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Sources of declarative memory impairment in bipolar disorder: Mnemonic processes and clinical features

Carrie E. Bearden [a,*], David C. Glahn [b], E. Serap Monkul [c], Jennifer Barrett [b], Pablo Najt [d], Simerjit Kaur [d], Marsal Sanches [d], Veronica Villarreal [d], Charles Bowden [d], Jair C. Soares [d,e]

[a] *Department of Psychiatry & Biobehavioral Sciences, University of California Los Angeles, 300 Building Medical Plaza, Suite 2265, Los Angeles, CA 90095, USA*
[b] *Division of Schizophrenia and Related Disorders, Department of Psychiatry, The University of Texas Health Science Center at San Antonio, San Antonio, TX, USA*
[c] *Department of Psychiatry, Dokuz Eylul University School of Medicine, Izmir, Turkey*
[d] *Division of Mood and Anxiety Disorders, Department of Psychiatry, The University of Texas Health Science Center at San Antonio, San Antonio, TX, USA*
[e] *South Texas Veterans Health Care System, Audie L. Murphy Division, San Antonio, TX, USA*

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Abstract

Background: There is mounting evidence that declarative memory processes are impaired in patients with bipolar disorder. However, predictors of the observed impairment are not well understood. This study seeks to: (i) better characterize the nature of declarative memory impairment in bipolar disorder, and (ii) determine the relationship between clinical variables and memory function in bipolar disorder.
Methods: 49 adult patients with bipolar disorder in varying mood states and 38 demographically matched healthy participants completed a comprehensive neurocognitive battery assessing general cognitive functioning, processing speed, and declarative memory. The California verbal learning test was used to characterize learning and memory functions.
Results: Although patients with bipolar disorder utilized a similar semantic clustering strategy to healthy controls, they recalled and recognized significantly fewer words than controls, suggesting impaired encoding of verbal information. In contrast, lack of rapid forgetting suggests relative absence of a storage deficit in bipolar patients. While severity of mood symptomatology and illness duration were not associated with task performance, gender and family history significantly affected memory function.
Conclusions: Results suggest that declarative memory impairments in bipolar patients: (1) are consistent with deficits in learning, but do not appear to be related to different organizational strategies during learning, and (2) do not appear to be secondary to clinical state, but rather may be associated with the underlying pathophysiology of the illness.

Keywords: Bipolar disorder; Clinical state; Declarative memory; Cognition; Gender

1. Introduction

Verbal declarative memory impairments are among the most consistently reported cognitive difficulties in clinical remitted patients with bipolar disorder (Cavanagh et al., 2002; Clark et al., 2001; Deckersbach et al.,

* Corresponding author. Tel.: +1 310 206 2983; fax: +1 310 794 9517.
E-mail address: cbearden@mednet.ucla.edu (C.E. Bearden).

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2004; van Gorp et al., 1999). Given that these deficits have also been observed in unaffected relatives of patients with bipolar illness (Ferrier et al., 2004; Keri et al., 2001), declarative memory dysfunction may represent a vulnerability marker for bipolarity. However, predictors of the observed impairment are not well understood.

Declarative memory, or the explicit recall of previously learned information, relies on the ability to adequately encode, store, and retrieve verbal information (Gabrieli et al., 1998; Kapur et al., 1996). Encoding involves converting a perceived event into a lasting neurophysiological trace (Kapur et al., 1996), while retrieval refers to the process that reactivates a stored representation, leading to an explicit 'memory' of the event (Deckersbach et al., 2004). These cognitive functions (encoding, storage, and retrieval) are thought to be subserved by distinct brain regions. In particular, medial temporal regions are involved in both encoding and retrieval of verbal information, while strategic or executive aspects of memory rely on prefrontal cortical function (Cabeza and Nyberg, 2000; Lepage et al., 1998).

Declarative memory deficits are of increasing interest in bipolar disorder because of their potential association with neurophysiologic and neuroanatomic abnormalities in frontal and temporal brain regions, which have been implicated in the pathophysiology of the illness (Deckersbach et al., 2004; Soares, 2003). In particular, there is increasing evidence for prefrontal cortical pathology in bipolar disorder; several studies have found volumetric reduction in subregions of the prefrontal cortex (Drevets et al., 1997; Sax et al., 1999; Hirayasu et al., 1999; Lopez-Larson et al., 2002), corroborating postmortem findings of reduced density of neuronal and glial cells in the dorsolateral prefrontal cortex (Rajkowska et al., 2001), and decreased clustering of neurons and decreased somal size in anterior cingulate cortex (Chana et al., 2003). However, evidence for temporal lobe pathology in bipolar disorder is less consistent, with various studies reporting volumetric increases (Harvey et al., 1994), decreases (Hauser et al., 1989), and no differences, as compared to normal controls (Johnstone et al., 1989; Altshuler et al., 2000). Similarly, the majority of studies have not reported structural abnormalities of the hippocampus in patients with bipolar disorder (see Monkul et al., 2003 for a review). Nevertheless, postmortem investigations have reported decreased density of non-pyramidal neurons in region CA2 of the hippocampus (Benes et al., 1998), as well as decreased hippocampal expression of GABA-synthesizing messenger RNA (Heckers et al., 2002) suggesting that more subtle hippocampal pathology may be present in bipolar disorder, in the absence of global volume deficits.

