



Contents lists available at ScienceDirect

Schizophrenia Research

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

## Deviation from expected cognitive ability across psychotic disorders

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### ARTICLE INFO

#### Article history:

Received 8 February 2017

Received in revised form 10 May 2017

Accepted 15 May 2017

Available online xxxx

#### Keywords:

Psychotic disorders

Brief assessment of cognition in schizophrenia

First-degree relatives

Cognitive decline

Premorbid cognition

### ABSTRACT

Patients with schizophrenia show a deficit in cognitive ability compared to estimated premorbid and familial intellectual abilities. However, the degree to which this pattern holds across psychotic disorders and is familial is unclear. The present study examined deviation from expected cognitive level in schizophrenia, schizoaffective disorder, and psychotic bipolar disorder probands and their first-degree relatives. Using a norm-based regression approach, parental education and WRAT-IV Reading scores (both significant predictors of cognitive level in the healthy control group) were used to predict global neuropsychological function as measured by the composite score from the Brief Assessment of Cognition in Schizophrenia (BACS) test in probands and relatives. When compared to healthy control group, psychotic probands showed a significant gap between observed and predicted BACS composite scores and a greater likelihood of robust cognitive decline. This effect was not seen in unaffected relatives. While BACS and WRAT-IV Reading scores were themselves highly familial, the decline in cognitive function from expectation had lower estimates of familiarity. Thus, illness-related factors such as epigenetic, treatment, or pathophysiological factors may be important causes of illness related decline in cognitive abilities across psychotic disorders. This is consistent with the markedly greater level of cognitive impairment seen in affected individuals compared to their unaffected family members.

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### 1. Introduction

Cognitive deficits are well established in psychotic disorders (Bilder et al., 2000; Dickinson et al., 2008; Hill et al., 2004; Keefe et al., 2006; Reilly and Sweeney, 2014). Typically, cognitive impairments are determined by evaluating neuropsychological performance in patient groups compared to normative data or a psychiatrically healthy control sample. However, performance on neuropsychological tests in controls may be related to both heritable familial intellectual ability (Bouchard, 2004) and illness-related factors that lead to a decline from that expected ability. Following this reasoning, the deviation score (decline from expected ability) is of potential interest as it may reflect the impact of disease on cognitive function more closely than level of performance. Indeed,

many schizophrenia patients display substantial discrepancy between neuropsychological performance and that predicted by factors such as parental education and personal premorbid ability as estimated by single-word reading (Keefe et al., 2005; Bryson et al., 1993; Palmer et al., 1997; Woodward and Heckers, 2015). However, some important issues have not been systematically investigated, including the extent of deviation from premorbid expectation in psychotic disorders other than schizophrenia and their unaffected family members, and the degree to which decline from expectation is itself a familial characteristic.

Though not investigated systematically, unaffected relatives of schizophrenia probands may show a degree of decline from expectation. Indeed, a recent population based investigation using a national registry indicated that familial cognitive aptitude (general intellectual ability) was distinct from neurodevelopmental factors that predispose one to schizophrenia (Kendler et al., 2016). This provides some indirect support for the notion that familial factors that determine intellectual ability may be distinct from disease-related factors impacting cognitive function.

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Thus, direct assessment of familial patterns of deviation in neuropsychological competence from expectation across psychotic disorders may be helpful for evaluating the extent to which significant decline from expected cognitive levels can be attributed to disease-related or shared familial factors impacting intellectual ability. Therefore, the present study evaluated the discrepancy of expected and current neuropsychological ability across psychotic disorders and in unaffected relatives, and the familiarity of these indices using a norm-based regression approach.

## 2. Methods

### 2.1. Participants

Cognitive testing and assessment of parental SES was performed as part of the Bipolar and Schizophrenia Network for Intermediate Phenotypes (B-SNIP) study. Recruitment strategy, procedures, and clinical characterization of the study sample have been reported previously (Tammimga et al., 2013), as were observed BACS composite scores in the sample (Hill et al., 2013). Probandes were required to have a consensus diagnosis based on SCID interviews (First et al., 1995) of schizophrenia, schizoaffective disorder, or bipolar disorder with psychotic features (see Table 1a & 1b). All participants had 1) no history of seizures or head injury with sustained loss of consciousness, 2) no diagnosis of substance abuse in the preceding 30 days or substance dependence in the prior 6 months, and a negative urine drug screen for drugs of abuse on the day of testing, 3) a stable medication regimen and clinical status over the prior month, 4) no history of systemic medical or neurological disorder known to affect cognitive abilities, and 5) age-corrected Wide Range Achievement Test-IV Reading standard score (SS)  $\geq 65$ . First-degree relatives with a lifetime history of psychosis were excluded from the present analyses in order to assess cognitive function in relatives unaffected by the presence of a psychotic disorder.

