disorder (such as loosening of associations), catatonic symptoms (including stupor and excitement), depressive symptoms, and manic symptoms. In addition, the MSSS rates chronicity of course and global outcome. All symptom variables were coded on 5-point scales. Details are available on request, but the following general guidelines were adopted for the symptomatic variables: 1, clearly not present; 2, possibly present but subthreshold; 3, clearly present but moderate; 4, clearly present and prominent; and 5, clearly present and severe. The reliability of the MSSS was tested on 47 cases with psychotic illness rated blindly by both psychiatrists. Intraclass correlations for these 11 variables ranged from 0.60 for catatonic symptoms to 0.91 for manic symptoms, with a mean±SD for all 11 variables of 0.77±0.11.

In this study, we performed analyses using 3 definitions of proband caseness: (1) probands with a *DSM-III-R* diagnosis of schizophrenia (n=127); (2) probands with diagnoses of schizophrenia, simple schizophrenia, and schizoaffective disorder (n=178); (3) probands with any of the above diagnoses as well as delusional disorder, schizophreniform disorder, brief reactive psychosis, and psychosis, not otherwise specified (n=216). We examined all first-degree relatives of these 3 proband groups, excluding those with diagnoses of schizophrenia, schizoaffective disorder, delusional disorder, schizophreniform disorder, brief reactive psychosis, and psychosis, not otherwise specified (n=309, 477, and 584, respectively).

### STATISTICAL ANALYSIS

A factor analysis was performed by the method of principal components with varimax rotation using the SAS procedure FACTOR<sup>34</sup> on the 9 symptoms of the MSSS, selecting factors with an eigenvalue of 1.0 or greater. As outlined previously,<sup>35</sup> this yielded the 3 factors: (1) negative—with high loadings on negative thought disorder, affective deterioration, positive thought disorder, and catatonia; (2) positive—with high loadings on schneiderian delusions, any delusions, and hallucinations; and (3) affective—with high loadings on manic and depressive symptoms. As detailed elsewhere,<sup>21</sup> a similar factor analysis was performed on all 25 items of the Structured Interview for Schizotypy. This yielded 7 factors: positive, negative, and avoidant symptoms, social dysfunction, suspicious behavior, and symptoms of borderline personality disorder (BPD).

Missing items were imputed by assigning them the mean score of the items in their respective factor. Subjects missing 50% or more of necessary data were excluded from analysis. All scale scores were transformed into standardized scores with mean of 0 and SD of 1. Regression analyses were performed with positive and negative scores of probands as independent variables and all 7 schizotypy factor-derived scores of relatives as dependent variables. Age and sex of relatives and relationship to proband were entered as covariates. A weighted least squares approach was used, weighting for the number of members per family. Analyses were implemented using the GLM procedure in SAS.<sup>34</sup> The results of the above analyses are presented without Bonferroni corrections. We present results using 2-tailed *P* values.

of schizophrenia.<sup>21-23</sup> Some are composed of attenuated forms of classical positive and negative symptoms. Positive schizotypy comprises ideas of reference, illusions, and magical thinking, while negative schizotypy includes poor rapport, aloofness, and guardedness.<sup>21</sup>

We know of only one study that has addressed the existence of a single continuum of liability for schizophrenic and schizotypal symptoms, showing that negative symptoms in schizophrenic probands were correlated, at the trend level ( $P < .10$ ), with negative symptoms in their relatives.<sup>24</sup> The correlation was greater than a similar one observed for positive symptoms. This study, however, included ill relatives in the analysis.

To further investigate this question, we examined the relationship between classic positive and negative symptoms of schizophrenic probands and dimensions of schizotypy in their first-degree relatives in the Roscommon Family Study. We hypothesized that positive and negative schizophrenic symptoms in probands would predict, respectively, positive and negative schizotypal symptoms. We also predicted relationships between proband negative symptoms and avoidant schizotypy and social dysfunction, as asociality is a prominent negative symptom,<sup>14</sup> and since negative symptoms are robustly related to social dysfunction.<sup>25,26</sup>

## RESULTS

The standardized regression slopes and  $P$  values of all analyses are presented in the **Table**. More inclusive definitions of caseness were generally associated with more statistically significant results. Proband negative symptoms predicted more schizotypy factors in relatives. These included the negative factor, odd speech, suspicious behavior, and social dysfunction. Negative symptoms also had an inverse relationship with symptoms of borderline personality disorder (BPD) in the analysis of schizophrenia, simple schizophrenia, and schizoaffective disorder probands. Positive symptoms in probands predicted positive schizotypy, BPD symptoms, and social dysfunction in relatives.

