



Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: [www.elsevier.com/locate/schres](http://www.elsevier.com/locate/schres)

## Determinants of different aspects of everyday outcome in schizophrenia: The roles of negative symptoms, cognition, and functional capacity<sup>☆</sup>

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### ARTICLE INFO

#### Article history:

Received 26 January 2015

Received in revised form 24 March 2015

Accepted 26 March 2015

Available online xxx

#### Keywords:

Schizophrenia

Cognition

Negative symptoms

Social functioning

Functional capacity

### ABSTRACT

Cognition, negative symptoms, and depression are potential predictors of disability in schizophrenia. We present analyses of pooled data from four separate studies (all  $n > 169$ ; total  $n = 821$ ) that assessed differential aspects of disability and their potential determinants. We hypothesized that negative symptoms would predict social outcomes, but not vocational functioning or everyday activities and that cognition and functional capacity would predict vocational functioning and everyday activities but not social outcomes. The samples were rated by clinician informants for their everyday functioning in domains of social and vocational outcomes, and everyday activities, examined with assessments of cognition and functional capacity, rated clinically with the Positive and Negative Syndrome Scale (PANSS) and self-reporting depression. We computed a model that tested the hypotheses described above and compared it to a model that predicted that negative symptoms, depression, cognition, and functional capacity had equivalent influences on all aspects of everyday functioning. The former, specific relationship model fit the data adequately and we subsequently confirmed a similar fit within all four samples. Analyses of the relative goodness of fit suggested that this specific model fit the data better than the more general, equivalent influence predictor model. We suggest that treatments aimed at cognition may not affect social functioning as much as other aspects of disability, a finding consistent with earlier research on the treatment of cognitive deficits in schizophrenia, while negative symptoms predicted social functioning. These relationships are central features of schizophrenia and treatment efforts should be aimed accordingly.

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### 1. Introduction

Everyday functioning is commonly impaired in schizophrenia, affecting domains of social functioning, vocational performance, and performance of everyday activities. Even among those patients classified as 'responders' to available pharmacological and psychosocial treatments, disability rates are high and functional outcomes have changed minimally compared to success in treating psychosis (Hegarty et al., 1994).

<sup>☆</sup> This research was supported by grants MH 63116 and MH078775 to Dr. Harvey, MH 93432 to Drs. Harvey, Penn, and Pinkham, and MH078737 to Dr. Patterson from the National Institute of Mental Health. Supplemental funding was provided by Genentech.

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Cognitive deficits and negative symptoms are thought to represent the main drivers of disability, (Breier et al., 1991; Carone et al., 1991) although influences outside of the individual such as opportunities and disincentives such as disability compensation meaningfully affect certain domains of functioning (Rosenheck et al., 2006; Harvey et al., 2009). While positive symptoms usually improve with treatment, or can otherwise be compensated for (Ventura et al., 2009) both cognitive deficits and negative symptoms receive minimal benefit despite the fact that current antipsychotics control psychosis to the point that clinical remission rates are close to 50% in some studies (Harvey and Bellack, 2009).

Moreover, negative and cognitive symptoms of schizophrenia, often present prior to the emergence of frank psychosis (Meyer et al., 2013), appear to be related but separable domains with different functional implications (Harvey et al., 2006; Couture et al., 2011). Ventura et al. (2009) concur that cognitive and negative symptoms both predict

<http://dx.doi.org/10.1016/j.schres.2015.03.033>

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Please cite this article as: Strassnig, M.T., et al., Determinants of different aspects of everyday outcome in schizophrenia: The roles of negative symptoms, cognition, and functional capacity, Schizophrenia Research (2015), <http://dx.doi.org/10.1016/j.schres.2015.03.033>

outcome, but note that negative symptoms partially mediate the longitudinal relationship between cognition and outcome, and suggest therefore that cognition has both direct and indirect effects on functioning. Similarly, Lin et al. (2013) suggest that negative symptoms mediate the influence of cognition on outcome. Some of our own work has suggested that different domains of everyday functioning may not be as highly intercorrelated as previously thought and may also have different potential determinants. For instance, we previously reported that cognitive and functional capacity deficits predicted impairments in everyday activities (with the exception of social outcomes) and that negative symptoms were related to poor social outcomes to a greater extent than to other aspects of everyday outcome (Leifker et al., 2009). Meta-analyses have suggested that non-social cognitive deficits show less relation to social deficits when compared to the influence of social cognition (Green et al., 2000, 2004; Fett et al., 2011), and we have found that social deficits were less responsive to interventions aimed at treatment of cognition and functional skills deficits compared to work and instrumental functions (Bowie et al., 2012). Finally, achievement of different functional milestones (work, residence, and social achievements) is minimally intercorrelated in schizophrenia, suggesting that global indices of disability may lack the requisite specificity (Harvey et al., 2012) and that there are likely specific predictors of impairments in different domains of everyday functioning.

