Positive and negative symptoms in families with schizophrenia

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Abstract

Positive and negative symptoms are measurable characteristics that may represent core features of schizophrenia and offer a quantitative approach for studying the genetics of schizophrenia and related disorders. The Positive and Negative Syndrome Scale (PANSS) was used to assess 72 members of five families segregating schizophrenia. The study confirmed high internal reliability of PANSS scales in this sample with diverse lifetime diagnoses. Gender but not alcoholism affected scores. Schizophrenia/schizoaffective and schizophrenia spectrum disorder groups had higher mean scores for the positive and negative scales than other lifetime diagnostic groups, consistent with genetic transmission of these symptoms. Positive and negative symptom patterns did not subtype families. The results support the validity of positive and negative symptom measures as independent dimensions in familial schizophrenia.

Keywords

Negative symptoms; Familial; Genetics; Spectrum; (Schizophrenia)

INTRODUCTION

Diagnostic boundaries pose a significant challenge in the investigation of the genetics of schizophrenia. Early studies emphasized the concept of a spectrum of disorders related to schizophrenia which appeared at a higher than expected frequency in the biological relatives of probands with schizophrenia (Gottesman and Shields, 1982). With this approach, careful diagnostic assessments can be used to assign affected status in a hierarchical manner for genetic linkage studies (Weeks et al., 1990). An alternative approach to this model is to consider the possibility that the severity of specific symptom clusters may vary in the

relatives of probands with schizophrenia. Positive and negative symptoms represent important, relatively independent, components of schizophrenia (Barnes and Liddle, 1990; McGlashan and Fenton, 1992), and a dimensional concept of these symptoms appears to have greater longitudinal stability than a categorization of the illness into positive and negative syndromes (Maurer and Hafner, 1991). Therefore, since positive and negative symptoms are measurable characteristics that may represent core features of schizophrenia, they could offer a quantitative approach for studying the genetics of schizophrenia and related disorders.

Given that these core symptoms are relatively stable traits present in premorbid and residual stages of schizophrenic illness (Barnes and Liddle, 1990; Andreasen and Flaum, 1991; McGlashan and Fenton, 1992), the degree to which they are present in an individual could reflect genetic predisposition in families where schizophrenia appears to be segregating. If so, one would predict that both positive and negative symptoms would be present in non-schizophrenic relatives of schizophrenic patients, representing genetic vulnerability or variable expression of a pathogenic gene. Although formal measurements of positive and negative symptoms in direct interviews have rarely been done in non-schizophrenic relatives, the symptoms purported to represent subthreshold pathology in family, twin and adoption studies support this (Tsuang et al., 1991). Finding significant levels of measurable symptoms in non-schizophrenic relatives would be of potential importance to genetic studies of schizophrenia and could also serve to strengthen the validity of including both of these symptom groups in the diagnosis of schizophrenia (Robins and Guze, 1970).

There is substantial evidence that positive and negative symptoms can be reliably measured in schizophrenia, using instruments such as the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) or the Scale for the Assessment of Negative Symptoms (SANS) and Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen and Olsen, 1982). There is also significant support for validity of the measures (Andreasen and Flaum, 1991) and a high correlation between instruments that assess symptoms dimensionally (Fenton and McGlashan, 1992). In the acute stages of illness both positive and negative symptoms fluctuate and are responsive to treatment. In sub-chronic and later stages of illness, negative symptoms, and to a lesser extent positive symptoms, are relatively stable over time, and are predictive of medium-term and longer-term outcome in schizophrenia (McGlashan and Fenton, 1992). The few studies that have examined unrelated non-schizophrenic individuals for positive and negative symptoms have found preliminary evidence that negative symptoms are not strongly associated with diagnoses other than schizophrenia (Pogue-Geile and Harrow, 1984; Mundt et al., 1989; Lewine, 1990).

The present study investigated the presence of positive and negative symptoms in a sample of five families ascertained for genetic linkage studies of schizophrenia. Within the sample subjects carried a range of lifetime psychiatric diagnoses. The PANSS was selected as an instrument on the basis of its sound psychometric properties for rating symptoms dimensionally in schizophrenic samples (Kay, 1990a; 1990b). The psychometric properties of the PANSS in families with schizophrenia were compared to published data for schizophrenia alone. Because there has been some question as to whether familial schizophrenia is different from non-familial schizophrenia (e.g. Lewis et al., 1987), the

pattern of positive and negative symptoms in familial schizophrenia was compared to that available from a previously reported schizophrenia sample. The main scientific question of the study was then addressed: Are family members' symptom patterns compatible with the hypothesis that positive and negative symptoms are quantitative measures of genetic vulnerability to schizophrenia? Schizophrenic subjects were predicted to have positive and negative symptoms to a greater degree than individuals with schizophrenia spectrum disorders, who in turn were predicted to have these symptoms to a greater extent than relatives who belonged to neither of these two diagnostic groups. A related hypothesis was that predominantly positive or negative symptom patterns, perhaps representing genetic homogeneity, might differ between families and serve as a possible means of subtyping familial schizophrenia.

