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Unitary construct of generalized cognitive ability underlying BACS performance across psychotic disorders and in their first-degree relatives

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ABSTRACT

Despite robust evidence of neurocognitive dysfunction in psychotic patients, the degree of similarity in cognitive architecture across psychotic disorders and among their respective first-degree relatives is not well delineated. The present study examined the latent factor structure of the Brief Assessment of Cognition in Schizophrenia (BACS) neuropsychological battery. Analyses were conducted on 783 psychosis spectrum probands (schizophrenia, schizoaffective, psychotic bipolar), 887 of their first-degree relatives, and 396 non-psychiatric controls from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) consortium. Exploratory factor analysis of BACS subtest scores indicated a single-factor solution that was similar across all groups and provided the best overall data fit in confirmatory analyses. Correlations between the standard BACS composite score and the sum of subscale scores weighted by their loadings on this unitary factor were very high in all groups ($r \geq .99$). Thus, the BACS assesses a similar unitary cognitive construct in probands with different psychotic disorders, in their first-degree relatives, and in healthy controls, and this factor is well measured by the test's standard composite score.

1. Introduction

Cognitive deficits have been firmly established as a common debilitating feature of schizophrenia spectrum disorders (Bilder et al., 2000; Dickinson et al., 2008; Hill et al., 2004; Keefe et al., 2006; Reilly & Sweeney, 2014). These deficits are present at illness onset, stable, and minimally affected by antipsychotic treatment (Bilder et al., 2000; Hill et al., 2004; Hoff et al., 1999), and predict functional outcome (Bowie & Harvey, 2006; Green, 1996). A less severe pattern of generalized deficits has been reported in affective psychotic disorders and in first-degree relatives of patients with both affective and nonaffective psychotic disorders (Hill et al., 2014). However, the factor structure of deficits across disorders and in family members has not been systematically examined in a single study.

The Brief Assessment of Cognition in Schizophrenia (BACS) neuropsychological battery was designed to be easily and quickly administered (in <35 min), and sensitive to the profile of generalized impairment seen in schizophrenia (Keefe et al., 2004; Keefe et al., 2008). This scale has been widely used in schizophrenia research, especially in clinical trials as a cognitive outcome measure. Factor analytic research with schizophrenia patients has indicated that a single generalized factor accounts for a high percentage of the variance in scores on both the BACS (Hill et al., 2008) and larger neuropsychological batteries (Dickinson et al., 2006; Keefe et al., 2006), though additional factors have been identified in some studies. However, few studies have examined the degree to which the cognitive architecture of performance across a battery of neuropsychological measures is consistent across psychotic disorders, whether these latent constructs in patients are similar to those of their first-degree relatives (Sitskoorn et al., 2004; Snitz et al., 2006), and whether those structures are similar to that seen in healthy controls. These issues are important for diagnostic differentiation and to support the use of neuropsychological batteries as outcome measures across disorders.

The BACS was used by the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) consortium to address questions about diagnostic boundaries and familiarity of intermediate phenotypes in schizophrenia, schizoaffective disorder, and bipolar disorder. The initial report of cognitive deficits showed significant familiality and differences

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across disorders in the severity of deficit (Hill et al., 2014), but the composition of the deficit across disorders and in family members was not formally addressed previously and is the focus of this investigation. To date, no other studies have examined such a range of diagnostic and family groups in a large study of this nature. Clarifying the latent variable structure across disorders and any differences across groups is important to establish the utility of the BACS and other measures of general intellectual ability in assessing cognition across a broad range of psychiatric populations in clinical trials, and in tracking cognitive phenotypes in family genetic research.

A two-step, split-half, cross-validation method using complimentary exploratory and confirmatory factor analytic techniques (Gorsuch, 1983) was first applied to each subject group separately. Then, exploratory factor analysis (EFA) was conducted on half of each group (randomly selected) to determine the number of latent factors underlying BACS subscales in a data driven manner. The remaining half of each group was then separately examined using a confirmatory factor analysis (CFA) to validate the findings. The primary scientific questions pertained to the homogeneity of factor structure across proband groups, between proband groups and their respective family members, and between these groups and healthy controls.