## COMMENT

In this study, we examined the hypothesis that positive and negative symptoms of schizophrenia share familial etiological factors with corresponding dimensions of schizotypy by relating symptom scores in psychotic probands with scores on 7 schizotypy factors in their nonpsychotic relatives. Our purpose was to elucidate the etiological lines of demarcation in the schizophrenia spectrum and to further characterize the pathway between familial etiological factors and the expression of clinical phenotype in schizophrenia. Although a previous study of this sample showed that the deficit syndrome was associated with social isolation in relatives,<sup>36</sup> this is the first study to show that schizophrenia and schizotypy share familial etiological factors for both their positive and negative dimensions.

The results generally confirmed our hypotheses. Overall, negative symptoms had statistically significant relationships with more schizotypy factors than did posi-

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Schizotypy Factor	Positive Symptoms		Negative Symptoms	
	Slope	$P$	Slope	$P$
<b>Schizophrenia (n = 127)</b>				
Positive schizotypy	0.1531	.0752	0.0244	.7636
Negative schizotypy	0.0719	.3384	<b>0.2017</b>	<b>.0202</b>
Avoidant schizotypy	0.0256	.5035	0.0713	.6588
Suspicious behavior	0.0919	.2222	<b>0.3162</b>	<b>.0001</b>
Odd speech	0.1031	.2833	<b>0.3320</b>	<b>.0009</b>
Social dysfunction	0.0651	.3328	<b>0.2754</b>	<b>.0002</b>
Borderline personality	0.0796	.1807	0.0025	.9694
<b>Schizophrenia, Simple Schizophrenia, and Schizoaffective Disorder (n = 178)</b>				
Positive schizotypy	<b>0.1983</b>	<b>.0014</b>	-0.0158	.8099
Negative schizotypy	0.0642	.2416	<b>0.2104</b>	<b>.0004</b>
Avoidant schizotypy	-0.0065	.9027	0.0929	.2014
Suspicious behavior	0.0828	.1389	<b>0.2913</b>	<b>.0001</b>
Odd speech	0.1121	.1081	<b>0.2716</b>	<b>.0002</b>
Social dysfunction	0.0815	.1249	<b>0.2629</b>	<b>.0002</b>
Borderline personality	<b>0.1495</b>	<b>.0071</b>	<b>-0.1185</b>	<b>.05</b>
<b>All Nonaffective Psychoses (n = 216)</b>				
Positive schizotypy	<b>0.1972</b>	<b>.0004</b>	0.0116	.8430
Negative schizotypy	0.0382	.4408	<b>0.2069</b>	<b>.0002</b>
Avoidant schizotypy	-0.0072	.8808	0.1068	.6686
Suspicious behavior	<b>0.0613</b>	<b>.0520</b>	<b>0.2749</b>	<b>.0001</b>
Odd speech	0.0840	.1654	<b>0.2592</b>	<b>.0001</b>
Social dysfunction	<b>0.0719</b>	<b>.0489</b>	<b>0.2398</b>	<b>.0002</b>
Borderline personality	<b>0.1327</b>	<b>.0084</b>	-0.0956	.0746

\*Results in boldface indicate significant at  $P \leq .05$ .

tive symptoms. This coheres with the general notion that negative symptoms have greater familial, and possibly genetic, bases than do positive symptoms. Evidence suggesting this is their association with greater family history,<sup>37</sup> worse premorbid functioning,<sup>38-40</sup> and greater longitudinal stability.<sup>41-43</sup> Furthermore, the phenomenological resemblance between positive schizotypal symptoms such as magical thinking and illusions on one hand, and positive schizophrenic symptoms on the other, appears to be less than that between negative symptoms of schizotypy<sup>21</sup> and schizophrenia.<sup>14</sup>

The observed relationships between negative symptoms and negative schizotypy and social dysfunction have face validity, but those with suspicious behavior, odd speech, and BPD symptoms were unexpected. Suspicious behavior might be explained by possible phenomenological overlap with the negative symptoms asociality and poor rapport.<sup>14</sup> Furthermore, one of the items loading on our negative schizotypy factor was guardedness<sup>21</sup>, which intuitively resembles suspiciousness. Features of BPD, however, such as affective instability, inappropriate anger, and impulsivity, seem opposite to classic negative symptoms,<sup>14</sup> which may explain the inverse relationship between them.

