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Are Working Memory Deficits in Bipolar Disorder Markers for Psychosis?

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Working memory deficits have been identified in bipolar disorder, but there is evidence suggesting that these deficits may be markers for psychosis rather than affective disorder. The current study examined this issue by comparing two groups of individuals with bipolar disorder, one with psychotic features and one without psychotic features, with a group of normal controls. Working memory was conceptualized as a multicomponent system that includes auditory and visuospatial short-term stores, executive control processes, and an episodic buffer that allows for communication between short- and long-term memory stores (Baddeley & Logie, 1999). Results indicated that only executive control processes significantly differentiated the psychotic and nonpsychotic bipolar groups, although visuospatial working memory differentiated both bipolar groups from controls. The results support the idea that some aspects of working memory performance are markers for psychosis, while others may be more general markers for bipolar disorders.

Keywords: bipolar disorder, psychosis, neurocognitive, working memory, executive function, endophenotype

The distinction between affective and psychotic disorders is controversial. In fact, almost half of the individuals with bipolar disorder (BP) will experience psychotic features at some point in the illness (Keck et al., 2003) with comparable rates of major depressive episodes in those with schizophrenia (Johnson, 1988; Kim et al., 2006). The *Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition* (*DSM–IV*; American Psychiatric Association, 1994) diagnoses of schizoaffective disorder and BP with psychotic features highlights the substantial co-occurrence of affective and psychotic symptoms. Despite these separate diagnoses, it is not clear whether they do in fact reflect distinct neurobiological subtypes of affective and psychotic disorders or hold an intermediate position along an affective-psychosis continuum, although recent genetic studies have provided some evidence of a common link between affective and psychotic disorders (Hamshere et al., 2005; Hill, Harris, Herbener, Pavuluri, & Sweeney, 2008; Jones et al., 2007; Laursen et al., 2005).

One approach to examine this issue is the application of neuropsychological tests to determine whether neurocognitive profiles differ among patients who experience both affective and psychotic symptoms. Neuropsychological deficits are considered core features of psychotic and affective disorders, they are predictive of functional outcomes (Bello, Randall, Armstrong, Barney, Kazakov, & Allen, 2008; Brekke, Kay, Lee, & Green, 2005; Green, Kern, & Heaton, 2004; Martínez-Arán et al., 2007), and some have been suggested as endophenotypes (Bora, Yucel, & Pantelis, 2008; Ferrier, Chowdhury, Thompson, Watson, & Young, 2004; Frangou, Haldane, Roddy, & Kumari, 2005; Frantom, Allen, & Cross, 2008; McIntosh, Harrison, Forrester, Lawrie, & Johnstone, 2005). Deficits in working memory and executive function have been consistently identified in patients with schizophrenia (Bilder et al., 2000; Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005; Fleming, Goldberg, Gold, & Weinberger, 1995; Leiderman & Strejilevich, 2005; Park & Holzman, 1992) and their unaffected family members (Glahn et al., 2006; Warnick & Allen, 2005), in monozygotic and dizygotic twin pairs discordant for schizophrenia (Cannon et al., 1996), in populations at high risk for psychosis (Lencz et al., 2005; Warrick et al., 2006), and in first-break patients with psychosis (Brickman et al., 2004; Kenny et al., 1997; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009; Oie & Rund, 1999). Studies of schizoaffective disorder have produced mixed results, with some studies finding no neurocognitive differences from schizophrenia (Evans et al., 1999) and others suggesting more severe impairment in schizophrenia (Gruber, Gruber, & Falkai, 2006; Heinrichs, Ammari, McDermid, Vaz, & Miles, 2008; Stip et al., 2005) so that schizoaffective patients perform similarly to "high cognitive functioning" schizophrenia (Allen, Goldstein, & Warnick, 2003; Goldstein, Shemansky, & Allen, 2005; Reichenberg et al., 2008).

Studies of BP suggest less severe neurocognitive impairment than observed in schizophrenia (Goldberg et al., 1993; Krabbendam, Arts, van Os, & Aleman, 2005; Park & Holzman, 1992; Seidman et al., 2002) but also that psychotic features in BP are associated with more severe neurocognitive impairment (Albus et al., 1996; Kravariti, Dixon, Frith, Murry, & McGuire, 2005; Martínez-Arán, Vieta, Colom, et al., 2004, Martínez-Arán, Vieta, Reinares, 2004) so that neurocognitive functioning may distinguish between those with and without psychotic features (Bora et al., 2007; Glahn et al., 2007, 2006; Martínez-Arán et al., 2008, 2007; Selva et al., 2007). These studies are few in number, and their results are not entirely consistent. For example, spatial work-

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ing memory deficits distinguish BP with psychotic features from BP without psychotic features in some studies (Glahn et al., 2007) but not others (Bora et al., 2007). Executive functions also appear to differentiate BP patients with psychosis from those without psychosis (Bora et al., 2007; Glahn et al., 2007) and be more severe in bipolar patients who have a family history of psychosis (Tabarés-Seisdedos et al., 2003). It may then be that more severe working memory and executive function deficits in BP are markers for psychosis that are present even when psychotic and affective symptoms are remitted, and thus indicate that in those patients with symptoms of psychosis, neural systems including frontal-striatal networks are differentially impaired (Bearden et al., 2007; Bearden, Hoffman, & Cannon, 2001; Savitz, Solms, & Ramesar, 2005).