2. Methods

2.1. Participants

Recruitment strategy and patient characteristics of the BSNIP study sample have been reported previously (Tamminga et al., 2014). Patients were recruited from the community if they had a history of psychotic symptoms and at least one first-degree relative between the ages of 15–65 also willing to participate in the study. Probands were required to have a DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder with a history of psychotic symptoms determined using the Structured Clinical Interview for DSM Disorders (SCID) (First et al., 1995).

All participants had 1) no history of seizures or head injury with loss of consciousness (>10 min), 2) no diagnosis of substance abuse in the preceding 30 days or substance dependence in the preceding 6 months, 3) negative urine drug screen for common drugs of abuse on the day of testing, 4) no change in medication and generally clinically stable over the past month, 5) no history of systemic medical or neurological disorder known to affect cognitive abilities, 6) age-corrected Wide Range Achievement Test-IV Reading standard score (SS) >65, and 7) adequate fluency in English to complete testing.

2.2. Procedures

The Brief Assessment of Cognition in Schizophrenia (BACS) is a neuropsychological battery designed to evaluate global neuropsychological function in individuals with schizophrenia that has been demonstrated to be reliable and valid (Keefe et al., 2004; Keefe et al., 2008). 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, outliers were Winsorized (Tabachnick & Fidell, 2007) to a maximum absolute value of 4.0 for subtest z-scores before BACS composite scores were computed to reduce outlier effects on data analyses.

2.3. Data analytic plan

A two-step, split-half, cross validation method was utilized with complimentary exploratory and confirmatory approaches (Cudeck & Browne, 1983; Loehlin, 2004). Exploratory factor analysis (EFA) is an empirically guided technique that was used with a randomly selected half of each participant group to determine the number of latent factors underlying the BACS subtest scores and the loadings of subtests on the factor(s). The split-half groups within each diagnostic category were demographically similar and there were no significant differences between EFA and CFA groups in demographic or cognitive parameters after correcting for multiple comparisons (see Table 1).

Principal axis factoring was conducted with the first split-half of each group. To avoid over extracting factors (see Costello & Osborne, 1983), the Kaiser criterion (factors with Eigenvalues > 1.0) (Yeomans & Golder, 1982) was used to determine the maximum number of factors eligible for extraction and scree plots were used to optimize the final solution. In step two, a confirmatory factor analysis (CFA) was performed using the remaining half of each group to validate the derived model. As a secondary aim given the limited number of tests in the BACS battery, we also compared the single factor solution determined with the EFA to a model with more factors based on reports from some previous investigations about the cognitive structure of psychotic disorders (Lam et al., 2014; Keefe et al., 2004; McCleery et al., 2015). Model fit was evaluated using the following measures: Tucker–Lewis Index (TLI) (Bollen, 1989), Comparative Fit Index (CFI) (Bentler, 1990), Root Mean Square Approximation (RMSEA) (Browne & Cudeck, 1993), Akaike information criterion (AIC), Bayesian information criterion (BIC), and a Chi-square test of goodness of fit.

3. Results

3.1. Exploratory factor analyses

As illustrated in Fig. 1, findings clearly indicated a one-factor solution in all groups (see Table 2 for the amount of variance explained for each group). Because a single factor was extracted in all groups, there was no rotation or evaluation of factor correlations. Overall, these findings indicate a single, generalized cognitive factor underlying the BACS in all diagnostic groups, their relatives, and in healthy controls. As can be seen in Table 2, all subtests loaded meaningfully, and factor loadings of tests on the generalized factor were similar across all groups.