In this paper we present analyses of a unique set of data: four separately collected datasets with similar methodological strategies that allowed for the evaluation of the relationship between three different aspects of real-world functional outcomes: social functioning, vocational skills, and performance of everyday activities, assessed with the same scales and informant strategies, and an identical set of potential determinants of functioning: neuropsychological test performance, performance-based measures of functional capacity, and negative and depressive symptoms. All four separate large-scale ( $n = 169$  in the smallest; total  $n = 821$ ) studies contribute information on the correlational relationships between everyday outcomes and an array of potential predictors.

These studies were conducted in five separate geographical areas (New York, Atlanta, San Diego, Miami, and Dallas), have no overlap of patients or clinicians, and reflect a wide range of demographic and ethnic variation in the patients assessed, while the same real-world functional outcome measure, clinical ratings, self-reports of symptoms, and functional capacity measures were used. Cognition was assessed with batteries that have overlap of identical tests in 3/4 studies and a highly similar battery in the other study. While some results regarding correlational aspects between symptoms, functional capacity, and everyday outcomes have been published from three of the studies (see below), there has never been a systematic comparison of the influences of negative symptoms, depression, cognition, and functional capacity on everyday functioning across sequentially completed studies with the same assessment strategies.

Based on previous research delineated above, we hypothesized that negative symptoms would predict social deficits, but not impairments in everyday activities and vocational outcomes, while cognition and functional capacity would predict deficits in everyday activities and vocational outcomes, but not social outcomes. This is a cross-sectional hypothesis in a sample of relatively chronic patients. Previous research (Ventura et al., 2015) has found that negative symptoms early in the course of illness predict both social functioning and work/school functioning at a year after initial contact, suggesting that influences of reductions in motivation or emotional expression have broad impacts. However, in a sample where the illness is already fully developed, we hypothesized that negative symptoms would exert a greater influence on social outcomes than everyday activities. We also hypothesized that depression, negative symptoms, and cognition and functional would exert independent influences on the real-world outcomes of interest. We tested this model in the sample as a whole, as well as in each of the individual subsamples. We also computed a generic model,

wherein cognition and functional capacity, depression, and negative symptoms were hypothesized to be equally important for the prediction of all elements of real-world outcomes in the database.

We tested several hypotheses in these analyses of the substantive model and its comparator model:

1. A model specifying that negative symptoms will be have a more substantial predictive influence on social deficits than cognition or functional capacity will be the best fit to that data.
2. A model specifying that cognition and functional capacity will predict everyday activities and vocational outcomes more substantially than social outcomes will be the best fit to the data.
3. Depression will impact all aspects of functional outcomes.

## 2. Methods

### 2.1. Participants

The data are part of four study cohorts collected in five different geographical areas, aimed at identifying the course and correlates of change in functional status as well as the optimal method for rating everyday functioning among schizophrenia outpatients.

The study participants were patients ( $n = 821$ ) with schizophrenia or schizoaffective disorder receiving treatment at one of several different outpatient service delivery systems in Atlanta, Dallas, Miami, San Diego and New York City. Atlanta patients were either recruited at a private psychiatric rehabilitation program (Skyland Trail) or from the outpatient population at the Atlanta VA Medical Center. San Diego patients were recruited from the UCSD Outpatient Psychiatric Services clinic, a large public mental health clinic and other local community clinics, or by self-referral. Miami patients were recruited from the outpatient services at the University of Miami Miller School of Medicine. The Mount Sinai sample recruitment was conducted at the Bronx VA Medical Center, an outpatient clinic at a New York State Psychiatric Hospital, or Mount Sinai School of Medicine. The Dallas sample was collected from Metrocare Services, a large non-profit provider of mental health services in Dallas County, and other outpatient services associated with the University of Texas Southwestern Medical (UTSW) Center. All research participants provided signed informed consent according to standards approved by the responsible local Institutional Review Boards.

Patients from Atlanta, San Diego, and Miami were participants in one of two phases of the Validation of Everyday Real World Outcomes Study (VALERO), parts 1 or 2. UCSD and Atlanta patients participated in VALERO 1, and UCSD, Atlanta and Miami patients participated in VALERO 2, which was started 6 months after the conclusion of data analysis of VALERO 1. Dallas patients, as well as a completely new sample of Miami patients were participants in phase I of SCOPE (Pinkham et al., 2014) study. We examined the data from these studies based on the study in which they were collected. These data were collected between July 2007 and May 2014. The Mount Sinai Sample was collected between March 2003 and June of 2008.

All enrollees completed a structured diagnostic interview, administered by a trained interviewer. The Structured Clinical Interview for the DSM (SCID; First et al., 2002) was used at the Atlanta sites, the Mini International Neuropsychiatric Interview, 6th Edition (Sheehan et al., 1998) in Dallas, San Diego, and Miami, and the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992) in New York; all diagnoses were verified in local consensus procedures. Screening also included global cognitive function and premorbid functioning measured with the Mini-Mental State Examination (Folstein et al., 1975) and the Wide Range Achievement Test, 3rd Edition (WRAT3; Wilkinson, 1993) Recognition Reading subtest. Patients were excluded for a history of traumatic brain injury, brain disease such as seizure disorder or neurodegenerative condition, a MMSE score below 18 in the Mt. Sinai Sample, a reading score below the 6th grade in all samples, or the presence of another DSM-IV diagnosis that

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