In addition, these cognitive deficits are associated with persistent psychosocial difficulties, even in asymptomatic patients with bipolar disorder (Atre-Vaidya et al., 1998; Ferrier et al., 1999; Scott, 1995), raising the possibility that cognitive problems contribute significantly to lack of full functional recovery from affective episodes.

Despite the potential importance of memory deficits for the outcome of bipolar patients (Dickerson et al., 2003), there is debate about the nature of these impairments. While there is some evidence that poor memory performance is secondary to strategic or organizational dysfunction rather than impaired memory processes per se (Deckersbach et al., 2004), other studies suggest that memory deficits in patients with bipolar disorder may be secondary to clinical symptomatology (Kessing, 1998). Sweeney et al. (2000) identified widely distributed cognitive deficits in mixed/manic bipolar patients, while depressed bipolar and unipolar patients demonstrated impairments only on an episodic memory test, suggesting a more selective dysfunction in mesial temporal lobe function during depressive episodes. Yet, in one of the larger studies of memory functioning in bipolar disorder, Martinez-Aran et al. (2004) found little relationship between clinical state and neurocognitive deficits, suggesting that this relationship may be mediated by other factors. In particular, memory performance may be adversely affected by severity of illness, as measured by number of hospitalizations, number and duration of manic and/or depressive episodes, and age at onset (Cavanagh et al., 2002; Clark et al., 2002; Kessing, 1998; Tham et al., 1997), although others have found no relationship (Atre-Vaidya et al., 1998; Verdoux and Liraud, 2000). In addition, gender may modulate the severity of cognitive deficits in bipolar disorder, with male patients demonstrating poorer neurocognitive performance (Sweeney et al., 2000).

This disparity in findings is problematic and reflects the substantial variability in study design and methodology, as well as patient characteristics, that is common in much of the research to date (Burt et al., 1995). For instance, only recently have investigators made efforts to distinguish bipolar from unipolar affective illness, and to carefully assess mood state at time of testing (Bearden et al., 2001).

More recent studies that have assessed bipolar patients in the euthymic phase of illness using declarative memory tasks have identified significant verbal learning and memory impairments in the absence of prominent mood symptoms (e.g., Clark et al., 2002; Cavanagh et al., 2002; van Gorp et al., 1999, 1998; Altshuler et al., 2004). However, most have reported only overall scores or basic performance indices; to our knowledge only one study specifically attempted to delineate the underlying cognitive processes that may be disrupted (Deckersbach et al., 2004). In addition, while such studies have substantially advanced our understanding of trait aspects of cognitive function in bipolar disorder, it is not clear whether euthymic bipolar patients

are impaired relative to symptomatic patients, or only in comparison with normal controls.

This report attempts to overcome some of the limitations of previous studies by utilizing a well-validated verbal learning measure, the California verbal learning test (CVLT-2; Delis et al., 2000) that allows for in-depth examination of memory processes, in a large sample of patients with bipolar disorder who are well-characterized clinically with regard to mood state at time of testing, co-morbidities, medication usage, and family history. A recent study of Finnish twins discordant for bipolar disorder demonstrated that psychomotor processing speed may have a significant effect on encoding and learning efficiency (Kieseppa et al., 2004). Thus, in order to examine the effects of general performance differences on memory functions, we also included measures of general cognitive functioning and motor processing speed.

Specifically, the goals of the present study were: (i) to better characterize the nature of declarative memory impairment in individuals with bipolar disorder as a function of difficulties with encoding, storage, and/or retrieval of verbal information after a delay, and (ii) to determine the relationship between clinical status and performance on measures of verbal learning and memory in bipolar disorder, as compared with healthy controls. Based on prior studies, we hypothesized that patients with bipolar disorder would evidence difficulties in components of memory that are associated with both frontal (e.g. semantic organization) and temporal lobe function (e.g., delayed recall and recognition), with poorer performance observed in bipolar patients with substance abuse comorbidity and longer duration of illness.

2. Methods

2.1. Participants

49 patients diagnosed with bipolar disorder (41 type I and 8 type II) were recruited through the inpatient and outpatient research programs from the University of Texas Health Science Center at San Antonio (UTHSCSA), University Hospital, and the South Texas Veterans Health Care System. This study was approved by the UTHSCSA IRB, and written informed consent was obtained from all subjects prior to participation. Diagnoses were made by trained M.D. or Ph.D. level clinicians with the Patient Edition of the Structured Clinical Interview for DSM-IV (SCID-IV; Spitzer et al., 1994).

Patients were excluded if they did not currently meet DSM-IV criteria for bipolar disorder type I or II, or if they had any of the following: (i) another Axis I condition (with the exception of anxiety disorders and/or alcohol abuse or dependence); (ii) any serious medical illness or neurologic disorder that might affect cognitive function (e.g. epilepsy, migraine, head trauma with loss of consciousness); or (iii) borderline IQ/mental retardation (IQ less than 80). 38 healthy comparison subjects were recruited through advertisements in the community, according to the same exclusion criteria used for patients. In addition, control participants had no history of Axis I disorder based on SCID interview, and no history of affective disorder in first-degree relatives. Because onset of major mental illness may disrupt educational attainment and occupational function (Hill et al., 2004; Resnick, 1992), groups were matched for parental education, as well as age, sex, race, and intellectual level.