3.1.1. Factor loadings and relation to the standard BACS composite score

Using a norm-based approach, factor scores were computed (for all groups) based on the BACS subtest factor loadings observed in the healthy control group, with demographic variables used as covariates as determined by their relation to BACS performance in controls. This was done to provide a relatively unbiased and consistent approach for examining the similarity of a total test scores created by weighting subtest scores by their loading on the single factor from the exploratory factor analysis with the standard composite score used in previous BACS research which sums raw subtest scores (Keefe et al., 2004). These two measures were correlated separately for each group. The factor loading weighted sum of test scores and the standard BACS composite score were correlated very highly in each group ($r > .99$, $p < .001$). Thus, the standard BACS composite score and a score assessing the primary cognitive factor determined by factor analyses of the BACS subtests were essentially identical. It should be noted that for both scores we followed the standard procedure of first correcting for performance differences related to demographic factors.

3.2. Confirmatory factor analysis

3.2.1. Model evaluation

Cross-validation of the factor analysis solution provided by the exploratory factor analysis was performed using the second split-half of each participant group and then comparing the results to those from the exploratory analysis with the first half of the samples and more complex models. All CFA models were hierarchical and factor-correlated, with each model converging across all groups. Table 3 presents the results of the CFA. Although the three-factor model was a marginally better fit in bipolar and schizoaffective relatives, the unitary

Table 1
Demographic characteristics of split-half groups used for exploratory factor analysis and cross-validation (confirmatory factor analysis) groups. No significant differences between EFA and CFA groups were observed after correcting for multiple comparisons.

	HC			SZP			SZR			BPP			BPR			SzAffP			SzAffR		
	EFA	CFA	P	EFA	CFA	P	EFA	CFA	P	EFA	CFA	P	EFA	CFA	P	EFA	CFA	P	EFA	CFA	P
Age	37	37	.85	36	35	.54	41	44	.09	35	37	.17	40	40	.99	37	37	.73	37	43	.01
Sex																					
Male	45%	45%	.87	66%	68%	.74	34%	26%	.11	37%	35%	.74	37%	33%	.43	42%	39%	.63	36%	23%	.03
Female	55%	55%		44%	42%		66%	74%		63%	65%		63%	67%		58%	61%		64%	77%	
Race	–	–	.35	–	–	.93	–	–	.87	–	–	.37	–	–	.24	–	–	.70	–	–	.19
WRAT	104	102	.05	94	93	.53	97	97	.60	100	102	.32	103	103	.70	96	97	.79	99	100	.54