Some of the inconsistent findings may occur because of methodological differences between studies. For example, it has been common practice to combine multiple tests to form cognitive domain scores (e.g., Bora et al., 2007; Frantom et al., 2008; Glahn et al., 2007; Nuechterlein et al., 2004), which provide a more reliable and comprehensive assessment of a particular cognitive ability. However, for constructs such as executive function or working memory that are multifactorial in nature (Miyake, Friedman, Emerson, Witzki, & Howerter, 2000), this approach may serve to obscure differences in component processes that would otherwise be apparent if examined individually. Models of working memory conceptualize it as a multiple-component system (Miyake & Shah, 1999). Arguably, the most influential of these models was proposed by Baddeley and Hitch (1974) and includes a phonological loop, visuospatial sketchpad, central executive, and episodic buffer (Baddeley & Logie, 1999). The phonological loop and visuospatial sketchpad are short-term memory stores that allow for temporary storage and rehearsal of verbal and acoustic information (phonological loop) or visual information (visuospatial sketchpad). The central executive is an attentional control system that has no intrinsic storage capacity of its own but rather controls and manipulates information in the two short-term stores. Central executive functions include divided and focused attention and attentional manipulation and switching (Baddeley & Logie, 1999), among others. Finally, the episodic buffer is a temporary storage system that is controlled by the central executive but allows for integration of information from short- and long-term memory stores.

There has not yet been an attempt to examine the various components of working memory to determine whether they are differentially impaired in BP with psychotic features, although based on the literature one might expect more severe impairment in executive function and visuospatial working memory (VW). If the components of the working memory system were differentially impaired, then examination of the individual components would allow identification of these differential deficits. Furthermore, if markers for psychosis, these deficits are expected to be present in BP patients whose affective and psychotic symptoms are remitted. The purpose of the current study was to separately examine the components of working memory along the lines proposed by Baddeley to determine whether a differentiated profile of performance would emerge in BP patients with and without psychosis whose symptoms were remitted. Tests were selected to assess auditory working memory (AW) and VW, executive control processes (EC), and exchange of information between short- and long-term memory stores. Based on the existing literature, it was hypothesized that psychotic features in BP would be associated with more severe deficits in EC and VW, but not in AW or short- and long-term memory integration.

Method

Participants

The study included 77 individuals, 46 who were diagnosed with either Bipolar I disorder (BPI) ($n = 37$) or Bipolar II disorder (BPII) ($n = 9$), and 31 healthy controls (NC). Participants with BP were divided into two groups, one with psychotic features (BP+) ($n = 24$), and the other without psychotic features (BP−) ($n = 22$). Individuals were included in the BP+ group if they had ever experienced delusions or hallucinations during a mood episode as determined by the Structured Clinical Interview for *DSM–IV* Axis I Disorders (SCID). Those included in the BP− group denied ever experiencing hallucinations or delusions. Demographic and clinical information for the groups is presented in Table 1.

All participants were required to speak English as their first language. Exclusion criteria included a diagnosis of a neurological disorder, a diagnosis of substance use disorder within the past 6 months, current use of medications with known effects on central nervous system (CNS) function (with the exception of medications prescribed specifically for the treatment of BP), or a hearing or vision impairment that would interfere with completion of study measures. Individuals were also excluded from the control group if they had a first-degree relative diagnosed with BP, major depressive disorder, or schizophrenia, as determined by using a standardized interview. As can be seen from Table 1, participants with BP were taking a variety of medications. Mood stabilizers included lithium and anticonvulsants, and none of the participants were prescribed typical antipsychotic medications. The local institutional review board for protection of human subjects approved the study, and all participants provided informed consent prior to completing any of the study procedures.

Measures

Psychiatric diagnoses were established by using the SCID (First, Spitzer, Gibbon, & Williams, 2002), which was supplemented with information from available medical records. Symptom severity was evaluated using the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960), Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978), and Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962). Current IQ was estimated using the Wechsler Adult Intelligence Scale, Third Edition **(**WAIS-III; Wechsler, 1997) Vocabulary and Block Design subtests (Ringe, Saine, Lacritz, Hynan, & Cullum, 2002).

AW was assessed with the forward and backward Digit Spans from the WAIS-III. VW was assessed by using the forward and backward Spatial Span tasks from the Wechsler Memory Scale, Third Edition (WMS-III; Wechsler, 1997). The Digit Span and Spatial Span tasks are commonly used as measures of short-term or working memory and are largely free from processing speed requirements (Lezak, Howieson, & Loring, 2004). EC were assessed by using the Wisconsin Card Sorting Test (WCST; Grant &

Table 1
Demographic Characteristics for the Bipolar With Psychotic Conditions (BP+), Bipolar Without Psychotic Conditions (BP−), and Healthy Controls (NC) Groups

