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Working memory impairment in probands with schizoaffective disorder and first degree relatives of schizophrenia probands extend beyond deficits predicted by generalized neuropsychological impairment

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ABSTRACT

Objective: Working memory impairment is well established in psychotic disorders. However, the relative magnitude, diagnostic specificity, familiality pattern, and degree of independence from generalized cognitive deficits across psychotic disorders remain unclear.
Method: Participants from the Bipolar and Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study included probands with schizophrenia (N = 289), psychotic bipolar disorder (N = 227), schizoaffective disorder (N = 165), their first-degree relatives (N = 315, N = 259, N = 193, respectively), and healthy controls (N = 289). All were administered the WMS-III Spatial Span working memory test and the Brief Assessment of Cognition in Schizophrenia (BACS) battery.
Results: All proband groups displayed significant deficits for both forward and backward span compared to controls. However, after covarying for generalized cognitive impairments (BACS composite), all proband groups showed a 74% or greater effect size reduction with only schizoaffective probands showing residual backward span deficits compared to controls. Significant familiality was seen in schizophrenia and bipolar pedigrees. In relatives, both forward and backward span deficits were again attenuated after covarying BACS scores and residual backward span deficits were seen in relatives of schizophrenia patients.
Conclusions: Overall, both probands and relatives showed a similar pattern of robust working memory deficits that were largely attenuated when controlling for generalized cognitive deficits.

1. Introduction

Working memory deficits are a core cognitive feature of psychotic disorders (Lee and Park, 2005; De et al., 2013; Kelleher et al., 2013a; Koychev et al., 2012; Reichenberg and Harvey, 2007). Working memory encompasses a variety of cognitive processes ranging from relatively simple encoding and maintenance to more complex manipulation of stored information. Working memory impairments for basic maintenance and rehearsal both have been reported in schizophrenia patients (Lencz et al., 2003; Reilly et al., 2006, 2007; Park and Holzman, 1993) and in their relatives (Myles-Worsley and Park, 2002; Glahn et al., 2003; Saperstein et al., 2006; Kelleher et al., 2013b). Abnormalities have also been observed when more complex processing is required (MacDonald et al., 2005; Cannon et al., 2005; Tan et al., 2007; Kim et al., 2004). In recent years working memory impairments have come into focus as a cognitive feature in bipolar disorder with psychosis (Bora et al., 2010; Glahn et al., 2006; Brandt et al., 2014), suggesting that impairment in this RDoC domain extends across disorders. Yet, the relative magnitude of impairments across psychotic disorders and the extent to which these impairments are familial (Schulze et al., 2011; Bora et al., 2008) remains unclear. No studies have directly compared simple and complex working memory processes across psychotic disorders and among their first-degree relatives.

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This report was designed to 1) clarify the relative magnitude and diagnostic specificity of spatial working memory impairments (forward and backward span) across psychotic disorders, 2) examine whether forward and/or backward span impairments merely reflect the generalized cognitive impairments associated with psychotic disorders or specific informative cognitive deficits above those predicted by generalized impairments, and 3) assess the degree to which working memory impairments extend to first-degree relatives and estimate their familiality.

2. Methods

The five-site B-SNIP consortium (Maryland Psychiatric Research Center, University of Chicago/University of Illinois at Chicago, University of Texas — Southwestern, Wayne State University/Harvard University, and the Institute of Living/Yale University) was organized to address questions about diagnostic boundaries and familiality of intermediate phenotypes in psychotic disorders.

Identical inclusion criteria and testing procedures were employed across all sites. Recruitment and clinical assessment procedures have been reported previously (Tamminga et al., 2013). Probands were required to have a diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder with a history of psychosis based on the Structured Clinical Interview for DSM Disorders (SCID) (First et al., 1995). Probands were clinically stable and on stable medication regimens for the month prior to testing. Healthy participants were recruited from the community and were required to have no personal history of a psychotic disorder or recurrent depression and no known immediate family history of these disorders.

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 prior 30 days or substance dependence in the prior 6-months, 3) negative urine drug screen for common drugs of abuse on the day of testing, 4) no history of systemic medical or neurological disorder likely to impact cognitive abilities, 5) age-corrected Wide Range Achievement Test-IV Reading standard score (SS) >65, and 6) sufficient fluency in English to complete testing.