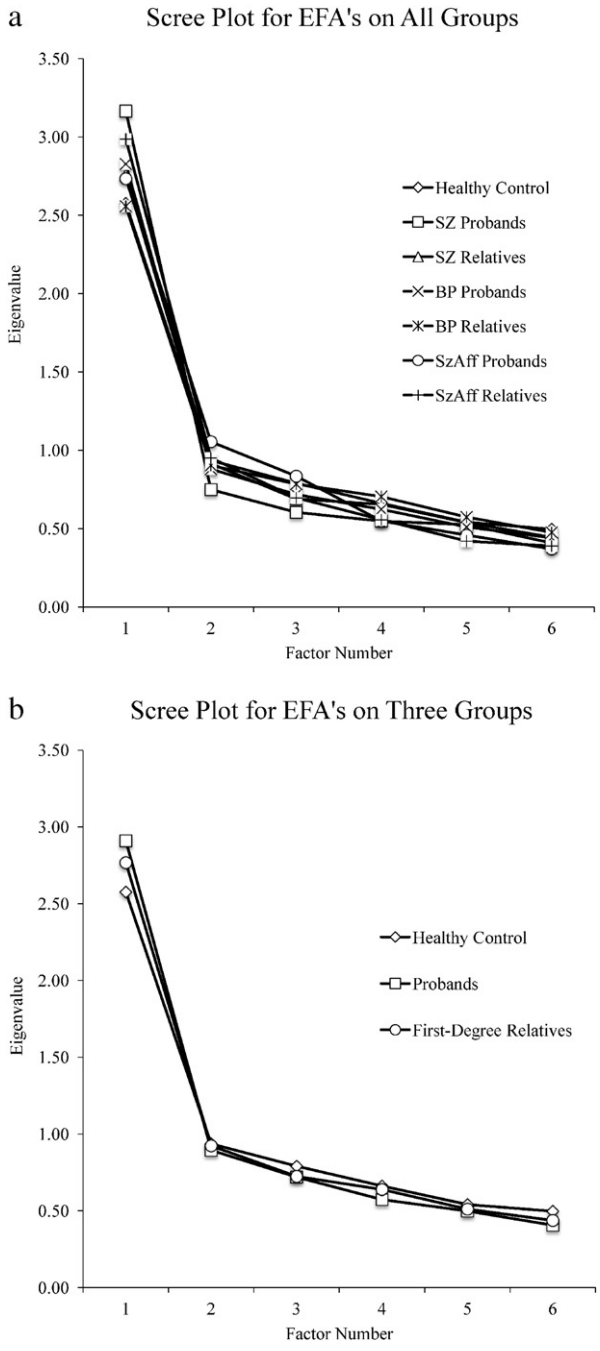

Fig. 1. a. Scree plot for exploratory factor analyses (EFA) indicates a single factor solution underlying the BACS in each group. b. Scree plot for exploratory factor analyses (EFA) for healthy controls, all first-degree relatives, and all psychotic probands.

latent factor had significantly greater support overall as in the exploratory analysis, and the single factor solution was the more parsimonious model, particularly for healthy controls and probands with psychotic disorders. Furthermore, factorial invariance was assessed using a metric invariance method. When loadings were constrained to be equal there were no significant differences between models for proband and relative groups [$\chi^2(25) = 32.02$, $p = 0.16$]. Thus, confirmatory factor analysis and factorial invariance both validated the EFA derived single factor model, and there was no evidence of appreciable divergence in the structure of that factor across groups, or any benefit to using more complex models to characterize the underlying cognitive architecture of the BACS battery.

4. Discussion

This study was the first to examine the cognitive architecture underlying the BACS battery and the structure of generalized cognitive impairment across psychotic disorders (schizophrenia, schizoaffective, and psychotic bipolar) and their first-degree relatives. A split-half, cross-validation analysis starting with a data-driven exploratory factor analytic technique was conducted separately for each group. Results indicated a single-factor solution underlying BACS performance that was similar in nature across all groups of patients and relatives as well as healthy control participants. This was complimented by a confirmatory factor analysis evaluating the single factor model derived in the exploratory analyses and more complex models. The cross-validation supported the exploratory findings of single-factor solution of generalized cognitive deficit and provided minimal support for a higher order models in which cognitive impairment was comprised of discrete deficits. Thus, the BACS battery seems to primarily assess a similar and unidimensional cognitive construct across patients with different psychotic disorders, in their first-degree relatives, and in controls alike.

The generalized factor resulting from the exploratory factor analysis was highly correlated with, and well characterized by, the standard BACS composite score. Thus, the standard composite score and a composite score derived by weighting individual tests by their loading on the generalized factor provide comparable indices of overall cognitive ability. Further, it is important that the structure of cognitive deficit was similar in form across psychotic disorders and in their first-degree relatives.

These findings have implications for psychopathology of cognition across disorders, and for the utility of the BACS across patient groups both as a treatment outcome measure and in family research. First, with regard to the cognitive deficits in psychotic disorders, the findings provide additional support to a growing body of literature suggesting that a global generalized deficit accounts for much of the cognitive impairment seen across psychotic disorders (Hill et al., 2014; Reilly & Sweeney, 2014; Reichenberg et al., 2009). Second, the findings provide novel evidence that the BACS battery assesses a similar cognitive deficit in schizophrenia, schizoaffective disorder, and bipolar disorder with psychotic features. While the severity of generalized cognitive deficit differs across disorders (Hill et al., 2014), the composition of this deficit

Table 2
BACS subtest factor loadings and percent variance in subtest scores explained by the first (and only) factor from an exploratory factor analysis for each diagnostic group.

