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Multianalyte markers of schizophrenia and bipolar disorder: A preliminary study

Faith Dickerson [a,*], Jennifer Schroeder [b], Cassie Stallings [a], Andrea Origoni [a], Sabine Bahn [c], Robert Yolken [d]

[a] Sheppard Pratt Health System, Baltimore, MD, USA
[b] Schroeder Consulting, Inc., Ellicott City, MD, USA
[c] University of Cambridge, Cambridge, UK
[d] Johns Hopkins School of Medicine, Baltimore, MD, USA

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ABSTRACT

Previous studies have identified altered molecular profiles in blood samples from individuals with schizophrenia and with bipolar disorder using multianalyte immunoassay platforms but there has been little comparison of the two groups in the same investigation. A total of 337 participants including 146 with schizophrenia, 79 with bipolar disorder, and 112 non-psychiatric controls had a blood sample drawn from which 166 analytes were measured. The initial dataset was split; classification models were developed in a training dataset and their performance evaluated in a test dataset. Principal component analysis was used to generate factor scores that were then compared between the groups. In a training set, a total of 7 independent factors were generated using 29 markers that were both normally distributed and significantly associated with diagnosis. Many of these analytes are components of the immune system and involved in the inflammatory response to infectious agents and foreign antigens. Two of the seven principal component scores discriminated between individuals with schizophrenia and with bipolar disorder; additional factors distinguished individuals with either schizophrenia or bipolar disorder from control individuals, while two factors were not significantly different between any of the diagnostic groups. In a test dataset, the schizophrenia vs. control Receiver Operating Curve (ROC) analysis shows an overall accuracy of 77% for schizophrenia vs. bipolar disorder, 84% for schizophrenia vs. controls, and 72% for bipolar disorder vs. controls. An increased understanding of the role of altered pathways in serious psychiatric disorders may lead to novel methods for disease diagnosis and therapy.

1. Introduction

Schizophrenia and bipolar disorder are serious psychiatric disorders whose etiologies are not fully characterized. The two disorders are separately classified in diagnostic systems and presumed to have different biological substrates (APA, 2013). However, recent studies show considerable overlap in genetic risk factors, neuroimaging findings, and psychosocial outcomes (Altamura et al., 2013; Dacquino et al., 2015; Goodkind et al., 2015; Jobe and Harrow, 2005; Treuer and Tohen, 2010). In addition, several medications have an FDA-approved indication for, and are commonly used in the treatment of, both disorders (Thronson and Pagalilauan, 2014). Studies of blood-based proteins may help to identify biological features that are shared between the disorders as well as those that differ. Such an approach should help to identify some of the neurobiological pathways underlying these traditionally-distinct clinical entities.

Abnormalities have been found in individuals with schizophrenia relative to demographically-matched controls, including changes in the levels of inflammatory markers such as interleukin-6, growth factors such as brain-derived neurotrophic factor (BDNF), markers of oxidative stress such as S100B (Guest et al., 2014) and hormones including prolactin and insulin (Chan et al., 2014; Schwarz et al., 2012a; van Beveren et al., 2014). However there is some heterogeneity in terms of the specific markers found in different studies. Abnormalities have also been found in individuals with bipolar disorder (Haenisch et al., 2014; Ortiz-Dominguez et al., 2007; Wadee et al., 2002), although a smaller number of studies have been performed in this patient population. There have been few systematic investigations in which individuals with schizophrenia and bipolar disorder have been compared with a full panel of analytes using the same clinical and laboratory methods on samples obtained and stored under identical conditions.

In this study we present the results of a multianalyte test platform applied to the measurement of blood-based proteins in individuals with schizophrenia, bipolar disorder and non-psychiatric controls enrolled and evaluated following the same research protocol.

* Corresponding author at: Stanley Research Program, Sheppard Pratt Health System, 6501 North Charles St, Baltimore, MD 21204, USA.
E-mail address: fdickerson@sheppardpratt.org (F. Dickerson).

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2. Methods

2.1. Sample

The study sample consisted of individuals in three groups: schizophrenia, bipolar disorder, and non-psychiatric controls.

The inclusion criterion for individuals with schizophrenia was a diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder. The inclusion criterion for individuals with bipolar disorder was a diagnosis of bipolar disorder including bipolar 1 disorder, bipolar II disorder, or bipolar disorder not otherwise specified. The psychiatric participants were recruited from inpatient and day hospital programs of Sheppard Pratt and from affiliated psychiatric rehabilitation programs. The diagnosis of each psychiatric participant was established by the research team including a board-certified psychiatrist and based on the Structured Clinical Interview for DSM-IV Axis 1 Disorders and available medical records.

The inclusion criterion for the non-psychiatric control individuals was the absence of a current or past psychiatric disorder as determined by screening with the DSM-IV Axis I Disorders, Non-patient Edition. These individuals were recruited from posted announcements at local health care facilities and universities in the same geographic area as the settings where the psychiatric participants were recruited.