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 PANSS assessment ($n = 75$). Local psychiatrists identified prospective pedigrees segregating schizophrenia. Families were selected for enrolment in the study if they had an extended family of two or more generations of adults, with a proband and at least one other relative having a diagnosis of chronic schizophrenia by DSM-III-R (American Psychiatric Association, 1987) criteria. Families with predominant bipolar affective disorder, known organic or physical disturbances causing major psychiatric illnesses, or bilineal schizophrenic illness (segregating down maternal and paternal sides) were excluded. The proband's first and second degree relatives were recruited first, and pedigrees were extended outward from these subjects, collecting each nuclear family branch if it contained a member with schizophrenia or schizoaffective disorder, after applying exclusion criteria. Ten family members refused to be interviewed.

After obtaining written informed consent, subjects had diagnostic assessments using the Structured Clinical Interviews for DSM-III-R: the Patient Edition (SCID-P) for Axis I which was selected over other editions for greater coverage of psychotic symptoms, and Personality Disorders (SCID-II) for Axis II (Spitzer et al., 1990a; 1990b). These instruments were modified to increase data obtained, the SCID-P to include data on the course of illness, long term functioning, additional psychotic symptoms, personal history and medical history, and the SCID-II to include supplemental information on schizophrenia spectrum disorders. A complete mental status examination including assessment of abstract thinking and Mini-Mental State Examination (Folstein et al., 1975) was also completed on each subject. A psychiatrist (ASB) participated in all diagnostic assessments and, immediately following, rated each subject using the PANSS (Kay et al., 1987). The diagnostic assessments took on average three hours to complete, incorporating the essential elements of the 45 minute interview recommended for the PANSS (Kay et al., 1987). PANSS assessments for this study were completed when subjects were in remission from acute psychiatric illnesses, such as major depression, or in stable states of chronic illnesses such as schizophrenia, with no change in level of functioning and/or medication dosage in the previous three months or longer.

Collateral (family history) information was obtained for each subject and medical records were collected for all subjects with a history of psychiatric hospitalization or other treatment. Diagnostic folders containing all available clinical information were reviewed first by the interviewing psychiatrist then by an independent psychiatrist (WGH) who was blind to the pedigree structure. 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) (Endicott, 1988).

Seventy-five subjects had a PANSS administered. Data from three male subjects were excluded from the analyses. One of the excluded subjects had dementia and another had pervasive developmental disorder at the time of assessment. One severely impaired subject with chronic schizophrenia was excluded because he had evidence on CT scan of an old infarction in the left parietal region that could cause a neglect syndrome. The sample for the current study therefore consisted of 72 subjects. These subjects, on the basis of DSM-III-R lifetime diagnoses, were divided into three groups based on a proposed diagnostic hierarchy for genetic studies (Weeks et al., 1990) and sample size considerations. Schizophrenia ($n = 15$) and schizoaffective disorders ($n = 7$) were combined in a schizophrenia/schizoaffective group (total $n = 22$), representing 30.6% of the total sample. Psychosis not otherwise specified ($n = 5$) and schizotypal ($n = 3$) and paranoid ($n = 1$) personality disorders were combined in a schizophrenia spectrum disorders group (total $n = 9$), 12.5% of the sample. The remaining 41 subjects (56.9%) comprised the 'other' group, with three sub-groups based on lifetime diagnoses. Alcohol abuse and alcohol dependence without other psychiatric conditions (total $n = 5$) made up an alcoholism subgroup. Major depression with psychosis ($n = 1$) and without psychosis ($n = 16$) formed a major depression sub-group (total $n = 17$). None of the subjects had a bipolar disorder. Subjects with no major psychiatric disorder (total $n = 19$) constituted the third sub-group. Ongoing follow-up resulted in a rediagnosis for three of the 72 subjects during the course of the study. This involved new PANSS and diagnostic assessments, with the new diagnosis taking the complete longitudinal history into account.

Subjects with both a major psychiatric disorder and a substance abuse or dependence disorder were assigned to the group appropriate for the major psychiatric disorder since the latter illnesses were generally more severe and persistent than the substance abuse. However, the effects of substance abuse were also analyzed as a comorbid condition, after excluding subjects with no major disorder ($n = 19$) or alcohol use disorder only ($n = 5$). Of the remaining 48 subjects, 22 had lifetime comorbid alcoholism, three with current diagnoses at the time of assessment. Drug abuse/dependence was not examined separately because there were few subjects with lifetime drug use disorders and these always occurred with alcoholism.

Individual items on the positive, negative and general psychopathology PANSS scales were summed to give total scores for each of the three scales. This dimensional scoring method served to maximize statistical power. Diagnostic group assignment was used for all analyses except those directly comparing psychometric properties of the PANSS to the results of Kay et al. (1987), the scale's developers. For the latter comparisons, data from the 15 subjects with schizophrenia from the current sample were used. Parametric statistical methods,

including both zero order and partial correlations and analysis of variance (ANOVA), were applied.

