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Association between changes on the Negative Symptom Assessment scale (NSA-16) and measures of functional outcome in schizophrenia

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ABSTRACT

We examined whether changes in negative symptoms, as measured by scores on the 16-item Negative Symptom Assessment scale (NSA-16), were associated with changes in functional outcome. A group of 125 stable outpatients with schizophrenia were assessed at baseline and at 6 months using the NSA-16, the Brief Psychiatric Rating Scale, and multiple measures of functional outcome. Baseline adjusted regression coefficients indicated moderate correlations between negative symptoms and functional outcomes when baseline values of both variables were controlled. Results were nearly identical when we controlled for positive symptoms. Cross-lag panel correlations and Structural Equation Modeling were used to examine whether changes in negative symptoms drove changes in functional outcomes over time. Results indicated that negative symptoms drove the changes in the Social and Occupational Functioning Scale (SOFAS) rather than the reverse. Measures of Quality of Life and measures of negative symptoms may be assessing overlapping constructs or changes in both may be driven by a third variable. Negative symptoms were unrelated over time to scores on a performance-based measure of functional capacity. This study indicates that the relationship between negative symptom change and the change in functional outcomes is complex, and points to potential issues in selection of assessments.

1. Introduction

Schizophrenia and schizoaffective disorder together have been identified as the fifth leading cause of disability world-wide (Jaeger et al., 2003). It has been estimated that the costs for treatment and loss in productivity associated with schizophrenia are as high as 60 billion dollars annually (Wyatt et al., 1995; Souêtre, 1997; Trauer et al., 1998) with approximately 46 billion dollars of this total associated with loss in productivity (Jaeger et al., 2003). Multiple domains of functional outcome are impaired for individuals with schizophrenia including performance of independent living skills, social functioning, and occupational/educational performance and attainment (Sharma and Antonova, 2003) Most patients require some public funding for support, and only 10 to 20% of patients are able to sustain full- or part-time competitive employment (Anthony and Blanch, 1987; Mueser et al., 2001; McGurk and Mueser, 2004). Improving functional outcomes for this group of individuals is a significant mental health priority.

While medication treatments are effective in improving the positive symptoms of schizophrenia, functional outcomes remain poor for those with schizophrenia compared with the general population (Sharma and Antonova, 2003; McGurk and Mueser, 2004). In contrast to the positive symptoms of the illness, negative symptoms are more difficult to treat and often persist long after positive symptoms have resolved or been substantially reduced. Significantly, negative symptoms have been found to be more predictive of concurrent and future functioning in the community than positive symptoms (Mueser et al., 1990; Breier et al., 1991; Velligan et al., 1997; Ho et al., 1998; Milev et al., 2005). In some studies, many cross-sectional in nature, cognition has been found to be a stronger predictor of functional outcome than negative symptoms (Green, 1996; Velligan et al., 1997; Puig et al., 2008). However, in a study of first episode patients followed for 7 years, negative symptoms predicted the majority of the variance in functional outcome over time (Milev et al., 2005). Moreover, negative symptoms and cognition explained shared variance in functional outcome.

In this article, we examine whether change in negative symptoms over time predicts change in functional outcomes over time. If it can be established that a decrease in negative symptoms improves community outcomes, and that improvements in negative symptoms are associated with improved community functioning over and above improvements due to changes in positive symptoms, this would suggest that negative symptoms are important targets for pharmacotherapy and psychosocial treatments, and that they should be the focus of more investigative efforts. We hypothesized that

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Table 1
Means for negative symptoms and functional outcome variables at baseline and 6 months.

Variable	Baseline mean (S.D.)	6-month mean (S.D.)	Absolute value of difference score	Cohen's *D*
BPRS	8.10 (4.11)	7.49 (4.38)	0.61	0.18
NSA-16	45.94 (11.38)	44.30 (10.62)	1.6	0.18
SOFAS	44.28 (14.37)	49.02 (11.82)	4.34	0.42
QLS	59.83 (19.45)	62.20 (18.10)	2.37	0.16
FNA	22.60 (2.58)	23.06 (2.04)	0.46	0.28

improvements in negative symptoms over time would be significantly correlated with improvements in functional outcomes over time. In the present study, we explored correlations among changes in positive symptoms, negative symptoms, and functional outcomes over a 6-month period. Functional outcomes included global level of social and occupational functioning, an interview-based measure of quality of life, and a performance-based measure of functional capacity.