Table 1 summarizes the demographic data and clinical characteristics of the sample. Bipolar and control participants did not differ with regard to age [$F(1,85) = 2.67$, $p = 0.11$, n.s.], gender ($\chi^2 = 1.78$, $p = 0.26$, n.s.),

Table 1
Demographic characteristics of study participants

	Patients with bipolar disorder ($N = 49$)	Healthy comparison subjects ($N = 38$)	Between group differences
Gender	*N* (%)		
Male	21 (43%)	11 (29%)	$\chi^2 = 1.78$, $p = 0.26$
Female	28 (57%)	27 (71%)	
Handedness	*N* (%)		
Right	46 (94%)	37 (97%)	$\chi^2 = 0.93$, $p = 0.63$
Left	2 (4%)	1(3%)	
Both	1 (2%)	0 (0%)	
Ethnicity	*N* (%)		
Hispanic/Latino	13 (27%)	13 (34%)	$\chi^2 = 7.33$, $p = 0.12$
Caucasian	30 (61%)	19 (50%)	
African-American	4 (8%)	1 (3%)	
Asian-American	0 (0%)	4 (10%)	
Biracial/other	2 (4%)	1 (3%)	
Age	Mean (SD)		
	37.6 (11.4)	33.6 (11.3)	$F = 2.67$, $p = 0.11$
Educational attainment	Mean (SD)		
Parent	13.2 (2.5)	14.2 (2.8)	$F = 2.79$, $p = 0.10$
Participant*	13.5 (1.9)	16.1 (3.0)	$F = 25.03$, $p < 0.001$
Estimated intelligence	Mean (SD)		
Full Scale[a]	105.2 (9.0)	108.7 (11.1)	$F = 2.58$, $p = 0.11$
Verbal[a]	105.3 (8.9)	108.3 (11.4)	$F = 1.97$, $p = 0.17$
Non-verbal[b]	100.5 (11.2)	103.8 (11.0)	$F = 1.86$, $p = 0.18$

[a] Based on reading ability.
[b] Based on progressive matrices performance.
* $p < 0.01$.

handedness ($\chi^2 = 0.93$, $p = 0.63$, n.s.), parental education [$F(1,85) = 2.79$, $p = 0.10$, n.s.], or estimated Full Scale, Verbal, or Non-verbal IQ [$F(1,85) = 2.58$, $p = 0.11$, n.s.; $F(1,85) = 1.97$, $p = 0.17$, n.s.; $F(1,85) = 1.86$, $p = 0.18$, n.s., respectively]. The ethnic and racial makeup of the groups did not differ from each other ($\chi^2 = 7.33$, $p = 0.12$, n.s.) and was representative of the South Texas community from which they were recruited. The groups did significantly differ with regard to years of education [$F(1,85) = 25.03$, $p < 0.001$]. For this reason, secondary statistical analyses of significant group differences were conducted in which education was covaried.

Psychiatric symptomatology at the time of assessment was determined with the 21-item Hamilton Depression scale (HAM-D; Hamilton, 1960) and the Young Mania Rating scale (YMRS; Young, 1978). At the time of testing, four bipolar patients (8%) were in a clinically remitted state, as defined by YMRS score $\leqslant 6$ and HDRS score $\leqslant 8$ (Martinez-Aran et al., 2004). 14 bipolar patients (29%) were in a depressed mood state, as defined by HDRS score $\geqslant 17$ at the time of testing, and 16 (33%) were in a mixed, hypomanic or manic mood state at testing, as defined by YMRS score $\geqslant 12$. The remaining 15 bipolar patients (30%) had mild to moderate mood symptomatology (i.e., HDRS scores of 9–16 and YMRS scores of 7–11).

Table 2 depicts clinical characteristics of the bipolar patient sample. 25 patients were taking mood stabilizer medications (lithium: $n = 4$, anticonvulsants: $n = 21$, including valproic acid, oxcarbazepine, lamotrigine, and topiramate). In addition to mood stabilizers, eight patients were taking antidepressants (including fluoxetine, fluvoxamine, sertraline, paroxetine, and citralopram), 12 patients were taking benzodiazepines (lorazepam, clonazepam, alprazolam), and 1 was taking a psychostimulant (Adderall). Nine patients were taking atypical antipsychotic medication (risperidone, olanzapine, quetiapine, and ziprasidone), seven as an adjunct to mood stabilizers or antidepressants.