RESULTS

Demographic and clinical characteristics of the sample are presented in Table 1. There were 31 males (43.1%) and 41 females (56.9%) distributed across the five lifetime diagnostic categories. Males and females were equally represented in the schizophrenia/schizoaffective group. Females made up two thirds of the no major disorder sub-group and over 80% of the major depression sub-group. Males were the majority in the spectrum group and were the only subjects in the alcoholism subgroup. Subjects ranged from 18 to 84 years of age, with no difference in mean age between males and females. Females were more likely to be married (51.2%) and males more likely to be never married (41.9%). Thirty-three subjects had completed grade eight or less (45.8%); relatively few had any post secondary education (11.4%). The mean length of stay for each hospitalization was 7.9 weeks for the schizophrenia/schizoaffective group. The high mean duration of illness for spectrum disorders may be explained by the relatively older mean age of this group and the assumption that personality disorders had onset at age 18. Slightly more than one third of the sample had a history of ever having alcohol abuse or dependence, with males being two and one half times more likely than females to have a lifetime diagnosis of a substance use disorder. However, only three subjects had active substance use disorders at the time of assessment.

For the schizophrenia-only group ($n = 15$), internal reliability measures of the individual PANSS scales (positive, negative and general psychopathology (GP)), assessed by Cronbach's coefficient alpha, were comparable to those obtained by the scale's developers (Kay et al., 1987) (Table 2). High internal reliability was maintained when the entire sample ($n = 72$) was used (Cronbach's coefficient alpha values of 0.83, 0.81 and 0.81 for positive, negative and GP respectively), and the scale scores were approximately normally distributed without substantial skewness or kurtosis. Comparing PANSS scores with those published by Kay et al. (1987), there were no significant differences in means or standard deviations of the scores between the present (familial) schizophrenia-only sample and the 101 schizophrenic subjects of Kay et al. (Table 2).

Zero order correlation coefficients between individual PANSS scales for the total sample of 72 subjects were similar to those of Kay et al. (1987) for schizophrenia alone. Both the positive and the negative scales correlated significantly with GP ($r = 0.60$, $p < 0.001$; $r = 0.71$, $p < 0.001$, respectively). For the present total sample positive and negative scores were significantly correlated ($r = 0.53$, $p < 0.001$). However, there was no significant correlation between positive and negative scales when shared variance with general psychopathology was excluded ($r_{12.3} = -0.18$, $F = 2.31$, $df = 1, 69$, $p > 0.05$). In the present schizophrenia-only sample ($n = 15$) none of the three scales were significantly correlated with each other (positive with GP, $r = 0.23$; negative with GP, $r = 0.35$; positive with negative, $r = -0.11$).

Mean values for each of the three PANSS scales showed moderate variability across lifetime diagnostic groups (Table 3). The highest mean scores for negative symptoms and GP were in

the schizophrenia/schizoaffective group. Of interest, the individual with schizophrenia and a parietal lobe infarction, who was excluded from the analysis, had the single highest negative symptom score (47). The schizophrenia/schizoaffective and spectrum groups had comparably high scores for positive symptoms. Because the subject families appear to have autosomal dominant-like transmission of schizophrenia, we examined results for the obligate carriers - individuals who had offspring and other first degree relatives with schizophrenia but who did not have the disorder themselves. There were five obligate carriers from four of the families, who had a mean score for positive symptoms of 12.0 (SD 4.2) and for negative symptoms 16.4 (SD 5.5). Individual scores (positive, negative) for the three men were: 8, 9; 8, 18; 14, 17; and for the two women: 12, 14; 18, 24. Only one had a lifetime diagnosis of a schizophrenia spectrum disorder.

Differences in mean PANSS scores from each of the three scales were highly significant across diagnostic categories. Mean comparisons (Table 3) indicated that both the schizophrenia/schizoaffective and spectrum groups were significantly greater than the 'other' group for all scales. Mean negative and GP scores for the schizophrenia/schizoaffective group were significantly higher than the spectrum group. Interestingly, the negative scale mean for the alcoholism sub-group was very similar to those for the schizophrenia/schizoaffective and spectrum groups. Belonging to a particular family did not influence symptom patterns (Table 4).

There is some evidence in schizophrenia for effects of gender on negative symptoms (Bardenstein and McGlashan, 1990) and substance use on psychotic symptoms (Cleghorn et al., 1991; Tien and Anthony, 1990). One-way analysis of variance (ANOVA), including correction for multiple tests of significance with the Student-Newman-Keuls procedure, was used to assess the influence of gender and comorbidity with alcoholism on the three PANSS scales (Table 4) in the current sample. Significant gender differences were noted for positive and negative symptoms with male subjects having higher scores for both scales. For the positive scale the results were: males mean = 14.39, SD = 6.3; females mean = 11.88, SD = 4.0; $F = 4.27$, $df = 71$, $p = 0.04$. For the negative scale the results were: males mean = 15.97, SD = 5.5; females mean = 12.37, SD = 4.4; $F = 9.49$, $df = 71$, $p < 0.003$. No significant differences were found between male and female subjects in the overall sample for GP. Because significant gender effects were found on positive and negative symptoms, we examined the interaction of gender by diagnostic category but found no significant interaction. However, the statistical power of this test was reduced because of the unequal distribution of men and women in the diagnostic groups other than schizophrenia/schizoaffective. Men in the schizophrenia/schizoaffective group ($n = 11$, mean = 20.3, SD 5.9) had a somewhat higher mean score for the negative scale than women ($n = 11$, mean = 16.1, SD 3.7) ($p = 0.06$). There were no significant gender differences in schizophrenia/schizoaffective subjects for either the positive or GP scales.