2. Methods

2.1. Subjects

Participants were 166 outpatients with schizophrenia or schizoaffective disorder recruited from community mental health centers for enrollment in a variety of outpatient medication and psychosocial treatment studies. Of the total subject pool, 125 received both baseline and 6-month comprehensive assessments of symptomatology and functional outcomes. Diagnoses were based upon the Structured Clinical Interview for Diagnosis (SCID) for the Diagnostic and Statistical Manual of Mental Disorders, versions III/IV (American Psychiatric Association, 1994). In addition to diagnosis, patients met the following inclusion criteria: They were 1) between the ages of 18 and 60; 2) had no documented history of mental retardation, head injury, or neurological disorder; and 3) had been residing in the community for a minimum of 3 months without a psychiatric hospitalization. Patients with a history of substance abuse or assault in the past month were excluded. Sixty-five percent of the subjects (108) were male. The mean age of subjects was 41.64 (S.D. = 8.60). On average subjects had less than a high school education ($M = 11.23$; S.D. = 3.39). Ninety-three individuals were Mexican-American (56%), 53 were Non-Hispanic White (32%), 16 (10%) were African-American, and four were Asian-American (2%). At baseline all patients were on antipsychotic medications, 66 individuals (35%) switched medications from baseline to follow-up while others remained on the same antipsychotic for the 6-month period. There were no baseline differences among subjects who dropped out of the study by 6 months and those who were retained in the study (all P's > 0.20). Mean scores for symptom and functional outcome rating scales at the baseline assessment and 3- and 6-month follow-up are presented in Table 1.

2.2. Procedures

After a complete explanation of study procedures, participants signed a consent form approved by an Institutional Review Board in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Prior to random assignment into treatment conditions for their respective studies, subjects were given a comprehensive battery that assessed symptoms and functional outcomes. In each of these studies, assessments were repeated following 6 months of treatment.

2.3. Symptom assessments

Positive symptoms were assessed using the Brief Psychiatric Rating Scale—Expanded Version (BPRS-E; Ventura et al., 1993). The BPRS is a 24-item anchored rating scale for evaluating a wide range of psychopathology on a series of Likert-type scales (1–7). Scores are based upon self-report, chart and collateral information, and observation of the subject during a structured interview. Higher scores indicate more severe symptomatology. A positive symptom factor is generated by taking a mean of items assessing hallucinations, delusions, and conceptual disorganization (Velligan et al., 2005).

Negative symptoms were assessed using the 16-item version of the Negative Symptom Assessment-16 (NSA-16; Alphs et al., 1989; Axelrod et al., 1993). The NSA-16 examines negative symptomatology including problems in communication, emotion, motivation, and sociality on a series of 7-point scales (0–6). A total negative symptom score is calculated by adding the items. Higher scores reflect more severe symptomatology. Scores on the NSA-16 were rated based upon a comprehensive semi-structured interview with the participant.

2.3.1. Functional outcome

The assessment of functional outcome in schizophrenia is complicated. Multiple instruments are available that utilize different methodological approaches. These measures can be classified into global or summary assessments, self-report measures, interviewer-rated measures that are commonly based upon self report, observer or caregiver ratings, and performance-based tests of capacity. In a recent review, McKibbin et al. (2004) articulate the problems with each methodology. In an effort to characterize community outcome broadly utilizing a variety of methods to compensate for problems with any one strategy, we included a summary or global measure, an interview-rated measure based on the participant's report, and a performance-based measure. Global level of functional outcome was assessed using the Social and Occupational Functioning Scale (SOFAS; American Psychiatric Association, 1994). The SOFAS rates global functioning on a scale from 0 to 100 in a manner similar to the Global Assessment of Functioning (GAF). However, unlike the GAF, the SOFAS rating does not take into account the individual's level of symptomatology. Higher scores indicate better functioning. Scores on the SOFAS were rated based upon a comprehensive semi-structured interview with the subject covering independence in activities of daily living, social functioning and role functioning. The assessor integrated all available information into the final rating, and scores were discussed with and reviewed by a research coordinator.