Table 2
Clinical characteristics of patients with bipolar disorder ($N = 49$)

Current symptomatology	Mean (SD) [Range]
Depressive symptoms (HAM-D)	17.1 (8.4) [0–32]
Manic symptoms (YMRS)	10.3 (7.5) [0–33]
General functioning (GAF)	64.2 (11.1) [45–95]
	Number of patients[a]
Remitted (HAM-D $\leqslant 8$, YMRS $\leqslant 6$)	4 (8%)
Mixed/Manic (YMRS $\geqslant 12$ & HAM-D $\geqslant 17$)	16 (%)
Depressed (HAM-D $\geqslant 17$)	14 (29%)
Clinical course	Mean (SD) [Range]
Bipolar type (I/II)	41/8
Age at onset	21.6 (9.9) [7–46]
Duration (years)	15.6 (10.6) [0–42]
Number of hospitalizations	1.73 (2.2) [0–10]
Clinical comorbidities	Number of patients
Any substance abuse (Lifetime/current)	23/14
Alcohol abuse/dependence (lifetime/current)	21/14
Drug Abuse/Dependence (Lifetime / Current)	6/0
PTSD (lifetime/current)	13/10
Other anxiety disorder (lifetime/current)[b]	22/22
Family history	1st or 2nd Degree relatives
Affective disorder	23
Bipolar disorder	9
Psychosis	7
Current medications	*N* (%)
None	17 (35%)
Mood stabilizers	50%
Lithium	4 (8%)
Sodium valproate	5 (10%)
Oxcarbazepine	3 (6%)
Other anticonvulsant	4 (8%)
More than 1 mood stabilizer	9 (18%)
Antipsychotic	9 (18%)
Typical	0 (0%)
Atypical	9 (18%)
Antidepressant	31%
SSRI	15 (31%)
Tricyclic	0 (0%)
Benzodiazepine	12 (25%)
Stimulant	1 (2%)
2 or more psychotropic medications	19 (39%)

[a] The remaining 15 patients had intermediate levels of depressive and manic symptoms.
[b] Five patients had both PTSD and another co-morbid anxiety disorder.

2.2. Materials

The primary declarative memory measure applied in this study was the California verbal learning test-2 (CVLT-II; Delis et al., 2000). The CVLT-II is a well-established list-learning paradigm in which subjects are asked to recall a list of 16 orally presented words over 5 trials, with free recall after each trial. An interference list is presented following the fifth recall trial. Short- and long-delayed (20 min) free recall of the initial list are assessed, followed by a delayed recognition test. Because words in the list may be grouped into 4 shared semantic categories, one can assess the extent to which subjects use semantic strategies to recall information (i.e., semantic clustering). Higher scores indicate more semantic clustering.

General intellectual abilities were approximated with two independent measures. The first, the Wechsler Test of Adult Reading (WTAR; Holdnack, 2001), is a single word reading test composed of 50 words with irregular pronunciations. The number of words correctly pronounced provides an estimate of premorbid level of intellectual functioning closely associated with IQ indices from the WAIS-III. The second measure was the Test of Nonverbal Intelligence-3 (TONI-3; Brown et al., 1997), an assessment of nonverbal intelligence and reasoning abilities, consisting of 50 non-verbal problem-solving tasks. Psychomotor speed was assessed with measures of: (1) simple reaction time for both dominant and non-dominant hands, and (2) choice reaction time; in this task the subject is instructed to indicate, by button press, whether a briefly displayed arrow points to the right or left.

2.3. Statistical analyses

Statistical analyses were conducted to examine differences in general cognitive function and declarative memory (learning, retention, strategy and recognition) between individuals with bipolar disorder and healthy comparison subjects. To that end, separate multivariate analysis of variance (MANOVA) analyses were performed with diagnostic group (bipolar vs. healthy comparison subjects) as the between subjects factor. When significant multivariate effects were found, univariate analyses (ANOVA) with Bonferroni corrections were used to determine the specific variables that distinguished bipolar patients from normal controls. For variables where the assumptions of a normal distribution were violated, non-parametric Mann–Whitney *U*-tests were used instead of parametric tests.

The initial MANOVA included performance on learning trials (trials 1–5) as a repeated measure variable, in order to examine potential group differences associated with learning verbal information. Potential group differences in retention of verbal information over short and long delay intervals were modeled in 2×2 MANOVAs examining free and cued recall over a short and long delay. These analyses were followed by univariate comparison of words retained over the delay. Differences in strategic processing (i.e., indices of semantic clustering and serial recall), error rates [i.e., number of perseverative errors (repeating the same item during a learning trial) and intrusions (recalling a word not on the list during the learning trials)], and recognition discriminability were examined using non-parametric Mann–Whitney *U*-tests.

The second aim of the statistical analyses was to explore the relationship between the hypothesized predictors and verbal memory measures. Based on previous findings by our group and others indicating possible associations with cognitive function in bipolar disorder, we considered the following variables as potential predictors in a two-stage analysis described below: age at onset, duration of illness, number of hospitalizations, age, level of social functioning (GAF), HAM-D and YMRS scores, gender, positive family history for affective disorder, current substance abuse, co-morbid post-traumatic stress disorder (PTSD), and antipsychotic medication at time of testing. Onset, duration, age, number of hospitalizations, GAF, HAM-D, and YMRS scores were modeled as continuous variables, while gender, family history, substance abuse, and medication were employed as binary variables. Following methods employed in Donaldson et al. (2003), we first used Pearson correlation coefficients to estimate and test the relationship between potential predictor variables and cognitive measures. Next, in order to examine the shared vs. independent contributions of variables that showed a significant association with performance, individual explanatory variables that significantly predicted task performance at $\alpha \leqslant 0.004$, two-tailed ($\alpha \leqslant 0.05$, Bonferroni-corrected for 12 comparisons) were utilized in a multiple regression model. Multiple regression analyses were then conducted in order to determine the relationship between empirically derived predictor variables and cognitive measures after adjusting for other empirical predictors.