A lifetime diagnosis of alcoholism was associated with increased GP scores but did not affect positive or negative symptoms scores. Although the mean age of the sample was older than most, there was no significant difference in age across diagnostic categories, as assessed by one way ANOVA ($F = 1.41$, $p = 0.240$) and no correlation between age at PANSS administration and positive ($r = 0.05$), negative ($r = -0.04$) or GP ($r = -0.14$) scores.

Neuroleptic use may have had some effect on PANSS negative scale results, since mean scores for the schizophrenia/schizoaffective group subjects, most of whom were taking neuroleptics at the time of assessment, were higher than those for the subjects in the spectrum groups, who were not on anti-psychotics.

DISCUSSION

The current study found that the instrument selected (PANSS) to measure positive and negative symptoms maintained its robust psychometric properties for family members with diverse diagnoses, and that the pattern of symptoms in familial schizophrenia was comparable to that for general schizophrenia. Turning to the central scientific question of the present investigation, relatives' symptom patterns were found to be compatible with the hypothesis that positive and negative symptoms are related to genetic predisposition. The principal findings, potential limitations, and conclusions of the study will be discussed in turn.

Psychometric properties of the PANSS

This study has shown that the psychometric properties of the PANSS were equally robust in subjects with diverse diagnoses from families where schizophrenia was segregating, as for a sample of subjects with schizophrenia alone (Kay et al., 1987). Each scale displayed high internal reliability with individual scale items contributing homogeneously to the scale coefficient alpha. The high alpha values also provide confidence in the additivity of the individual items of the scales and support the use of summary measures for both positive and negative symptoms and general psychopathology. Significant correlations of both positive and negative scales with general psychopathology scores in the sample as a whole indicated the scores on these two symptom scales were directly related to severity of illness. This finding offers support for the construct validity of the PANSS.

Familial schizophrenia

One of the striking findings of this study was the similarity in results between a rural, community based sample of familial schizophrenia in families of Celtic origin compared to the mixed sample of schizophrenic patients reported in Kay et al. (1987). The latter study included subjects both with and without a family history of psychosis, ascertained from a chronically hospitalized, urban population of various racial backgrounds. Kay (1990b) proposed that studies in a community based sample might have a different symptom profile from a hospitalized population, however results from the current study do not support this. Kay et al. (1987) suggested earlier that high negative symptom ratings were more closely associated with a family history of psychosis than were positive symptoms. Mean negative scale values using the familial sample in the present study were actually slightly, but not significantly, lower than those found by Kay et al. (1987). However, this could have been because the current schizophrenia sample was 53% female compared to 31% in the Kay et al. (1987) study.

Positive and negative symptoms in relatives

The finding that schizophrenia/schizoaffective and schizophrenia spectrum groups had higher mean scores for the positive and negative scales than the 'other' diagnostic group supports the hypothesis that these scales may be measuring genetic predisposition. The negative symptom results confirmed the prediction that symptoms should be highest in the schizophrenia/schizoaffective group, next highest in the spectrum and lowest in the other group. The observation that positive symptoms were no different in schizophrenia/schizoaffective and spectrum disorders suggests that positive symptoms may not distinguish individuals at greater genetic risk in precisely the same manner as negative symptoms, if genetic risk is on a continuum. However, there were individual subjects with other lifetime diagnoses who had high levels of positive and/or negative symptoms. Given that these sub-syndromal individuals are in families where schizophrenia is segregating, the results suggest the possibility that in some cases measurements of positive and negative symptoms may be more sensitive than current diagnostic classification to genetic influences in schizophrenia. Firm conclusions are impossible given the small number of subjects who would be obligate carriers assuming autosomal dominant transmission. However, the results for other subjects are consistent with genetic relatedness of negative and, to a lesser degree, positive symptoms in the subject families. This provides contributory familial evidence for the validity of both positive and negative symptoms in schizophrenia.

Although some studies suggest negative symptoms are more indicative of genetic influences than diagnostic classifications emphasizing positive symptoms (Dworkin and Lenzenweger, 1983; 1984), other research suggests both types of symptoms are important. Dworkin et al. (1991) recently reported that adolescent subjects at genetic risk for schizophrenia had greater positive and negative symptoms than normal subjects and adolescents at risk for mood disorders. They suggested higher levels of both symptom types may be specific to individuals at risk for schizophrenia. However, a study comparing first degree relatives of schizophrenic probands to first degree relatives of depressed probands found, in a preliminary logistic regression analysis, that negative but not positive symptom scores discriminated the two groups of relatives (Tsuang et al., 1991). Consistent with other studies involving schizophrenic subjects (reviewed by Barnes and Liddle, 1990 and McGlashan and Fenton, 1992), there was a lack of correlation between positive and negative scale ratings in the current study of mixed diagnoses (after taking into account severity as measured by general psychopathology) which indicates positive and negative symptoms are independent or semi-independent dimensions in familial schizophrenia. Both are therefore potentially useful as continuous measures for genetic studies.