Participants in all groups met the following additional criteria: age 18–65 (except the control participants who were aged 20–60); proficient in English; absence of any history of intravenous substance abuse; absence of mental retardation; absence of HIV infection; absence of serious medical disorder that would affect cognitive functioning; absence of a primary diagnosis of alcohol or substance use disorder.

The studies were approved by the Institutional Review Boards of the Sheppard Pratt Health System and the Johns Hopkins Medical Institutions following established guidelines. All participants provided written informed consent after the study procedures were explained.

2.2. Clinical assessments

All participants were individually administered a brief cognitive battery, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Form A at the study visit. All of the psychiatric participants were also interviewed and rated on the Positive and Negative Syndrome Scale (PANSS). Participants were asked about demographic variables including maternal education as a proxy for pre-morbid socioeconomic status. All participants were also asked about their current smoking status.

2.3. Serum collection and analysis

Each participant had a blood sample obtained using standard venipuncture methods. Plasma was separated from the blood by centrifugation and was stored at −70° until testing.

In each blood sample 166 markers were measured employing a panel of markers developed by Myriad Rules Based Medicine (Austin, TX). The samples were tested under code with the laboratory performing the testing unaware of the clinical variables of diagnosis of any of the participants.

2.4. Statistical analysis

The goal of the analysis was to determine how the markers cluster together, and how well these clusters of markers can distinguish persons in different diagnostic groups. As a means of cross-validation, classification models were developed using one dataset and their performance evaluated in a second, independent dataset. The initial dataset was split into training and test sets having the same proportions of individuals in each diagnostic group as in the initial dataset. Sixty percent of the observations were randomly assigned to the training set, and the remainder to the test set. This proportion was chosen to ensure an adequate sample size (i.e., at least 200) for Principal component analysis (PCA), while keeping the training set small enough to avoid over-fitting the classification models to the training set.

PCA was used to accomplish two purposes: (1) determine how markers correlated with one another, and (2) reduce the dimensionality of the marker dataset from 166 analytes to a smaller number of components, each of which consisted of several correlated markers. Once PCA had been performed, the resulting component scores were used as independent variables in a series of logistic regression models that evaluated the ability of the component scores to identify individuals in different diagnostic groups, after adjusting for other relevant covariates. Three different series of logistic regression models were run: (1) comparing individuals with schizophrenia to controls, excluding individuals with bipolar disorder; (2) comparing individuals with bipolar disorder to controls, excluding individuals with schizophrenia; and (3) comparing individuals with schizophrenia to individuals with bipolar disorder, excluding controls. The most parsimonious model for each two-group comparison was found using a backward selection procedure. The initial model consisted of all covariates (all component scores plus age, gender, race, total cognitive score, total symptom score, current smoking status). Two-tailed z tests were performed to determine if the regression coefficient for each covariate differed significantly from zero; the covariate having the highest p-value was removed and the model re-fit. This continued until all covariates in the model were significantly different from zero ($p < 0.05$).

The performance of the logistic regression classification models developed using the training set was evaluated on the test set. The test set was processed in a manner identical to that used on the training set: the markers found to be both normally distributed and associated with psychiatric diagnosis in the training set were selected from the original 166 markers. The principal component scores were calculated using the same component loadings derived from the training set. The performance of the final logistic regression model for each of three two-group comparisons using the training set was evaluated using the test set by generating a confusion matrix and Receiver Operating Curve (ROC).

3. Results

3.1. Participant characteristics

The study sample consisted of a total of 337 participants, 146 with schizophrenia, 79 with bipolar disorder, and 112 non-psychiatric controls. Characteristics of the diagnostic groups are shown in Table 1. Statistically significant associations with diagnostic group were observed for all of the variables [tabulated above]. Diagnostic groups differed by age ($F_{2,334} = 18.7$, $p < 0.0001$), gender (chi square $p < 0.0001$), race (chi square $p = 0.0016$), maternal education ($F_{2,330} = 4.02$, $p = 0.019$),

Table 1
Characteristics of study sample (N = 337).

	Diagnosis		
	Schizophrenia N = 146	Bipolar disorder N = 79	Controls N = 112
Demographic variables			
Age (years)	40.6 ± 11.5	34.3 ± 12.2	32.0 ± 11.2
Gender (% female)	37.7%	72.2%	70.5%
Caucasian (% white)	43.2%	63.3%	62.5%
Maternal education (years)	12.6 ± 2.9	13.2 ± 2.9	13.5 ± 2.6
Clinical variables			
PANSS[1] symptom score	71.3 ± 12.6	75.1 ± 12.6	NA
RBANS[2] cognitive score	64.5 ± 11.1	75.2 ± 13.2	86.2 ± 12.3
Current smoker	91 (62.3%)	79 (32.9%)	22 (19.6%)

[1] Positive and Negative Syndrome Scale.
[2] Repeatable battery of neuropsychological status.