3. Results

3.1. Processing speed

There were no significant differences in simple reaction time between patients with bipolar disorder (426.5 ± 141 ms) and healthy comparison subjects [385.7 ± 84 ms; $F(1,85) = 2.33$, $p = 0.13$, n.s], nor did the groups differ on the choice reaction time measure [$F(1,85) = 2.40$, $p = 0.13$, n.s]. This result indicates that group differences on verbal learning and memory tests may be attributed primarily to higher-level cognitive processing differences, as opposed to effects of generalized impairment and/or motor slowing.

3.2. Memory tasks

Table 3 indicates the number of words recalled during trials 1–5, learning slope over the 5 trials, short- and long-delayed free and cued recall, retention and recognition performance, as well as the degree of semantic and serial clustering during learning for bipolar and control participants.

Results of MANOVA analysis indicated significant main effects of diagnosis on CVLT-II performance [Wilks' $F(5,81) = 3.1$, $p < 0.02$]. As can be seen in Fig. 1 and Table 3, bipolar participants learned fewer words over the five learning trials compared with control participants [$F(1,85) = 11.7$, $p = 0.001$]. Post hoc univariate comparisons indicated that the discrepancy became more pronounced over repeated exposures to the word list, as participants with bipolar disorder did not significantly differ from controls after Bonferroni correction for multiple comparisons ($0.05/5 = 0.01$) on trials 1 and 2 [$F(1,85) = 5.46$, $p = 0.02$; $F(1,85) = 3.71$, $p = 0.06$], but recalled significantly fewer words on trials 3, 4 and 5 [$F(1,85) = 13.10$, $p = 0.000$; $F(1,85) = 8.56$, $p = 0.004$; $F(1,85) = 11.73$, $p = 0.001$]. In addition, 2×2 MANOVA comparisons indicated that bipolar participants recalled fewer words than control participants at both the short-delayed free and cued recall [$F(2,84) = 4.66$, $p = 0.01$] and long-delayed free and cued recall [$F(2,84) = 3.74$, $p = 0.03$]. Univariate analyses indicated that participants with bipolar disorder performed more poorly on all recall measures. However, bipolar patients did not differ significantly from controls

Table 3
CVLT-II performance in participants with bipolar disorder and controls: mean (SD)

	Patients with bipolar disorder ($n = 49$)	Healthy comparison subjects ($n = 38$)	Between group differences
Learning			
Learning Trial 1 recall[a]	6.00 (1.8)	7.00 (2.2)	$F = 5.46$, $p = 0.02$
Learning slope index	1.40 (0.44)	1.58 (0.68)	$F = 2.30$, $p = 0.13$
Learning trial 5 recall**	11.6 (2.4)	13.4 (2.3)	$F = 11.73$, $p = 0.001$
Total recall trials 1–5**	47.9 (10.0)	55.3 (10.2)	$F = 11.70$, $p = 0.001$
Short term memory			
Free recall**	10.7 (3.1)	12.2 (3.0)	$F = 9.35$, $p = 0.003$
Cued recall*	11.2 (2.6)	12.5 (2.8)	$F = 6.27$, $p = 0.01$
Long term memory			
Free recall**	10.7 (3.1)	12.2 (3.0)	$F = 7.27$, $p = 0.008$
Cued recall*	11.3 (2.8)	12.7 (2.7)	$F = 6.54$, $p = 0.01$
Recognition			
Number correct**	43.1(4.6)	45.8 (2.5)	$F = 11.1$, $p = 0.001$
Discriminability index**	0.94(.06)	0.97(.03)	$Z = -3.4$, $p = 0.001$
Rate of forgetting			
Short–long recall	−0.21 (1.9)	−0.08 (1.8)	$F = 0.15$, $p = 0.70$
Organizational strategies			
Semantic clustering	0.71 (1.3)	1.37 (2.1)	$Z = -1.47$, $p = 0.14$
Serial positioning	0.61 (0.91)	0.79(.90)	$Z = -1.14$, $p = 0.26$
Errors			
Total intrusions*	3.6 (3.7)	2.1 (3.3)	$Z = -2.5$, $p = 0.01$
Total repetitions	6.0 (4.6)	4.7 (3.2)	$Z = -.95$, $p = 0.34$

[a] Univariate test not significant after Bonferroni correction.
* $p < 0.05$.
** $p < 0.01$.

in the number of words retained between short-and long-delayed recall [$F(1,84) = 0.15$, $p = 0.70$, n.s.].

With regard to organizational strategies during learning, non-parametric ANOVA (Mann–Whitney U-tests) indicated no differences in the degree of semantic or serial clustering during learning [$U = 759$, $Z = -1.47$, $p = 0.14$, n.s.; $U = 798$, $Z = -1.14$, $p = 0.26$, n.s., respectively]. However, there were group differences in recognition discriminability [$U = 544$, $Z = -3.4$, $p = 0.001$], indicating that bipolar patients recognized fewer words from the original list than control participants. Finally, bipolar patients had more total intrusions than control participants [$U = 629.5$, $Z = -2.5$, $p = 0.01$], indicating that they erroneously recalled more words not on the original list than did normal controls.