Studies quantifying positive and negative symptoms in dimensional analyses are in contrast to studies designed to subtype probands into positive or negative syndromes. Interestingly, a study of concordance rates in monozygotic (MZ) and dizygotic (DZ) twins that sought to maximize the MZ/DZ ratio, in order to obtain the most 'genetic' definition of schizophrenia, found the ratio to be maximized in the mixed type subjects with both positive and negative symptoms (McGuffin et al., 1987). More recently, using family data, McGuffin et al. (1991) reported that probands with both positive and negative symptoms tended to have more affected relatives than probands with only positive symptoms.

Sub typing

With respect to subtyping, or identifying clinical homogeneity, that could indicate underlying genetic homogeneity, the current study found no differences between families using PANSS scores. This could be due to underlying genetic homogeneity in the current sample, especially given the subject families' similar ethnic origins, or insufficient sensitivity of the instrument to detect differences. However, the finding is also consistent with genetic heterogeneity that is not reflected in positive and negative symptom differences between families. McGuffin et al. (1991) have some preliminary evidence indicating that positive and negative symptoms fail to sub-classify schizophrenia. Using family data and testing a liability/threshold model, they found that the favoured model was one in which positive and mixed positive/negative forms of schizophrenia differed quantitatively along the same continuum of liability, with the positive symptom form less severe than the mixed form. They stated the results were 'suggestive of quantitative rather than qualitative differences'. However, analyses using larger, more diverse samples, or examining other categorical symptom clusters, such as Liddle's (1987) three syndromes or the deficit syndrome (Carpenter et al., 1988), may prove to be more sensitive for subtyping.

Limitations

Any conclusions from this study, however, must take its limitations into account. First, PANSS ratings are cross-sectional and therefore may reflect the state of an individual, rather than enduring traits. As previously noted, in the non-acute stages of schizophrenia the stability of these symptoms suggests they are trait phenomena. However, how these symptoms behave longitudinally in non-schizophrenic disorders is unknown. There may be significant fluctuations in individuals on a day to day basis. One might expect these to be most pronounced in acute illness episodes. We attempted to minimize these potential effects by examining subjects in non-acute, relatively stable states, for all lifetime diagnoses.

Second, families were selected on the willingness of most family members to participate in the study, using inclusion criteria that attempted to optimize genetic influences. Even so, ten family members refused to be interviewed. There could therefore have been ascertainment biases with unforeseen effects on the results. As well, there was a possibility of rater bias because the diagnostic interviews and PANSS assessments were usually done simultaneously. This possibility was minimized by the specific anchor points used to rate each PANSS item. Also, although the mean age of the subjects was 49.9 years, the youngest subject was 18 years old and several others were still within the age of risk for developing schizophrenia. Lifetime diagnoses may therefore be expected to change for some individuals with time. Symptoms observed may have been prodromal or premorbid to psychotic illnesses, although genetic risk reflected by positive and negative symptoms could presumably still be identified on cross-sectional assessment. However, longitudinal follow-up remains essential.

Possible confounding factors

Consistent with some studies (Kay et al., 1987; Haas et al., 1989; Ring et al., 1991), but not others (Andreasen and Olsen, 1982; Pogue-Geile and Harrow, 1984; Lewine, 1985; Dworkin, 1990), men with schizophrenia tended to have higher mean negative symptom

scores than women. Some investigators have suggested the lower negative symptoms in female subjects could be due to social or biological factors common to women, while others have proposed etiological or mechanistic factors relating to schizophrenia as an illness (Goldstein and Tsuang, 1990). Unfortunately, the current study does not allow testing of these possibilities, which are of interest for future investigations.

Possibly because of the low rate of current alcohol problems, a lifetime history of alcohol abuse or dependence comorbid with other psychiatric illness did not affect positive or negative symptom ratings. However, results from the present study suggest that men with alcoholism alone who belong to families where schizophrenia is segregating have negative symptom levels comparable to individuals with schizophrenia spectrum disorders. More definitive conclusions regarding this intriguing finding will await larger sample sizes.

Other than gender and comorbid alcoholism, possible factors that could confound PANSS results are age and neuroleptic effects. The mean age of the present sample was older than most (49.9 years). However, consistent with others' findings summarized by McGlashan and Fenton (1992), age had no apparent effect on positive and negative symptom ratings. Data from the current study are not comparable to studies examining the effects of neuroleptics on symptom profiles. However, the comparatively high scores for negative symptoms in the mainly neuroleptic-free alcoholism and spectrum diagnostic groups indicated neuroleptic side effects likely did not play a major role in negative symptom generation, consistent with some previous reports (Barnes and Liddle, 1990). The high positive symptom ratings in the spectrum group suggest these untreated individuals have productive symptoms to approximately the same degree as individuals with schizophrenia whose symptoms are treated. The failure to find effects of age could have been due to insufficient sensitivity of the PANSS to detect differences. However, the instrument was sensitive enough to show effects of gender, and the PANSS, like the SANS, is widely considered to be a useful instrument because of its sensitivity (McGlashan and Fenton, 1992).