	BP+ ($n = 24$)	BP− ($n = 22$)	NC ($n = 31$)	Between-group differences
Demographic information				
Age (*SD*)	35.8 (13.9)	32.6 (13.4)	30.3 (10.0)	$F = 1.31$ $p = 0.28$
Education (*SD*)	14.9 (2.2)	14.2 (2.4)	14.5 (1.3)	$F = 0.72$ $p = 0.49$
% Females	63	68	55	$\lambda = 0.03$ $p = .61$
% Bipolar II disorder	13	27	0	$\lambda = 0.10$ $p = .31$
Current symptoms				
HRSD (*SD*)	7.5 (4.3)	8.1 (6.3)	1.7 (2.2)	$F = 18.20$ $p < 0.001$
YMRS (*SD*)	3.5 (2.6)	3.8 (3.0)	0.4 (0.7)	$F = 20.15$ $p < 0.001$
Clinical course				
Duration of illness, years (*SD*)	17.2 (12.5)	15.4 (11.6)		$F = 0.22$ $p = 0.63$
No. of hospitalizations (*SD*)	2.5 (2.3)	1.1 (1.4)		$F = 3.99$ $p = .02$
IQ (*SD*)	105.4 (10.2)	103.9 (12.2)	110.0 (10.8)	$F = 2.33$ $p = 0.11$
Current psychiatric medications				
% Unmedicated	21	23		$\lambda = 0.03$ $p = .74$
% Anticonvulsants	75	41		$\lambda = 0.23$ $p = .22$
% Lithium	8	0		$\lambda = 0.07$[a] $p = .10$
% Antipsychotics (atypical)	58	36		$\lambda = 0.12$ $p = .55$
% Antidepressants	54	50		$\lambda = 0.02$ $p = .83$
% Benzodiazepines	38	9		$\lambda = 0.15$ $p = .39$

Note. HRSD = Hamilton Rating Scale for Depression; YMRS = Young Mania Rating Scale.
[a] Uncertainty coefficient was calculated rather than λ because of a nonvalued cell.

Berg, 1948; Heaton, Chelune, Talley, Kay, & Curtiss, 1993). The WCST assesses a number of abilities, including set shifting. Integration of auditory and visual information between short- and long-term memory was assessed by using the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) and the Biber Figure Learning Test-Expanded (BFLT-E; Glosser, Goodglass, & Biber, 1989). The BFLT-E is designed to be a visual analog of the CVLT (Glosser, Cole, Khatri, DellaPietra, & Kaplan, 2002) and involves a series of five learning trials, an interference or distractor trial, an immediate recall condition, a delayed recall condition, and a cued recall condition. However, instead of words, the stimuli for the BFLT-E are a series of geometric figures. For the CVLT and the BFLT-E, the first learning trial and the distractor trial were used. These measures were selected from the CVLT and BFLT-E because they reflect short-term memory processing (recency effects), as well as long-term memory processing (primacy effects).

These neurocognitive tasks were selected based on theoretical considerations as well as factor analytic studies establishing that they assessed the intended constructs and represented separable cognitive domains (Allen et al., 1997; Genderson et al., 2006; Kremen, Seidman, Faraone, Pepple, & Tsuang, 1992; Mirsky, Anthony, Duncan, Ahearn, & Kellam, 1991; Mirsky, Pascualvaca, & Duncan, 1999; Park, Allen, Barney, Ringdahl, & Mayfield, 2009). For example, Genderson et al. (2006) demonstrated the forward and backward digit span tasks loaded together, and separate from the WCST. Similarly, studies of various tests of attention indicate that digit span loads on a factor distinct from the WCST, Trail Making, and the Continuous Performance Test (CPT; Kremen et al., 1992; Mirsky et al., 1991, 1999; Park et al., 2009). The WCST has been used in some models of attention to assess the shifting component of attention (Mirsky et al., 1991, 1999), and in studies of working memory to reflect the preservation of central executive functioning in amnestic disorders (Baddeley & Wilson, 2002; Gooding et al., 2005). Finally, factor analytic studies of the CVLT have confirmed that List A Trial 1 and Trial B load together to form a factor separate from other CVLT scores (Donders, 2008; Griffiths et al., 2006; Wiegner & Donders, 1999).

Procedures

Subjects for the study were recruited from the community through referrals from private mental health practitioners, mental health clinics, support groups, and community college and university campuses. Following the screening and diagnostic interview, all participants were given the same neuropsychological tests in a fixed order. Doctoral level graduate students who were extensively trained in the reliable and valid administration of the assessment procedures individually conducted all evaluations in a quiet, private room.

Data Analysis

Preliminary analyses examined whether there were significant differences among the three groups (BP+, BP−, and NC) on variables known to impact neurocognitive test performance, including age, years of education, and IQ. Likelihood ratios were utilized for analysis of categorical variables and analysis of variance (ANOVA) was used for continuous variables, followed by post hoc comparisons when overall significant differences were identified. A principal components analysis (PCA) with varimax rotation was used to determine whether the tests included in this study loaded on factors in a way that would confirm their measurement of the various working memory components. Based on the results of the PCA, composite scores were calculated to directly compare the groups on the AW, VW, EC, and short-term long-term memory communication (SL). Composite scores were calculated by first converting raw test scores into *z*-scores based on

the performance of the control group. Then, means of the *z*-scores for measures within each of the working memory components were calculated, resulting in four composite scores that were standardized based on the performance of the normal controls, thus allowing for direct comparisons across the composites among the groups.