Because patients with bipolar disorder had significantly lower educational attainment than controls, the primary analyses were repeated after covarying for education. This did not affect the significance of any of the results: the main effect of diagnosis on total words learned across trials remained significant [Wilks' $F(5,80) = 2.51$, $p = 0.04$], and bipolar participants continued to show significantly poorer memory for the word list, as compared to controls, at both the short-delayed free and cued recall [$F(2,83) = 3.45$, $p = 0.04$] and long-delayed free and cued recall [$F(2,83) = 3.10$, $p = 0.05$]. Education was not significantly related to performance on any of the memory measures.

3.3. Medication effects

To evaluate effects of different medication regimens, bipolar participants were divided into three subgroups: those currently on no medications ($n = 17$), those taking mood stabilizers or antidepressants only [$n = 11$ (lithium and anticonvulsants, $n = 10$; paroxetine, $n = 1$)], and those taking a combination of 2 or more psychotropic medications of different classes ($n = 19$). A Kruskal–Wallis analysis of variance indicated no significant differences between groups for total learning over 5 trials [$\chi^2(2) = 3.6$, $p = 0.16$, n.s.], nor for short and long delayed free recall [$\chi^2(2) = 0.86$, $p = 0.65$, n.s.; $\chi^2(2) = 4.5$, $p = 0.11$, n.s, respectively]. Because the division into smaller subgroups reduced statistical power for detecting group differences, we also dichotomized the sample into patients on any medication (N=32) vs. no medication (N=17). Similarly, this analysis indicated no differences as a function of medication for total learning over 5 trials [$F(1,47) = 0.005$, $p = 0.94$, n.s.], nor for short and long delayed free recall [$F(1,47) = 0.61$, $p = 0.44$, n.s.; $F(1,47) = 2.4$, $p = 0.13$, n.s, respectively]. In addition, the effects of current antipsychotic usage were also evaluated using correlational and multiple regression analysis, as described below.

3.4. Course of illness and clinical symptomatology

Table 4 presents associations of hypothesized predictor variables with performance on the primary declarative memory outcome measure (CVLT-2 total score, trials 1–5). Of these, gender and positive family history were associated with verbal memory performance at $\alpha \leqslant 0.004$. While current substance abuse was associated with poorer performance, this association did not reach statistical significance after correcting for multiple comparisons. Based on these results, a hierarchical regression model utilizing CVLT-2 total score as a dependent variable was generated to predict the severity

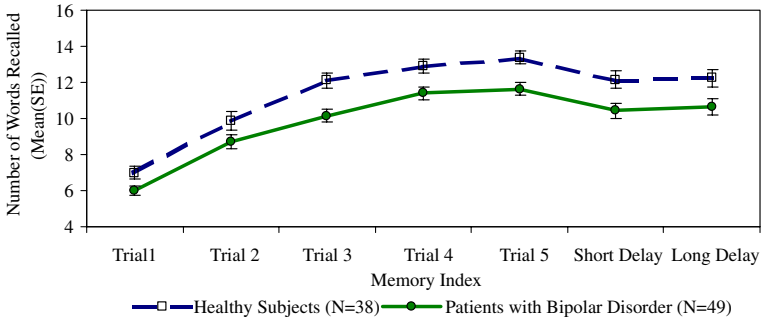

Fig. 1. Number of words recalled over trials 1–5 and after short and long delays for participants with bipolar disorder and controls. MANOVA analysis indicated that patients with bipolar disorder learned fewer words over the five learning trials compared with control participants [Wilks' $F(5,81) = 3.1$, $p < 0.02$]. Post hoc univariate comparisons indicated that the discrepancy became more pronounced over repeated exposures to the word list, as participants with bipolar disorder did not significantly differ from controls after Bonferroni correction for multiple comparisons ($0.05/5 = 0.01$) on trials 1 and 2 [$F(1,85) = 5.46$, $p = 0.02$; $F(1,85) = 3.71$, $p = 0.06$], but recalled significantly fewer words on trials 3, 4 and 5 [$F(1,85) = 13.10$, $p = 0.000$; $F(1,85) = 8.56$, $p = 0.004$; $F(1,85) = 11.73$, $p = 0.001$].

Table 4
Association between potential predictors and verbal memory performance

	CVLT-II total score	
	Pearson correlation coefficient (r)	p-Value
Antipsychotic medication	0.17	0.97
Age	−0.22	0.14
Illness duration	−0.03	0.87
Age at onset	−0.22	0.14
HDRS	0.05	0.75
Y-MRS	0.22	0.15
Family history	0.42[a]	0.002
Substance abuse	−0.33	0.02
PTSD	0.25	0.08
GAF	−0.20	0.21
# of Hospitalizations	0.03	0.86
Gender	0.43[a]	0.002

[a] $\alpha = (0.05/12) = 0.004$.

of memory deficits in participants with bipolar disorder. Results indicated that, when considered together in the regression model, gender [$\beta = 0.32$ (95% CI = 1.15–11.8), $p \leqslant 0.02$] and family history [$\beta = 0.32$ (95% CI; 1.07–11.6), $p \leqslant 0.02$] were both independent significant predictors of total score over five learning trials [$R^2 = 0.27$, $F(2,46) = 8.70$, $p = 0.001$]. Female gender and positive family history were associated with a 6.5 and 6.3 point increase, respectively, in total learning score. In order to illustrate performance across subgroups in further detail, Table 5 presents verbal learning and memory performance for patients with bipolar disorder with and without clinical comorbidities (anxiety disorder and substance abuse), as well as psychotropic medication usage, in terms of effect sizes. As can be seen in the table, the only clinical variable that had an appreciable impact on declarative memory function is comorbid substance abuse; effect sizes for other subgroups were comparable across conditions.