Conclusions

The results of the present study indicate that quantitative ratings of positive and negative symptoms might be used as continuous phenotypic variables for genetic studies of schizophrenia. This may be particularly important for identifying individuals who carry a schizophrenia gene but do not have the full schizophrenic syndrome. A much larger familial sample and studies in normal controls would be necessary to determine if it would be possible to estimate threshold values that could indicate probability of gene carrier status. These results may be compared with those recently found by researchers using psychophysiological measures such as P300 auditory evoked electroencephalographic responses (AER) and smooth pursuit eye movement measurements (SPEM) (Blackwood et al., 1991; Clementz et al., 1992). There is evidence that these measures, which have the advantage of being state independent, may differentiate families and/or indicate subsyndromal forms of genetic vulnerability. Future studies examining the convergence of both positive/negative symptom approaches and psychophysiological measures would be of interest.

If positive and negative symptoms were to become useful as quantitative traits for genetic studies, several parameters would need to be considered. Results from this study suggest that gender differences may need to be taken into account for negative symptom ratings since men tended to have higher scores than women, although this needs to be confirmed. This is consistent with findings for other quantitative genetic traits which appear to have important gender differences. For example, a recent report found gender specific genotype effects on cholesterol levels (Reilly et al., 1991). Besides gender, there is a likelihood of some change in symptom levels with clinical state, making examination during remission, or in a chronic stable state, prudent. A final caveat is that subjects should be evaluated comprehensively to exclude conditions, such as cerebral infarction, which could influence positive and negative symptom ratings independent of a psychiatric illness.

Further research is essential to replicate the results of this study. Alternatives to positive and negative symptom delineations are also gaining prominence and should be similarly examined in familial samples. Several researchers using factor analytic approaches have suggested novel regroupings of individual symptom scores in schizophrenia (Bilder et al., 1985; Liddle, 1987; Kay, 1990b). Of note, Liddle et al. (1992) have some evidence from imaging studies that their three syndromes, which include specific positive and negative symptom clusters as well as a disorganization (thought disorder and inappropriate affect) symptom cluster, may be related to pathophysiology in schizophrenia. Analyses using such alternative symptom groupings may prove to be more sensitive than positive and negative symptoms for quantitative trait studies, and perhaps subtyping. However, until there is more evidence that other factors better reflect the mechanism of illness, positive and negative symptoms remain useful clinical and research concepts. If future studies confirm that positive and negative symptom scores appear familial, ratings of these symptoms may become important quantitative traits in alternative strategies for genetic studies of schizophrenia.

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References

- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. APA Press; Washington: 1987.
- Andreasen NC, Flaum M. Schizophrenia: the characteristic symptoms. *Schizophr Bull.* 1991; 17:27–49. [PubMed: 2047788]
- Andreasen NC, Olsen S. Negative and positive schizophrenia: definition and validation. *Arch Gen Psychiatry.* 1982; 39:789–794. [PubMed: 7165478]
- Bardenstein KK, McGlashan TH. Gender differences in affective, schizoaffective, and schizophrenic disorders: a review. *Schizophr Res.* 1990; 3:159–172. [PubMed: 2278981]
- Barnes, TRE., Liddle, PF. Evidence for the validity of negative symptoms. In: Andreasen, NC., editor. *Modern Problems of Pharmacopsychiatry, ., Schizophrenia: Positive and Negative Symptoms and Syndromes.* Vol. 24. Karger; Basel: 1990. p. 43-72.