MANOVAs were then used to examine differences between the groups for each of the composite scores. Composite scores served as dependent variables in these MANOVAs and group membership (BP+, BP−, and NC) served as the between subjects factor. When MANOVAs for the composites were significant, univariate *F* tests were used to determine whether the pattern of differences between the groups was consistent with our a priori hypotheses. Associations among the composite scores were then examined using Pearson correlations. Finally, the influence of diagnosis (BPI or BPII), hospitalizations, medications, and symptoms on working memory performance were examined. Spearman's ρ correlations were used when variables were not continuous.

Results

Demographic and Clinical Variables

Table 1 contains descriptive statistics for demographic and clinical variables for each group, as well as the results of preliminary analyses. No significant differences were found among the groups for age, education, or current IQ. In addition, likelihood ratios indicated nonsignificant differences for sex and race. Significant differences were present for manic and depressive symptoms (see Table 1). Post hoc analyses indicated that BP+ and BP− groups exhibited significantly more manic and depressive symptoms than the controls ($p < .01$, ds > 1.36), although they did not differ from each other for depression (HDRS), $F(1, 44) = .16$, $p = .69$, $d = .11$, or for mania (YMRS), $F(1, 44) = .15$, $p = .70$, $d = .11$. These findings were expected for comparisons made between healthy controls and bipolar groups. Scores from the HRSD and YMRS indicated that overall, the patients were euthymic. Also, none were experiencing a current major depressive, mixed or manic episode when evaluated, as determined by the SCID. Consistent with the absence of current mood episode, none of the participants were actively psychotic at the time of evaluation, as determined by the Brief Psychiatric Rating Scale (BPRS), which was administered to 42 BP participants and 13 controls. For example, on the BPRS Hallucinatory Behavior and Unusual Thought Content (delusions) items, means (and *SD*s) for the bipolar patients were 1.02 (0.27) and 1.19 (0.63), while comparable scores for the controls were 1.0 ($SD = 0.0$) and 1.0 ($SD = 0.0$) on these BPRS items. These differences were not significant (all ps $> .17$).

Diagnosis (BPI vs. BPII) and duration of illness did not differ between the BP+ and BP− groups. Although number of hospitalizations was low for both groups, the BP+ group had significantly more hospitalizations, which is consistent with the more severe course commonly reported when psychotic features are present in BP. Also, the BP+ group was more often taking anticonvulsant medication than the BP− group. Given these differences, hospitalizations and anticonvulsant medications were examined in the main analyses to determine what influence, if any, they had on the working memory composites.

Factor Analysis of Working Memory Tests

To establish the construct validity of the factors, neurocognitive tests were subjected to principal components analyses (varimax rotation). The Kaiser-Guttman criteria indicated the presence of four factors. As can be seen from Table 2, these four factors accounted for 66.4% of the variance. Also, they corresponded to the hypothesized working memory components that the neurocognitive measures were selected to assess, including EC, VW, AW, and SL. The tests exhibited strong loadings on their respective factors, and did not load strongly on other factors, supporting the factorial validity of the solution (bold face font in Table 2 indicates primary loadings).

Group Comparisons on Working Memory Composite Scores

Descriptive statistics, results of the ANOVAs, and effect sizes for the working memory measures are presented in Table 3. Figure 1 presents composite scores for the working memory domains. ANOVA comparing the three groups on the AW composite indicated that the differences among the groups were not significant, although both BP groups performed below the controls and did not differ markedly from each other (see Figure 1). For the VW composite, the difference among the groups was significant. Planned comparisons indicated that difference between the BP+ and BP− groups was not significant ($p = .94$, $d = .01$), although the BP+ and the BP− groups significantly differed from controls ($p = .04$, $d = .57$, and $p = .03$, $d = .60$, respectively). For the SL composite, differences among the groups were not significant, although both the BP groups performed below the controls and did not differ markedly from each other. For the EC composite, significant differences were present among the groups. The BP+ group performed signifi-

Table 2
Principal Components Analysis for Neurocognitive Tests

Neurocognitive test score	Factor scores			
	EC	VW	AW	SL
WCST CAT	**.89**	−.08	.04	−.18
WCST PE	**.84**	.09	.09	−.29
WCST FMS	**.61**	−.35	−.21	.05
SSF	−.01	**.82**	−.06	.19
SSB	−.15	**.78**	.08	.21
DSF	.01	−.07	**.83**	.06
DSB	−.01	.11	**.80**	.15
Biber trial 1	−.09	.29	.18	**.74**
Biber distractor	−.08	.33	.24	**.71**
CVLT List B	−.16	−.06	.10	**.69**
CVLT Trial 1	−.12	.16	−.10	**.68**
Eigenvalues	3.41	1.61	1.26	1.02
% Variance	31.08	14.62	11.43	9.28

Note. EC = executive control factor; VW = visuospatial working memory factor; AW = auditory working memory factor; SL = short-term long-term memory integration factor; WCST CAT = Wisconsin Card Sorting Test Categories Completed; WCST PE = Wisconsin Card Sorting Test Perseverative Errors; WCST FMS = Wisconsin Card Sorting Test Failure to Maintain Set; SSB = Spatial Span Backward; SSF = Spatial Span Forward; DSF = Digit Span Forward; DSB = Digit Span Backward; CVLT = California Verbal Learning Test.