We were unable to confirm our hypothesis that negative symptoms would predict avoidant schizotypy in relatives. This was indeed surprising, as asociality is an important negative symptom.<sup>14</sup> Our avoidant schizotypy

factor, however, while including social isolation, also loaded on the anxiety-related traits hypersensitivity, anxiety, and social anxiety, making an etiological relationship with negative symptoms less intuitively appealing. Furthermore, proband clinical features did not predict anxiety disorders in relatives in a prior study of this sample.<sup>35</sup>

We did not expect to find an etiological relationship between negative symptoms and odd speech. However, in several factor analyses,<sup>44,45</sup> including the one performed on this sample,<sup>35</sup> the negative factor loaded on odd speech or disorganization. Furthermore, parents of nonparanoid schizophrenic individuals manifest greater levels of formal thought disorder than do parents of paranoid schizophrenic individuals,<sup>46</sup> and this subtype should be associated with lower levels of negative symptoms than are other subtypes, based on its operational definition in *DSM-III-R*.<sup>28</sup>

Positive symptoms were significantly related to positive schizotypy, social dysfunction, and BPD symptoms. Social dysfunction had significant relationships with both positive and negative symptoms, which may indicate that it is etiologically related to severity of illness rather than specific symptom dimensions. The relationship with BPD symptoms may be related to the propensity for some patients with BPD to exhibit stress-induced paranoia or other mild psychoticlike symptoms, as operationalized in the *DSM-III-R* criteria.<sup>28</sup>

The effect sizes (regression slopes) of the analyses did not change substantially when the definition of proband affection was broadened to include nonschizophrenic psychotic disorders, while significance levels increased substantially. This supports the spectrum concept of schizophrenia—that several disorders share with schizophrenia the same underlying liability.<sup>47-50</sup> This was consistent with a previous study of this sample in which the spectrum concept was formally tested by fitting a multiple threshold model to the data.<sup>50</sup>

Our results indicate that from a familial perspective, the positive and negative dimensions of schizophrenia “breed true” as their attenuated personality-based variants in nonpsychotic individuals. This suggests that the influence of familial etiological factors determining the expression of these symptom dimensions reaches across the boundary of psychotic illness to phenomena currently classified under the rubric of personality. The specificity of the relationships between the positive schizophrenic and schizotypy factors, as well as between the negative schizophrenic and schizotypy factors, further validates the etiological distinctness of some schizophrenic symptom domains, as suggested by sibling resemblance for clinical features.<sup>51-57</sup>

These results provide validation for quantitative phenotype definition in genetic linkage and association studies. As genes are likely to comprise substantial components of the familial etiological factors shared by the dimensions of schizophrenia and schizotypy, the same genes would presumably be involved in both phenotypes. This strategy may increase the power of such studies by including more “units” of genetic liability to schizophrenia in analysis.<sup>12,58</sup>

These results should be interpreted in the context of 4 methodological limitations. First, neither the Struc-

tured Interview for Schizotypy nor the MSSS examined all possibly relevant signs and symptoms of schizotypy and schizophrenia, respectively. Furthermore, the 2 scales differ in their comprehensiveness, with the Structured Interview for Schizotypy containing many more items than the MSSS. Both the assessment instrument used and the number of items included in factor analysis may have a significant impact on the composition and number of factors extracted. Perhaps the use of other instruments would have led to different relationships between the factors of schizophrenia and schizotypy. Our use of only 2 factors may be an oversimplification of the multifaceted variability of schizophrenic psychopathology, but there is no consensus in the field about the number of dimensions that best represents the full clinical picture of schizophrenia.<sup>19</sup> We opted to use positive and negative symptoms because of their historical prominence and their conception in the minds of many clinicians as core illness dimensions.

Second, the use of different covariates may have resulted in different relationships between the factors of schizophrenia and schizotypy. We used age, sex, and relationship to proband. It may be argued that we should have also controlled for social class of the relatives, as this predicted several schizotypy factors.<sup>21</sup> However, when this covariate was used in a prior study, it had no impact on the prediction of proband diagnoses of psychotic disorders by schizotypy factors.<sup>21</sup>

Third, it is not possible to determine whether the results obtained herein are due to genetic as opposed to environmental factors. In addition, an argument made by Kendler et al<sup>51</sup> with respect to sibling resemblance for psychotic syndromes may apply here. This would hold that the correlations between relatives as reported here might be due not only to susceptibility genes for schizophrenia but also to genes determining temperament and intellect. Future studies should attempt to partial out these effects.

Fourth, while we tested a hypothesis about primary negative symptoms, or those due to the disease itself, it was not possible to differentiate between these and secondary negative symptoms in probands. Secondary negative symptoms may result from depression, medication-induced parkinsonism, and chronicity.<sup>59-61</sup> To differentiate between these and primary negative symptoms, it would have been necessary to perform negative symptom ratings before and after treatment,<sup>60</sup> which would be impractical in a genetic-epidemiological sample such as ours. This possible confound may have decreased the effect sizes obtained in the regression analyses, although a recent study showed that while negative symptoms were associated with greater family history, the deficit syndrome was not.<sup>62</sup>

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*Corresponding author and reprints: Ayman Fanous, MD, Box 980126, Richmond, VA 23298-0126 (e-mail: ahfanous@hsc.vcu.edu).*

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