Quality of Life was assessed using the Quality of Life Scale (QLS; (Heinrichs et al., 1984), a 21-item clinician-rated measure of interpersonal relationships, occupational role, sense of purpose, and the possession of common necessary objects. Items are rated on 7-point Likert scales (0–6) with higher scores indicating a better quality of life. A total score of all items reflects overall quality of life.

In addition to the primary outcome measures described above, we included a performance-based measure of functional outcome—the Functional Needs Assessment (FNA; Dombrowski et al., 1990). The FNA is a measure of the capacity to perform basic activities of daily living, including self-care and care of living quarters. Scores are based upon the individual's performance of specific tasks during testing (e.g., Show me how you would make a sandwich). Scores on each item range from 0 to 25, with higher scores indicating better performance. A total score is computed by averaging item scores. While performance-based tests are more objective measures of functional capacity, it is unclear how closely related these measures are to actual functional outcomes. This measure was included because measures such as this are proposed in current schizophrenia studies as co-primary outcome measures for pharmacotherapy that address cognitive impairments or negative symptoms (Green et al., 2008).

2.4. Rater training and reliability

All raters were research assistants who participated in a comprehensive rater training and quality assurance program. Prior to rating participants in the study, each rater was required to reach a criterion of 0.80 intraclass correlation coefficient on a series of videotaped and live interviews for each of the rating instruments. Throughout the study, raters were observed by the study coordinator during subject assessments to evaluate and improve their skills for eliciting necessary information, to reinforce accurate rating, and to reinforce proper administration and scoring of the performance-based test. In addition, monthly quality assurance meetings were held throughout the study to prevent rater drift. Procedures were modeled after those developed for the expanded version of the Brief Psychiatric Rating Scale.

2.5. Data analysis

We report change over time using standard effect sizes. Correlations can be attenuated when there is a restriction in range. However, the variability of change scores within individuals on the key variables over time is more important than group change over time. The unreliability of change scores is well known, so we explored change using partial correlation to examine the relationships between negative symptoms and functional outcomes at 6 months while controlling for negative symptoms and functioning at baseline (Cronbach and Furby, 1970). In addition, cross-lagged panel correlational analyses were used to explore hypotheses about causality, i.e., whether changes in negative symptoms over time drove changes in functional outcomes (SOFAS, Quality of Life, FNA; Kenny, 1979; Campbell and Kenny, 1999). Cross-lagged panel correlation was specifically designed for longitudinal data and in its simplest form involves an examination of two cross-lagged correlations (variable A at time 1 with variable B at time 2, versus variable B at time 1 with variable A at time 2) in an effort to make inferences about causality. Note that Kenny indicates that cross-lagged panel correlation requires at least moderate sample sizes (75-300), variables that change within individuals, lagged effects and data that meet assumptions of stationarity and synchronous correlation (Kenny, 1979; Campbell and Kenny 1999). These conditions were satisfied by the current data. As recommended by Campbell and Kenny (1999), we used the Pearson–Filon test to determine whether the differences between the two cross-lagged correlations were significantly different from one another.

As pointed out by Finkel (1995), a criticism of cross-lagged panel correlation is that significant cross-lagged correlations are not enough to infer causality. This author and others recommend doing cross-lagged panel correlation to reject the hypothesis of spuriousness, and then to test causality directly by conducting two multiple regression analyses, predicting each of the time-2 variables from both time-1 variables and comparing the results. To infer causality, one of these models should be significant and the other should not.

When differences in cross-lagged correlations were found, we also examined the fit of a simultaneous equation model (SEM) with negative symptoms at baseline predicting the functional variable across a 6-month lag using SAS CALIS. In addition, we examined the model in reverse to determine whether the functional outcome