### 2.2. General cognitive function

The Brief Assessment of Cognition in Schizophrenia (BACS) is a neuropsychological battery designed to evaluate global neuropsychological function (Keefe et al., 2004). The BACS consists of six subtests covering four domains (Verbal Memory, Processing Speed, Reasoning, and Problem Solving, and Working Memory). Subtest scores were converted to z-scores using published norms (Keefe et al., 2008). To limit the impact of extreme values on group means, subtest scores were winsorized to a maximum absolute value of 4.0.

### 2.3. Estimating decline in cognitive ability compared to intellectual potential

#### 2.3.1. Predictor variables

Deviation-based approaches for evaluating decline in cognitive function have used a mixture of norm-based and premorbid indices to estimate familial intellectual potential. This approach has been used successfully in broad sample of patients with schizophrenia (Keefe et al., 2005; Woodward and Heckers, 2015), high-functioning schizophrenia (Vaskinn et al., 2014), and traumatic brain injury (Johnstone et al., 1995) using single word reading scores and parental education. A variety of parental and patient demographic variables (parental education and occupation, patient educational achievement) have been used to estimate intellectual potential in the schizophrenia and dementia literatures, and are used in the clinical practice of neuropsychology. Single-word reading (e.g., NART, WRAT reading) (Bright et al., 2002; Gladsjo et al., 1999) combined with parental education (Kareken et al., 1995; Kremen et al., 2000) provides a reliable estimate of familial or premorbid intellectual potential (Keefe et al., 2005). These parameters were utilized in the present study based on the prior findings and a failure of other factors such as personal years of education and parental income estimates.

**Table 1a**  
Demographic and clinical data for probands with a history of psychosis and healthy controls.

	Healthy controls n = 391	Schizophrenia probands n = 321	Schizoaffective probands n = 200	Bipolar probands n = 258	Findings
Age in years					
Mean(SD)	37.62(12.57)	35.70(12.87)	36.85(11.79)	36.04(12.76)	F = 1.61 <sup>ns</sup>
Years of education					
Mean (SD) <sup>a</sup>	14.92(2.52)	12.76(2.28)	13.04(2.14)	14.16(2.35)	F = 58.96 <sup>***</sup>
WRAT-IV: reading					
Mean(SD) <sup>b</sup>	103.29(13.76)	94.47(15.45)	97.00(14.73)	101.56(14.09)	F = 25.41 <sup>***</sup>
Gender <sup>c</sup>					
Male	45.0%	67.6%	40.5%	36.4%	$\chi^2 = 68.95^{***}$
Female	55.0%	32.4%	59.5%	63.6%	
Race <sup>d</sup>					
Caucasian	62.7%	46.4%	55.0%	75.2%	$\chi^2 = 60.61^{***}$
African-American	28.1%	44.9%	40.0%	19.4%	
Other	9.2%	8.7%	5.0%	5.4%	
Clinical data					
MADRS <sup>e</sup>		8.22(7.92)	14.79(10.32)	10.09(9.08)	F = 31.76 <sup>***</sup>
PANSS positive <sup>f</sup>		16.69(5.72)	17.97(5.26)	12.78(4.63)	F = 63.12 <sup>***</sup>
PANSS negative <sup>g</sup>		16.50(5.82)	16.04(5.15)	11.82(3.94)	F = 67.22 <sup>***</sup>
YMRS total <sup>h</sup>		5.56(5.82)	7.56(6.68)	5.87(6.80)	F = 6.24 <sup>**</sup>

WRAT-IV: Wide Range Achievement Test: Fourth Edition.

YMRS: Young Mania Rating Scale.

PANSS: Positive and Negative Syndrome Scale.

MADRS: Montgomery Asberg Depression Rating Scale.

\*\*  $p < 0.01$ .

\*\*\*  $p < 0.001$ .

<sup>a</sup> Healthy control > schizophrenia, schizoaffective, & bipolar; bipolar > schizophrenia & schizoaffective.

<sup>b</sup> Healthy control > schizophrenia and schizoaffective; bipolar > schizophrenia and schizoaffective.

<sup>c</sup> Males over-represented in Schizophrenia group.

<sup>d</sup> African-Americans over-represented in Schizophrenia group.

<sup>e</sup> Schizoaffective > bipolar > schizophrenia.

<sup>f</sup> Schizoaffective > schizophrenia > bipolar.

<sup>g</sup> Schizophrenia & schizoaffective > bipolar.

<sup>h</sup> Schizoaffective > schizophrenia & bipolar.

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