	HC	SZ proband	BP proband	SzAff proband	SZ relative	BP relative	SzAff relative
Sample size	396	323	260	200	349	301	237
Verbal memory	.563	.666	.685	.723	.682	.674	.747
Digit sequencing	.610	.673	.606	.724	.653	.614	.722
Token motor	.326	.538	.414	.352	.436	.420	.388
Verbal fluency	.587	.675	.625	.547	.620	.512	.690
Symbol coding	.672	.791	.716	.790	.641	.700	.772
Tower	.656	.637	.576	.611	.567	.615	.569
Variance explained (%)	44.17	53.49	47.36	49.93	46.88	45.89	52.31

is very similar and provides a basis for using the BACS to assess general cognitive deficit across psychotic disorders.

Third, the similarity of the cognitive architecture in family members and patients indicates that the BACS battery may have utility in assessing a comparable dimension of generalized cognitive deficits across disorders in a variety of research designs (e.g., clinical trials, family studies). As is the case with comparisons of the severity of deficit across disorders, this would be much more challenging if there were significant differences in the latent cognitive structure of illness-related or familial cognitive performance. The findings of a similar structure to cognitive deficit in probands and relatives provides support for interpreting the general deficit assessed by the BACS as reflecting a similar cognitive deficit as an endophenotype associated with familial risk for illness across psychotic disorders. The similar cognitive structure of generalized deficit also suggests that the BACS test may provide a useful outcome measure in clinical trials targeting cognitive deficit across psychotic disorders, rather than only in schizophrenia where it has been most frequently used.

4.1. Factor structure of the BACS

Factor analytic approaches require large sample sizes and a high ratio of indicators to factors. The B-SNIP study was sufficiently large to accommodate a conservative analytic approach using both data driven exploratory and top-down confirmatory factor analytic techniques that yielded similar solutions and provide internal replication for the primary findings. However, while the BACS test has the advantage of being a brief and efficient approach for assessing generalized deficit, this benefit is a disadvantage for addressing the question of potential higher order structures to cognitive deficit in psychotic disorders because it does not provide a high ratio of indicators to factors or coverage of all cognitive processes.

The literature regarding the higher order factor structure underlying neuropsychological batteries and cognitive deficit in psychotic disorders has been mixed, perhaps related to methodological issues and/or approaches to factor extraction. Multi-factor models have been reported in schizophrenia samples when evaluating intelligence tests (Allen et al., 1998) as well as brief (Keefe et al., 2004) and larger neuropsychological batteries (Gladsjo et al., 2004; Green et al., 2002; Hobart et al., 1999). Some of these studies may have over-extracted factors as some studies extracted factors with eigenvalues less than 1.0 or strictly adhered to the Kaiser criterion without incorporating scree plots when determining the number of factors to retain (Green et al., 2002; Hobart et al., 1999; Keefe et al., 2004). Some studies recently reported multiple factors underlying neuropsychological batteries (Lam et al., 2014; McCleery et al., 2015) and provided the basis for the more complicated model in the confirmatory factor analysis. Yet, in contrast, the present findings clearly favored a unitary cognitive dimension of the BACS battery. This finding provides broader support for a unitary dimension of generalized cognitive deficit in the literature in step with stronger methodology and more sophisticated statistical analyses (Strauss & Summerfelt, 2003). Additionally, Dickinson et al. (2008) reported that a single common factor accounted for the majority of intellectual and memory deficits in schizophrenia patients (compared to controls) and higher order models accounted for little unique between-group variance. Despite extracting a three-factor solution from a lengthy neuropsychological battery, Green and colleagues argued that a large reliable general factor (accounting for 45% of total variance) justified combining all variables into a single composite to evaluate pharmacological treatment effects (Green et al., 2002).