- Bilder RM, Mukherjee S, Rieder RO, Pandurangi AK. Symptomatic and neuropsychological components of defect states. *Schizophr Bull.* 1985; 11:409–419. [PubMed: 4035304]
- Blackwood DHR, St Clair DM, Muir WJ, Duffy JC. Auditory P300 and eye tracking dysfunction in schizophrenic pedigrees. *Arch Gen Psychiatry.* 1991; 48:899–909. [PubMed: 1929759]
- Carpenter WT, Heinrichs DW, Wagman AMI. Deficit and nondeficit forms of schizophrenia: the concept. *Am J Psychiatry.* 1988; 145:578–583. [PubMed: 3358462]
- Cleghorn JM, Kaplan RD, Szechtman B, Szechtman H, Brown GM. Substance abuse and schizophrenia: effect on symptoms but not on neurocognitive function. *J Clin Psychiatry.* 1991; 52:26–30.
- Clementz BA, Grove WM, Iacono WG. Smooth-pursuit eye movement dysfunction and liability for schizophrenia: implications for genetic modelling. *J Abnorm Psychol.* 1992; 101:117–129. [PubMed: 1537958]
- Dworkin RH. Patterns of sex differences in negative symptoms and social functioning consistent with separate dimensions of schizophrenic psychopathology. *Am J Psychiatry.* 1990; 147:347–349. [PubMed: 2309954]
- Dworkin RH, Lenzenweger MF. DSM-III and the genetics of schizophrenia. *Am J Psychiatry.* 1983; 140:646.
- Dworkin RH, Lenzenweger MF. Symptoms and the genetics of schizophrenia: implications for diagnosis. *Am J Psychiatry.* 1984; 141:1541–1546. [PubMed: 6542318]
- Dworkin RH, Bernstein G, Kaplansky LM, Lipsitz JD, Rinaldi A, Slater SL, Cornblatt BA, Erlenmeyer-Kimling L. Social competence and positive and negative symptoms: a longitudinal study of children and adolescents at risk for schizophrenia and affective disorder. *Am J Psychiatry.* 1991; 148:1182–1188. [PubMed: 1882996]
- Endicott, J. Best Estimate Clinical Evaluation and Diagnosis Form (BECED). Department of Research Assessment and Training, New York State Psychiatric Institute; New York, NY: 1988.
- Fenton WS, McGlashan TH. Testing systems for assessment of negative symptoms in schizophrenia. *Arch Gen Psychiatry.* 1992; 49:179–184. [PubMed: 1567273]
- Folstein MF, Folstein SE, McHugh PR. 'Mini-Mental State': a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975; 12:189–198. [PubMed: 1202204]
- Goldstein JM, Tsuang MT. Gender and schizophrenia: an introduction and synthesis of findings. *Schizophr Bull.* 1990; 16:179–183. [PubMed: 2374879]
- Gottesman, IL., Shields, J. Schizophrenia: The Epigenetic Puzzle. Cambridge UP: Cambridge; 1982.
- Haas G, Hien D, Waked W, Sweeney J, Weiden P, Frances A. Sex differences in schizophrenia. *Schizophr Res.* 1989; 2:11.
- Kay SR. Positive-negative symptom assessment in schizophrenia: psychometric issues and scale comparison. *Psychiatr Quar.* 1990a; 61:163–178.
- Kay SR. Significance of the positive-negative distinction in schizophrenia. *Schizophr Bull.* 1990b; 16:635–652. [PubMed: 2077641]
- Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull.* 1987; 13:61–276.
- Lewine R. Schizophrenia: an amotivational syndrome in men. *Can J Psychiatry.* 1985; 30:316–318. [PubMed: 3896452]
- Lewine RRJ. A discriminant validity study of negative symptoms with a special focus on depression and antipsychotic medication. *Am J Psychiatry.* 1990; 147:1463–1466. [PubMed: 1977328]
- Lewis SW, Reveley AM, Reveley MA, Chitkara B, Murray RM. The familial/sporadic distinction as a strategy in schizophrenia research. *Br J Psychiatry.* 1987; 151:306–313. [PubMed: 3322466]
- Liddle PF. The symptoms of chronic schizophrenia: a re-examination of the positive-negative dichotomy. *Br J Psychiatry.* 1987; 151:145–151. [PubMed: 3690102]
- Liddle PF, Friston KJ, Frith CD, Hirsch SR, Frackowiak RSJ. Patterns of cerebral blood flow in schizophrenia. *Br J Psychiatry.* 1992; 160:179–186. [PubMed: 1540757]
- McGlashan TH, Fenton WS. The positive-negative distinction in schizophrenia: review of natural history validators. *Arch Gen Psychiatry.* 1992; 49:63–72. [PubMed: 1728252]

- McGuffin P, Farmer A, Gottesman II. Is there really a split in schizophrenia? The genetic evidence. *Br J Psychiatry*. 1987; 150:581–592. [PubMed: 3307978]
- McGuffin, P., Harvey, M., Williams, M. The positive/negative dichotomy: does it make sense from the perspective of the genetic researcher?. In: Marneros, A.Andreasen, NC., Tsuang, MT., editors. *Negative Versus Positive Schizophrenia*. Springer-Verlag; Berlin: 1991. p. 250-264.
- Maurer, K., Hafner, H. Dependence, independence or interdependence of positive and negative symptoms. In: Marneros, A.Andreasen, NC., Tsuang, MT., editors. *Negative Versus Positive Schizophrenia*. Springer-Verlag; Berlin: 1991. p. 160-182.
- Mundt C, Kaspar S, Huerkamp M. The diagnostic specificity of negative symptoms and their psychopathological context. *Br J Psychiatry*. 1989; 155(suppl 7):32–36.
- Ott J. Linkage analysis with misclassification at one locus. *Clin Gen*. 1977; 12:119–124.
- Pogue-Geile MF, Harrow M. Negative and positive symptoms in schizophrenia and depression: a followup. *Schizophr Bull*. 1984; 10:371–387. [PubMed: 6474100]
- Reilly SL, Ferrell RE, Kottke BA, Kamboh MI, Sing CF. The gender specific apolipoprotein E genotype influence on the distribution of lipids and apolipoproteins in the population of Rochester, N.M. I. Pleiotropic effects on means and variances. *Am J Hum Gen*. 1991; 49:1155–1166.
- Ring N, Tantam D, Montague L, Morris J. Negative symptoms in chronic schizophrenia: relationship to duration of illness. *Br J Psychiatry*. 1991; 159:495–499. [PubMed: 1751858]
- Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness: Its application to schizophrenia. *Am J Psychiatry*. 1970; 126:107–111.
- Spitzer, RL., Williams, JBW., Gibbon, M., First, MB. *Structured Clinical Interview for DSM-III-R-Patient Edition (SCID-P, Version 1.0)*. American Psychiatric Press; Washington, D.C: 1990a.
- Spitzer, RL., Williams, JBW., Gibbon, M., First, MB. *Structured Clinical Interview for DSM-III-R-Personality Disorders (SCID-II, Version 1.0)*. American Psychiatric Press; Washington, D.C: 1990b.
- Tien AY, Anthony JC. Epidemiological analysis of alcohol and drug use as risk factors for psychotic experiences. *J Nerv Ment Dis*. 1990; 178:473–480. [PubMed: 2380692]
- Tsuang, MT., Gilbertson, MW., Faraone, SV. Genetic transmission of negative and positive symptoms in the biological relatives of schizophrenics. In: Marneros, A.Andreasen, NC., Tsuang, MT., editors. *Negative Versus Positive Schizophrenia*. Springer-Verlag; Berlin: 1991. p. 265-291.
- Weeks DE, Brzustowicz L, Squires-Wheeler E, et al. Report of a workshop on genetic linkage studies in schizophrenia. *Schizophr Bull*. 1990; 16:673–686. [PubMed: 2077644]