2.1. Measures

All participants completed the Brief Assessment of Cognition in Schizophrenia (BACS) neuropsychological battery and the WMS-III Spatial Span subtest was included to assess maintenance and manipulation aspects of spatial working memory.

2.2. Statistical analyses

Demographic and clinical sample characteristics are presented in Table 1 for probands and Table 2 for first-degree relatives. Consistent with our prior B-SNIP reports (Hill et al., 2013, 2014), neither antipsychotic dose nor the presence (vs. absence) of current antipsychotics, mood stabilizers or antidepressants were meaningfully related to forward or backward span scores in probands or relatives (r's <0.22). Thus, neither dosage nor medication status was modeled in the analyses. Our prior B-SNIP report indicated statistically significant group differences for age, race, and sex (Hill et al., 2013). Therefore, age, race, and sex were used as covariates in all analyses. Using a normative based regression approach, hierarchical linear modeling (HLM) was used to test for group differences. Post-hoc comparisons were conducted where indicated by a significant omnibus finding. Primary hypothesis testing was completed using a Hochberg correction (Hochberg, 1988) for multiple comparisons. The previous B-SNIP findings demonstrated significant generalized cognitive deficits across psychotic disorders as measured by the BACS (Hill et al., 2013). In addition to investigating working memory deficits in probands and relatives, this report sought to determine whether performance deficits on the Spatial Span test were independent of the generalized cognitive deficit by examining

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

	Healthy controls		Schizophrenia		Schizoaffective		Bipolar w/ psychosis		Findings
	n = 289		n = 289		n = 165		n = 227		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age (years)	37.78	(12.67)	36.01	(12.67)	36.58	(11.81)	36.19	(12.79)	$F = 1.119^{ns}$
Education (years)	15.1	(2.58)	12.75	(2.25)	13.06	(2.22)	14.18	(2.37)	$F = 51.803^{\S,a}$
Wide range achievement Test–IV: Reading test (SS)	103.01	(13.77)	93.79	(15.42)	96.68	(14.76)	101.35	(13.76)	$F = 23.179^{\S,a}$
	n	%	n	%	n	%	n	%	
Sex									
Male	123	42.6%	197	68.2%	67	40.6%	85	37.4%	$\chi^2 = 64.033^{\S,b,c}$
Female	166	57.4%	92	31.8%	98	59.4%	142	62.6%	
Race									
Caucasian	181	62.8%	135	46.7%	89	53.9%	169	74.4%	$\chi^2 = 55.832^{\S,d}$
Afr.-American	79	27.4%	137	47.4%	66	40.0%	47	20.7%	
Other	29	9.7%	17	5.9%	10	6.1%	11	4.8%	
Clinical variables			Mean	SD	Mean	SD	Mean	SD	
PANSS total			65.19	17.0	67.7	15.3	53.4	14.1	$F = 50.51^{\S,e}$
PANSS positive			16.6	5.6	17.7	4.8	12.8	4.5	$F = 52.26^{\S,e}$
PANSS negative			16.6	5.9	15.7	4.9	12.1	4.0	$F = 53.32^{\S,e}$
YMRS			5.3	5.8	7.0	6.6	5.9	6.6	$F = 3.52^{*,f}$
MADRS			8.6	7.7	14.9	10.2	10.4	9.2	$F = 25.81^{\S,g}$

PANSS: Positive and Negative Syndrome scale; YMRS: Young Mania Rating Scale; MADRS: Montgomery-Åsberg Depression Rating Scale.
[a] Controls > schizophrenia, schizoaffective, and bipolar; schizoaffective > schizophrenia and bipolar.
[b] Disproportionate number of females in bipolar group.
[c] Disproportionate number of males in schizophrenia group.
[d] Disproportionate number of African-Americans and Caucasians in both schizophrenia and bipolar groups.
[e] Bipolar < schizophrenia and schizoaffective.
[f] Schizoaffective > schizophrenia.
[g] Schizoaffective > bipolar and schizophrenia.
* $p < .05$.
§ $p \leq .001$.