Exploratory factor analysis of both the BACS and CATIE batteries in a large sample of first episode psychosis patients indicated a general cognitive factor underlying both batteries regardless of whether the batteries were analyzed separately or together (Hill et al., 2008). Unitary and multi-factor models were directly compared using confirmatory factor

Table 3
Model fit statistics for one- and three-factor models for BACS subtest structure. CFI and TLI scores at 0.90 or above, lower AIC and BIC, and RMSEA scores less than 0.05, indicate a good fit.

	CFI	TLI	χ^2 (p-value)	RMSEA (90% CI)	AIC	BIC
One-factor						
HC	0.977[a]	0.961[a]	14.81 (0.10)[a]	0.056 (0.000–0.105)[a]	3565.90[a]	3625.72[a]
SZ proband	0.994[b]	0.989[b]	10.83 (0.29)[b]	0.035 (0.000–0.097)[a]	2959.00[a]	3015.34[a]
BP proband	0.978[a]	0.963[a]	12.00 (0.21)[a]	0.054 (0.000–0.126)[a]	1961.02[a]	2010.11[a]
SzAff proband	0.917[a]	0.862[a]	18.81 (0.027)[a]	0.111 (0.036–0.182)[a]	1660.18[a]	1704.77[a]
SZ relative	0.993[a]	0.988[a]	10.67 (0.30)[a]	0.032 (0.000–0.094)[a]	3014.21[a]	3071.28[a]
BP relative	0.969	0.949	14.25 (0.11)	0.063 (0.000–0.122)	2543.56	2597.39[a]
SzAff relative	0.954	0.923	19.40 (0.02)	0.097 (0.035–0.156)	2061.44	2112.21
Three-factor						
HC	0.969	0.934	14.67 (0.041)	0.073 (0.015–0.126)	3569.76	3636.22
SZ proband	0.995	0.989	8.49 (0.29)	0.036 (0.000–0.105)	2960.67	3023.26
BP proband	0.970	0.936	11.11 (0.13)	0.072 (0.000–0.148)	1964.12	2018.67
SzAff proband	0.909	0.806	17.78 (0.01)	0.132 (0.057–0.210)	1663.15	1712.69
SZ relative	0.990	0.978	9.41 (0.22)	0.044 (0.000–0.109)	3016.95	3080.36
BP relative	0.997[a]	0.994[a]	7.52 (0.38)[a]	0.022 (0.00–0.106)[a]	2540.82[a]	2600.63
SzAff relative	0.964[a]	0.926[a]	14.77 (0.04)[a]	0.095 (0.020–0.162)[a]	2060.81[a]	2117.22[a]

[a] Indicates best model fit (across one- and three-factor models).
[b] Indicates equivalent model fit (across one- and three-factor models).

analysis of the CATIE neuropsychological battery and a single-factor model provided a better fit than a more complicated model (Keefe et al., 2006). Furthermore, principal components analysis of the CATIE data resulted in a single component exceeding 1.0 eigens (Keefe et al., 2006). Finally, in a comparison of a hierarchical model representing one broad cognitive dimension and a multifactor model consisting of separate cognitive dimensions, the unitary cognitive factor was a better fit for performance in chronic schizophrenia (Dickinson et al., 2006). Overall, findings from a variety of methodologies across a wide range of neuropsychological measures in chronic and early course schizophrenia samples were consistent with the present findings of a general cognitive factor underlying the cognitive deficit associated with psychotic disorders.

However, given that the BACS is a brief battery with a limited number of tests to define discrete higher order factors, the present findings do not provide a strong basis for drawing inferences about whether different cognitive factors might be differentiated in a more extensive battery covering broader range of neurocognitive dimensions. Thus, while the BACS captures generalized cognitive deficits efficiently, addressing the broader question of the complexity of the cognitive architecture of neurocognitive deficits in psychotic disorders almost certainly requires a much larger test battery.