Table 3
Neuropsychological Variables for the Bipolar With Psychotic Features (BP+), Bipolar Without Psychotic Features (BP−), and Healthy Controls (NC) Groups

	Group									
	BP+ (n = 24)		BP− (n = 22)		NC (n = 31)					
Variables	*M*	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*	Contrasts	η_p^2
AW composite (*z*-score)	−0.32	0.97	−0.29	0.82	0.00	0.84	1.13	.33		.030
Digit span forward	10.4	2.3	11.7	2.2	11.1	2.2				
Digit span backward	7.7	2.3	6.7	1.9	8.3	1.9				
VW composite (*z*-score)	−0.48	0.83	−0.49	0.79	0.00	0.84	3.23	.045	B+, B− < N	.080
Spatial span forward	8.6	1.9	8.5	1.4	9.5	2.4	2.13	.13	ns	.054
Spatial span backward	7.7	1.9	7.8	2.0	8.7	1.8	2.61	.08	ns	.066
SL composite (*z*-score)	−0.38	0.88	−0.36	0.74	0.00	0.76	1.94	.15		.050
BFLT Series A trial 1	17.2	6.3	16.8	6.4	19.5	5.2				
BFLT distractor list	15.8	6.7	14.9	7.4	16.6	7.2				
CVLT List A trial 1	7.1	2.3	7.1	1.4	7.6	1.5				
CVLT List B	6.5	2.0	7.1	2.1	8.0	2.4				
EC composite (*z*-score)	−0.91	1.19	0.07	0.68	0.00	0.83	8.71	.001	B+ < N, B−	.191
WCST PE	18.8	13.0	10.3	8.7	9.7	7.1	6.75	.001	B+ > B−, N	.154
WCST CAT	4.5	2.0	5.7	0.9	5.3	1.7	3.70	.03	B+ < N, B−	.091
WCST FMS	1.3	1.4	0.5	0.9	0.6	0.8	5.06	.01	B+ > B−, N	.120

Note. AW = auditory working memory composite; VW = visuospatial working memory composite; SL = short-term long-term memory integration composite; BFLT = Biber Figure Learning Test; CVLT = California Verbal Learning Test; EC = executive control; WCST PE = Wisconsin Card Sorting Test Perseverative errors; WCST CAT = Wisconsin Card Sorting Test Categories Completed; WCST FMS = Wisconsin Card Sorting Test- Failure to Maintain Set.

cantly worse than the BP− group (p = .001, d = 1.01) and the controls (p = .0001, d = .89), although the difference between the BP- group and control group was not significant (p = .78, d = .09).

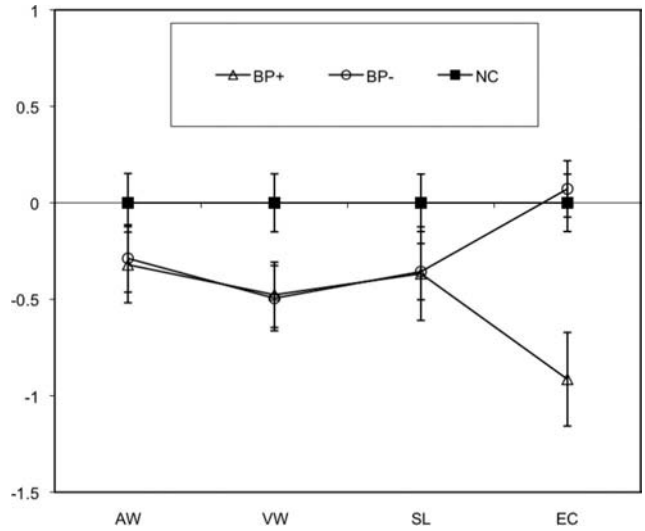

Figure 1. Auditory working memory, visuospatial working memory, short-term long-term memory integration, and executive control composite scores for the bipolar and control groups. BP+ = bipolar disorder with psychotic features group; BP− = bipolar disorder without psychotic features group; NC = normal control group; AW = auditory working memory composite; VW = visuospatial working memory composite; SL = short-term long-term memory integration composite; EC = executive control composite.

Given differences between groups on the VW and EC composite scores, post hoc univariate *F* tests were conducted for the individual test scores contributing to the composites, and these results are also presented in Table 3. For the EC composite, significant differences were present for WCST Perseverative Errors, WCST Categories Completed, and WCST Failure to Maintain Set. Subsequent analyses further indicated that the BP + group performed significantly worse than the BP- and NC groups on WCST Perseverative Errors (p = .004, d = .76, and p < .001, d = .87, respectively), WCST Categories Completed (p = .01, d = .77, and p = .05, d = .43, respectively), and WCST Failure to Maintain Set (p = .008, d = .68, and p = .006, d = .61, respectively).[1] For the VW composite tests, no significant differences were detected among the groups on Spatial Span Forward or Spatial Span Backward.

Correlations between the working memory composites indicated significant associations (p < .05) were present between all of the composite scores with the exception of the correlations between the AW and VW composites, and the AW and EC composites (see Table 4).