Given that measures of mood symptomatology were not correlated with verbal memory performance, we also conducted categorical analyses of clinically remitted ($N = 4$), mixed/manic ($N = 16$), as compared to depressed ($N = 14$) bipolar patients in order to determine whether performance differences were only evident in more severely symptomatic patients. This analysis also indicated no performance differences between groups [$F(2,31) = 1.42$, $p = 0.26$]. In addition, no differences in total recall score were observed between patients with mild mood symptoms, as defined by YMRS $\leqslant 10$ and HDRS scores $\leqslant 13$ ($N = 10$) as compared to bipolar

Table 5
Effect sizes (η^2) for various clinical comorbidities

	Bipolar disorder only (no comorbid diagnoses; $N = 19$)	Comorbid anxiety disorder ($N = 22$)	Comorbid substance abuse ($N = 14$)	Psychotropic medication ($N = 32$)
Learning trials (items recalled)				
Trial 1	0.021	0.041	0.125	0.062
Trial 5	0.050	0.114	0.295	0.133
Total recall trials 1–5	0.050	0.102	0.259	0.119
Delay trials (items recalled)				
Short delay	0.059	0.059	0.151	0.093
Long delay	0.073	0.016	0.165	0.101
Recognition				
Recognition	0.104	0.085	0.228	0.16

patients with moderate to severe depressive and/or manic symptoms, as defined by YMRS $\geqslant 12$ and/or HDRS scores $\geqslant 17$ ($N = 30$; $F[1,38] = 0.28$, $p = 0.60$, n.s.).

4. Discussion

These findings provide new information regarding the nature of impairment across multiple aspects of memory in patients with bipolar disorder. Compared with demographically matched control participants, study participants with bipolar disorder had difficulties learning the CVLT word list and recalled fewer words at both the short- and long-delayed recall trials, but did not have difficulties retaining words once learned. The absence of a performance decrement over a long delay indicates that differences in delayed recall were related to poor encoding, rather than rapid forgetting. The presence of a significant recognition deficit provides further evidence that the primary process underlying memory impairment in patients with bipolar disorder is difficulty with encoding, rather than retrieval, of information. This finding suggests that effort was not a major determinant of performance. In addition, bipolar patients did not differ from normal controls on measures of motor processing speed, nor on measures of general intellectual function, suggesting that these results are not attributable to generalized impairment and/or motor slowing.

Consistent with Martinez-Aran et al. (2004), we found that both acute and remitted bipolar patients displayed poor verbal memory performance in terms of free recall. However, while Martinez-Aran and colleagues found significantly poorer recognition performance only in acutely ill patients, we found evidence for recognition impairment regardless of clinical state. Rubinsztein et al. (2000) also noted recognition deficits in clinically remitted bipolar patients on a spatial memory task, suggesting impairment in recognition memory may not be specific to the verbal domain.

In the current study, memory deficits in patients with bipolar disorder were not associated with reduced strategic or organizational processing, as indicated by the absence of group differences in semantic clustering. In addition, within the patient group, depressive or manic symptoms were not correlated with performance, suggesting that memory impairment in bipolar disorder, as assessed by the CVLT, is not a function of clinical symptomatology.

While this pattern of findings is generally consistent with earlier studies of patients with both bipolar disorder and major depression (Golinkoff and Sweeney, 1989; van Gorp et al., 1999; Wolfe et al., 1987), some discrepancies from previous studies deserve mention. In particular, we did not observe the semantic clustering deficit reported by Deckersbach et al. (2004). However, it should be noted that, while bipolar patients had lower semantic clustering scores than controls in that study, delayed recall remained impaired when semantic clustering was analyzed as a mediating variable, indicating that recall difficulties in bipolar patients could not be fully accounted for by poor semantic clustering strategies.

Contrary to our hypotheses, we did not find a significant effect of duration of illness on memory performance. This contrasts with some previous studies (Martinez-Aran et al., 2004), although is consistent with others (Atre-Vaidya et al., 1998; Deckersbach et al., 2004; Verdoux and Liraud, 2000). The reasons for this discrepancy are not clear, although it may be that illness duration is often confounded with other factors, such as negative symptoms, virulence of illness course, or their interaction, which, when examined independently, may be more strongly associated with memory function. For example, van Gorp et al. (1999) found that verbal memory performance was negatively correlated with lifetime months of mania and depression, but not with number of illness episodes. While some studies have reported an association between number of illness episodes and poorer performance (Deckersbach et al., 2004; Kessing, 1998), suggesting that there may be increasing cerebral dysfunction associated with severe, recurrent mood episodes, we found that number of episodes could not be reliably quantified due to the number of patients that reported episodes that were "too numerous to count", or alternatively that they had been continuously symptomatic for several years. As such, we used number of hospitalizations as an objective index of severe illness episodes, but did not find a significant association between this variable and declarative memory performance. Such discrepancies highlight the importance of improving methodology for independently quantifying duration and severity of illness.