4.2. Generalized versus specific deficits

Generalized cognitive deficits are characteristic of psychotic disorders with some variability in level of severity. Brief batteries can capture this broad factor in a useful way for clinical trials and potentially for family studies. There are two advantages of assessing generalized cognitive deficits for these purposes. First, neuropsychological assessment of generalized impairment can be done quickly in an efficient manner (Gold & Harvey, 1993; Hill et al., 2008). Second, available evidence indicates that generalized impairment has broad clinical relevance more than specific cognitive measures, being more consistently related to important functional outcomes in the domains of interpersonal functioning, personal care skills, and work skills (Bowie & Harvey, 2000). Generalized cognitive impairment thus seems to have stronger generalization to real-world competencies than measures of specific cognitive domains, at least in so far as this issue has been addressed to date (Bowie et al., 2014). The present findings support the BACS as an efficient measure that can be used to assess this deficit across a wide range of cognitive investigations for studies of diverse psychotic disorders and family studies of affected individuals.

4.3. Limitations

While showing a unidimensional nature of BACS subtest scores that was similar across disorders and relative groups, the present data cannot demonstrate that there is a unidimensional nature to cognitive impairments in psychotic disorders, only that the deficit assessed by the BACS battery appears to be unidimensional. More extensive neurocognitive batteries incorporating biomarkers or neurocognitive measures (i.e., eye movement, EEG, translational) may have the breadth in terms of both multiple measures of domains and broader coverage of potentially relevant domains contributing to complex neurocognitive architectures. While the findings with the BACS battery in the present study show it to be a useful way for tracking a similar generalized deficit across disorders and family groups, its comparative utility vs. other approaches in terms of optimal characterization and efficiency of testing remains a question for future research.

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The funding agencies had no role in the design and conduct of the study collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Contributors

Mr. Hochberger is the lead author and was involved in all aspects of the report. Dr. Hill was involved in all aspects of the report. Dr. Sweeney is the senior author, was a site PI, and was involved in all aspects of the report. Ms. Nelson was involved in data analysis, literature review, compilation of the main tables, and writing early drafts of the report. Dr. Reilly has been involved in all aspects of the project including data collection, clinical characterization, data processing and quality control, conducted the heritability analysis, and advised on further data analysis and interpretation. Dr. Keefe provided the BACS battery, training for the BACS, quality control of the BACS throughout the study, and consultation regarding the statistical analytic approach. Drs. Godfrey, Keshavan, and Tamminga were site PIs and PIs for the respective linked RO1 grants (see Acknowledgments). All authors have approved the final version.

Conflict of interest

Dr. Tamminga has received support from Intracellular Therapies (ITI, Inc.), PureTech Ventrues, Eli Lilly Pharmaceuticles, Sunovion, Astellas, Merck (ad hoc consulting), International Congress on Schizophrenia Research (unpaid volunteer), NAMI (unpaid volunteer), American Psychiatric Association (Deputy Editor), and Finnegan Henderson Farabow Garrett & Dunner, LLP. Dr. Keefe has received investigator-initiated support from the Department of Veteran's Affair, Feinstein Institute for Medical Research, GlaxoSmithKline, National Institute of Mental Health, Novartis, Psychogenics, Research Foundation for Mental Hygiene, Inc., and the Singapore National Medical Research Council. Dr. Keefe has received honoraria, served as a consultant, or advisory board member for Abbvie, Akebia, Amgen, Astellas, Asubio, BMS, Roche, and Eli Lilly, EnVivo, Helicon, Lundbeck, Merck, Mitsubishi, Otsuka, Pfizer, Roche, Shire, Sunovion, Takeda, Targacept. Dr. Keefe is a shareholder in Sengenix and NeuroCog Trials, Inc. and receives royalties from the BACS testing battery and the MATRICS Battery (BACS Symbol Coding). Dr. Bishop has received research support from Ortho-McNeil Janssen. Dr. Keshavan has received support from Sunovion and GlaxoSmithKline. Dr. Sweeney has received support from Takeda, BMS, Roche, and Eli Lilly and research funding from Janssen. The other authors have nothing to disclose.

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