[1] To mitigate the potential influence of nonnormality in EC test scores, analyses were repeated on ranked data to obtain nonparametric equivalent statistics to the parametric analyses (Conover, 1999). Nonparametric analyses produced results consistent with parametric analyses. All WCST variables differentiated between the groups, including perseverative errors, $\chi^2(2) = 9.00$, p = .011; categories completed, $\chi^2(2) = 9.46$, p = .009; and failure to maintain set $\chi^2(2) = 7.90$, p = .019 (compare with Table 3), with significant differences between the BP+ and BP− groups for the WCST perseverative errors, $\chi^2(1) = 4.82$, p = .03, categories completed, $\chi^2(1) = 7.53$, p = .006, and failure to maintain set, $\chi^2(1) = 5.76$, p = .016.

Table 4
Correlations Among the Working Memory Composite Scores

	Working memory composites			
	AW	VW	SL	EC
AW	1.0			
VW	0.10	1.0		
SL	0.25*	0.43**	1.0	
EC	0.06	0.23*	0.36**	1.0

Note. $N = 77$. AW = auditory working memory composite; VW = visuospatial working memory composite; SL = short-term long-term memory integration composite; EC = executive control composite.
* $p < .05$. ** $p < .01$.

Diagnosis, Hospitalizations, Medications, Symptoms, and Working Memory

Diagnosis and working memory. Because there is some evidence that BPII is associated with less severe cognitive impairment than BPI (Simonsen et al., 2008), the composite score analyses were performed again after excluding subjects with diagnoses of bipolar II disorder. Consistent with the results when both diagnoses were included, there was no difference among the groups for the AW composite, $F\ (2,65) = 1.73$, $p = .19$, $\eta_p^2 = .051$, and significant differences were present for the VW composite, $F(2, 65) = 3.95$, $p = .02$, $\eta_p^2 = .108$, and EC composite, $F(2, 65) = 9.66$, $p < .001$, $\eta_p^2 = .229$. However, a significant difference was present for the SL composite, $F(2, 65) = 3.56$, $p = .03$, $\eta_p^2 = .099$, after excluding the participants with BPII. Post hoc analyses (Scheffé) of the VW and EC composites indicated the same findings as were reported for the entire sample. Post hoc analyses of SL composite indicated that the BP+ group performed significantly worse than controls ($p < .05$, $d = .75$) after excluding BPII participants, although no other differences were present. After excluding BPII, the SL composite score means for the NC, BP−, and BP+ groups were 0.00 ($SD = .76$), −.34 ($SD = .79$), and −.55 ($SD = .70$), respectively.

Hospitalizations and working memory composites. Given differences in number of hospitalizations between the bipolar groups, correlations were calculated with the cognitive composite scores. The correlations between number of hospitalizations and the AW, VW, SL, and EC composites were .05, −.04, .23, and −.20, respectively (all ps $> .12$; $N = 46$).

Medication and working memory composites. Correlations were then calculated between medications presented in Table 1 and the AW, VW, SL, and EC composites. While the majority of these correlations were not significant ($p > .05$), correlations between atypical antipsychotic medications (ATYP) and the AW and VW composites were significant (rs = −.42 and −.42, ps = .004, respectively), indicating that those who were taking antipsychotic medications performed better on the composites. Given these significant correlations, analyses of covariance (ANCOVAs) were completed for the AW and VW composite scores, with ATYP serving as the covariate, composite scores as the dependent variables and group membership as the between subjects factor. For the AW Composite, the effect for group was not significant, $F(1, 43) = .18$, $p = .67$, $\eta_p^2 = .004$, although ATYP was a significant covariate, $F(1, 43) = 9.78$, $p = .003$, $\eta_p^2 = .185$. For the VW composite, the effect for group was not significant, $F(1, 43) = .22$, $p = .53$, $\eta_p^2 = .009$, although ATYP was a significant covariate, $F(1, 43) = 9.44$, $p = .004$, $\eta_p^2 = .180$. These analyses indicate that antipsychotic medications did not influence the lack of differences originally found between the BP + and BP- groups on the AW and VW composites.

Medication effects were further examined by comparing medication-free patients to those who were medicated. There was no significant difference in the number of medication free participants in the BP+ group ($n = 4$) and BP− groups ($n = 5$). The small number of unmedicated patients precluded comparisons between the BP + and BP− groups, but correlations were performed between medication status (medication free vs. medicated) and the AW, VW, SL, and EC composites, which were not significant (ps $> .16$), and were −.18, −.21, −.13, and −.13, respectively. There were also no significant differences between the medicated and unmedicated groups on age $F(1, 44) = .72$, $p = .40$, $d = .35$, education $F(1, 44) = .09$, $p = .77$, $d = .11$, number of hospitalizations, $F(1, 44) = 1.11$, $p = .30$, $d = .44$, HRSD scores, $F(1, 44) = .04$, $p = .84$, $d = .07$, or YMRS scores, $F(1, 44) < .01$, $p = .99$, $d = .007$.

Symptoms and working memory composites. Although there were no differences between the bipolar groups on depressive and manic symptoms, correlations were accomplished to examine possible associations between the working memory composite scores and symptoms. Correlations between the symptom measures and the working memory composite scores were not significant (ps $> .10$), ranging from −.24 for the correlation between the HRSD and VW composite, to .11 for the correlation between the YMRS and VW composite.