TABLE 1

Characteristics of 72 subjects from five families

Lifetime diagnostic group	Male		Female		Age (years)			Married			Duration of illness (years)			Number of admissions		On neuro-leptics		Lifetime comorbidity with alcoholism	
	n	%	n	%	Mean	SD	n	%	n	%	Mean	SD	Mean	SD	n	%	n	%	
Schizophrenia/schizoaffective disorders (<i>n</i> = 22)	11	50.0	11	50.0	43.9	14.8	4	18.2			18.4	13.2	9.7	9.1	16	72.7	13	59.1	
Schizophrenia spectrum disorders (<i>n</i> = 9)	5	55.6	4	44.4	55.8	17.0	3	33.3			27.1	23.4	4.0	9.9	1	11.1	3	33.3	
Other (<i>n</i> = 41)	14	34.1	27	65.9	51.7	17.4	26	63.4			5.3	8.4	0.05	0.2	0	0	-	-	
Alcoholism (<i>n</i> = 5)	5	100	0	0	48.4	19.7	3	60.0			15.3	12.1	0	0	0	0	0	0	
Major depression (<i>n</i> = 17)	3	17.6	14	82.4	49.3	16.1	12	70.6			3.2	5.6	0.1	0.3	0	0	6	35.3	
No major disorder (<i>n</i> = 19)	6	31.6	13	68.4	54.9	18.4	11	57.9			0	0	0	0	0	0	0	0	

TABLE 2
Positive and Negative Syndrome Scale results for schizophrenia compared to published results from Kay et al. (1987)

PANSS scale	Mean ^a	SD	Median	Range	Alpha
Positive (7 items)					
Current study (<i>n</i> = 15)	16.73	4.23	18	9–26	0.70
Kay et al. (1987) (<i>n</i> = 101)	18.20	6.08	18	7–32	0.73
Negative (7 items)					
Current study (<i>n</i> = 15)	16.87	4.57	17	11–26	0.65
Kay et al. (1987) (<i>n</i> = 101)	21.01	6.17	20	8–38	0.83
General psychopathology (GP) (16 items)					
Current study (<i>n</i> = 15)	33.93	6.46	33	25–54	0.64
Kay et al. (1987) (<i>n</i> = 101)	37.74	9.49	36	19–63	0.79

^aMeans for each scale did not differ significantly ($p > 0.05$) between the two studies. The t -values for the scales were as follows: $t = 0.250$ (positive), $t = 0.691$ (negative) and $t = 0.415$ (GP).

TABLE 3

Positive and Negative Syndrome Scale scores across diagnostic groups

Lifetime diagnostic group	Positive scale			Negative scale			General psychopathology scale		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Schizophrenia/schizoaffective disorders (<i>n</i> = 22)	16.96 ^c	5.2	9–28	18.18 ^{bc}	5.3	11–30	35.96 ^{bc}	7.8	25–54
Schizophrenia spectrum disorders (<i>n</i> = 9)	17.44 ^c	5.1	9–25	14.78 ^{ac}	4.4	8–24	30.78 ^{ac}	7.1	20–44
Other (<i>n</i> = 41)	9.82 ^{ab}	2.4	7–15	11.40 ^{ab}	3.6	7–22	24.12 ^{ab}	4.9	16–36
Alcoholism (<i>n</i> = 5)	9.80	3.1	7–14	15.60	4.0	12–22	23.20	4.6	16–28
Major depression (<i>n</i> = 17)	9.53	1.6	7–12	10.71	2.9	7–18	26.06	4.7	19–36
No major disorder (<i>n</i> = 19)	10.10	2.7	7–15	11.00	3.5	7–19	22.63	4.9	16–33
Total (<i>n</i> = 72)	12.96	5.2	7–28	13.92	5.2	7–30	28.57	8.2	16–54

^{abc} Significant differences (*p* < 0.05) in mean scores were found for groups: a = schizophrenia/schizoaffective, b = schizophrenia spectrum, c = other diagnosis (alcoholism, major depression, and no major disorder).

TABLE 4

Univariate analysis of variance of the Positive and Negative Syndrome Scale

Factor	Positive scale		Negative scale		General psychopathology scale	
	F	p ^a	F	p ^a	F	p ^a
Diagnostic group (n = 72)	32.3	< 0.0001	18.1	< 0.0001	26.7	< 0.0001
Gender (n = 72)	4.3	<0.05	9.5	0.01	2.5	NS
Comorbid alcoholism (n = 48)	1.4	NS	2.7	NS	8.6	0.01
Family membership (n = 72)	0.6	NS	0.8	NS	1.4	NS

^aThe one-way ANOVA multiple comparison procedure used was the Student-Newman-Keuls (SNK) test statistic.