Discussion

The primary objective of the current study was to provide detailed analyses of working memory to determine whether presence of psychosis in BP was associated with differential deficits in specific components of the working memory system. When this approach was used, the component of working memory that was uniquely affected by the presence of psychotic symptoms in BP was EC. It was here that a clear distinction was present between psychotic and nonpsychotic bipolar groups, with psychotic features associated with a differential impairment of executive abilities. In contrast, while both bipolar groups performed worse than controls on the AW, VW, and SL composites, the difference was only significant for the VW composite, and there was no evidence that any of these domains distinguished between the bipolar groups with and without psychosis. Thus, while visual working memory deficits may be more general markers for BP and suggest a common neurobiological disturbance between patients with and without psychosis, EC appear uniquely sensitive to the presence of psychosis. Bora et al. (2007) and Glahn et al. (2007) also found that individuals with BP and a history of psychosis were significantly more impaired on WCST Categories Completed relative to a nonpsychotic BP group, which is consistent with more general findings of impaired executive function in schizophrenia (Glahn, 2003; Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997).

The development of working memory composite scores was guided by theoretical considerations, as well as factor analytic findings in the current sample and reported elsewhere (Allen et al., 1997; Genderson et al., 2006; Kremen et al., 1992; Mirsky et al., 1991, 1999; Park et al., 2009). However, some controversy exists

regarding the assessment of working memory, particularly with regard to the appropriateness of various tests to assess the components proposed by Baddeley. For example, the forward and backward span tasks require varying amounts of executive function, with the backward spans generally considered to rely more heavily on central executive processing. However, in the current study and in others, factor analysis demonstrates that forward and backward Digit Span tasks load together to form a factor separate from other tests that have higher central executive working memory demands, such as N-back tasks, as well as from measures of executive functions, such as the WCST, and from measures of attention, such as the CPT (Allen et al., 1997; Genderson et al., 2006; Kremen et al., 1992; Mirsky et al., 1991, 1999; Park et al., 2009), possibly because even though a difference in executive processing is required, the demands are not so great that backward spans are differentiated from the forward spans. With regard to the EC composite, it is important to note that the WCST assesses only some aspects of executive function, and in models of attention has typically been used as an indicator of attentional shift (Mirsky et al., 1991; 1999), or alternatively as an indicator of executive capacity or central executive functioning (Baddeley & Wilson, 2002). In this regard, the combination of poor performance on perseverative errors (PEs) and failure to maintain set (FMS) suggest two possible mechanisms. FMS relies on the ability to hold a problem solving set in mind while sorting the cards and in this way is similar to the demands of tasks that assess the VW. PEs, on the other hand, reflects an inability to shift problem-solving set once it has been established, and in this sense is unique from what is accomplished by the other working memory components. Inability to shift problem solving set on sorting tasks such as the WCST is also considered to be a distinct aspect of poor performance in schizophrenia (Pantelis et al., 1999). Thus, the results provide evidence for a unique deficit in the ability to shift problem solving sets similar to what is observed in psychotic disorders, providing additional evidence for a link between BP with psychotic features and psychotic disorders such as schizophrenia. However, it would be important to determine whether other abilities attributed to the central executive, such as focused and divided attention, and attentional manipulation, are similarly impaired when psychosis occurs in BP.

It is also of interest that the BP− group performed much like controls on the WCST and even exceeded the controls in some cases (e.g., categories completed), although not significantly so. A similar finding was reported using a sorting test like the WCST, wherein the BP- group performed slightly better then controls on Categories completed, while the BP+ group performed worse than controls (Glahn et al., 2007). Executive function deficits in BP have been inconsistently reported, with some studies finding these deficits and others reporting no deficits (Atre-Vaidya et al., 1998; Bulbena & Berrios, 1993; Coffman, Bornstein, Olson, Schwarzkopf, & Nasrallah, 1990; El Badri, Ashton, Moore, Marsch, & Ferrier, 2001; Frantom et al., 2008; Gruzelier, Seymour, Wilson, Jolley, & Hirsch, 1988; Rubinsztein, Michael, Paykel, & Sahakian, 2000; Sapin, Berrettini, Nurnberger, & Rothblat, 1987; Tham et al., 1997; Thompson et al., 2009). Failure to control for presence of psychosis may explain some of the inconsistency, as the current results (also see Glahn et al., 2007) demonstrate that individuals who have BP without psychotic features exhibit less severe executive function deficits as assessed by the WCST. It is also noteworthy that we and others have found these diminished EC in BP+ utilizing a minimum criterion of at least one psychotic mood episode, which is a low threshold criterion. Executive function deficits may be even more pronounced in patients who have experienced repeated psychotic episodes (Glahn et al., 2007).

The lack of differences between the bipolar groups on tests of AW were expected given that a number of studies have reported negative findings in this regard (Bora et al., 2007; Glahn et al., 2007; Glahn et al., 2006). However, differences between the BP + and BP− group were expected in VW, but we did not find differences in this sample. VW deficits have been previously identified in BP populations in general (Bearden et al., 2001; Basso, Lowery, & Neel, 2002) with some studies demonstrating such impairment in unaffected, first degree relatives of individuals with BP (Frantom et al., 2008). There is also the suggestion that executive function deficits may underlie VW deficits in BP (Bearden et al., 2001; Thompson et al., 2006), and we did find stronger associations between the EC and VW composites ($r = .36$) relative to the EC and AW composite ($r = .06$). However, the difference in these correlations may simply result from modality specific effects (visual/nonverbal vs. auditory verbal), and in any case the increased impairment of executive functions in BP+ did not result in similar findings with regard to VW.

There is also evidence to suggest that VW deficits may be at least partially determined by clinical variables including disease chronicity, symptom severity and medication effects so that when these variables are controlled differences between psychotic and nonpsychotic bipolar groups are no longer significant (Glahn et al., 2007). We did not find evidence supporting a specific effect of diagnosis, medication, number of hospitalizations, or affective symptoms on VW performance, although there was an association between atypical antipsychotic medications and better performance on the AW and VW composites. The current results also suggest differences in neurobiological dysfunction underlying BP with and without psychotic features. As yet, a link has not been established between EC deficits in BP and the neural networks that underlie them, although growing evidence supports involvement of the frontal striatal networks (Bearden et al., 2007, 2001; Savitz et al., 2005).

There may also be genetic alterations detectable in patients with BP with psychosis (Kerner, Brugman, & Freimer, 2006). Genetic studies have identified mutations that are expressed in both disorders, such as the Disc1 gene mutation (for review see Porteous, Thomson, Brandon, & Millar, 2006). Also, separate lines of research have identified single nucleotide polymorphisms on several chromosomes, for example 22q in bipolar patients (Potash et al., 2008), or TGFB-induced factor on chromosome 18p (Chavarría-Siles et al., 2007). Gene products such as the COMT variants have also been identified in populations at high risk for psychosis (McIntosh et al., 2007) as well as in BP (Burdick et al., 2007). Presence of cognitive impairments that are sensitive to BP with psychotic features may parallel genetic evidence that is accumulating as risk factors for BP with psychosis and in this way serve as an endophenotype for psychosis in BP.

The current results are limited in a number of ways. The majority of the patients were medicated when evaluated and were prescribed a number of different mood stabilizers, antidepressant, antipsychotic, and anxiolytic medications, so we could not rigorously evaluate the impact that medications were having on neuropsychological test performance. Results of studies that assess medication effects on neurocognition in affective and psychotic

disorders indicate normalization of neurocognition (and brain function) resulting from medication treatments in schizophrenia (Keefe et al., 2007; Wittorf, Sickinger, Wiedemann, & Klingberg, 2008), major depressive disorder (Fales et al., 2009), and BP (Gruber, Rogowska, & Yurgelun-Todd, 2004; Phillips, Travis, Fagiolini, & Kupfer, 2008), although there is contradictory evidence particularly with regard to BP (see Savitz et al., 2005). However, because neurocognitive deficits do persist even in medication free states in BP and schizophrenia (e.g., Goswami et al., 2001; Pavuluri et al., 2006), some neurocognitive deficits are more likely to be trait markers for the disorders that represent functional changes in neural networks that are genetically driven (Burdick et al., 2007; Savitz et al., 2005). Thus, medications are unlikely to account for the executive function and VW deficits reported in this study and in others. Also, our sample included individuals with BPI and BPII diagnoses. There is ample evidence indicating that individuals with BPI spend more time in subsyndromal manic/hypomanic phases (Joffe, MacQueen, Marriott, & Young, 2004), more often experience psychosis, and are hospitalized more frequently (Vieta, Gasto, Otero, Nieto, & Vallejo, 1997) than are those with BPII. Individuals with BPII may also experience less severe cognitive impairment than those with BPI (Simonsen et al., 2008; Torrent et al., 2006). However, excluding patients with BPII in our secondary analyses did not alter the findings with regard to EC, suggesting that diagnosis did not substantially influence these findings.

Increased executive dysfunction is but one of a number of negative features associated with psychosis in BP including greater symptom severity, increased morbidity, earlier onset of illness, greater premorbid impairment, and overall decreases in IQ (Basso et al., 2002; Sigurdsson, Fombonne, Sayal, & Checkley, 1999; Tohen, Waternaux, & Tsuang, 2000). Whether these negative outcomes indicate a unique pattern of neurobiological dysfunction remains to be seen. However, deficits in neurocognitive function are associated with poorer functional outcomes in schizophrenia (Brekke et al., 2005; Green et al., 2004). An important direction for further evaluation will be to investigate whether working memory impairments, and other neurocognitive deficits, are predictive of functional outcomes in BP populations. There is some evidence to support this assertion (Altshuler et al., 2008; Bello et al., 2008; Martínez-Arán et al., 2007). Given the potential implication these deficits have for treatment, development of a consensus battery similar that developed for schizophrenia may help advance research and treatment (MATRICS; Kern et al., 2008). Finally, the literature has been divided as to the nosological status of the affective and psychotic disorders, stemming largely from the overlap in these disorders with regard to phenomenology and impairment, with BP with psychotic features and schizoaffective disorder sharing many common features. The current results provide evidence for a specific neurocognitive link between BP and schizophrenia when psychotic features are present in BP.

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