Nevertheless, performance in bipolar patients was significantly influenced by other clinical and demographic factors; in particular, female gender and family history of mood disorder were associated with better declarative memory performance. Although substance abuse comorbidity was associated with poorer performance, this difference did not reach statistical significance after controlling for multiple comparisons. While van Gorp et al. (1999) previously reported poorer performance on tasks of memory and executive function in bipolar patients with a history of comorbid alcohol abuse, that study examined males only. Factors such as gender and family history are often not directly addressed in investigations of bipolar disorder (Quraishi and Frangou, 2002). Our findings suggest that these variables may significantly impact cognitive function in bipolar disorder, and thus are likely to play a role in contradictory and inconsistent findings across published studies.

We found no effect of psychoactive medication usage on memory function. The absence of an effect of mood stabilizer medications is consistent with other studies suggesting that lithium and anticonvulsants do not have a clinically significant impact on cognitive function (Devinsky, 1995; Engelsmann et al., 1988). However, Donaldson et al. (2003) found that antipsychotic medication was associated with poorer memory and overall cognitive functioning in patients with bipolar disorder. This difference may be a function of the type of antipsychotic medication prescribed, as all patients in the current sample were treated exclusively with atypical antipsychotics, which are generally believed to have a much better side effect profile with regard to cognition and memory than typical neuroleptic agents (Beuzen et al., 1999).

Similar to previous investigations (Sweeney et al., 2000), we found that female gender was associated with significantly better verbal memory performance in patients with bipolar disorder. Although a similar pattern was observed in the normal comparison subjects in this study, this difference was not statistically significant [$F(2,36) = 2.81$, $p = 0.10$]. In healthy adult women, better verbal memory performance has been shown to correspond to greater bilateral blood flow in mid-temporal brain areas (Ragland et al., 2000), suggesting that these gender differences may relate to underlying neurophysiological differences. While there is some evidence for higher rates of co-morbid substance abuse in males with bipolar disorder (Kessing, 2004), co-morbidity of other medical and psychiatric conditions may be more common in women (Arnold, 2003). At present there is no clear evidence for better prognosis or less severe course of illness in women with bipolar disorder (Kessing, 2004), suggesting that the observed gender differences in memory function are not mediated by other clinical variables. In our sample, we found that even when we examined only patients without substance abuse (11 males, 24 females), female participants with bipolar disorder performed significantly better than males [52.8 ± 10.1 vs. 43.8 ± 7.3; $F(1,33) = 6.89$ $p = 0.013$], suggesting an independent effect of gender that was not attributable to increased rates of substance comorbidity in male participants.

Positive family history of affective illness was associated with better overall performance. This finding remained significant after adjusting for gender. While seemingly counter-intuitive, a prior study of a representative cohort of patients with bipolar disorder also reported better intellectual functioning in those with a family history of mood disorder (Donaldson et al., 2003), suggesting that, in contrast to schizophrenia, generalized cognitive impairment is not a feature of familial risk for bipolar illness; rather, the opposite appears to be true. Other studies have suggested that neuropsychological impairment may, in part, reflect an expression of genetic liability to schizophrenia but not bipolar disorder (Kremen et al., 1998). Nevertheless, the mechanism that may account for this result is unknown, and clearly warrants further investigation and replication in other studies.

These findings indicate that verbal declarative memory is impaired in patients with bipolar disorder regardless of mood symptomatology, and is largely accounted for by deficits in the encoding stage of information processing. The rate of forgetting did not appear to deviate from healthy controls. However, bipolar patients had a higher rate of intrusions, indicating a deficit in source monitoring (Brâebion et al., 2002), a function dependent on prefrontal cortical systems (Schacter et al., 1998). This qualitative pattern is similar to that observed in patients with schizophrenia (Cirillo and Seidman, 2003); elevated recall intrusions have also been associated with genetic loading for schizophrenia (Cannon et al., 2000) . These findings, however, differ from the pattern seen in adults with ADHD, who appear to rely less on a semantic organizational strategy than do control subjects (Roth et al., 2004; Seidman et al., 1998). In contrast, patients with bipolar disorder appear to utilize semantic organization as a strategy to encode verbal information to the same extent as comparison subjects. Thus poorer verbal learning and memory performance in patients with bipolar disorder is not merely a function of their ability to organize to be remembered information. Adequate semantic and serial processing indicates that bipolar patients are engaged by the memory task and suggest that the memory impairments measured by the CVLT are not secondary to gross attentional deficits.

In studies of patients with schizophrenia, verbal memory deficits have been linked to anomalous activation patterns in left hemisphere language-processing regions (Mozley et al., 1996), as well as to structural volumetric reductions in the hippocampus (Weiss et al., 2004). Thus, while the observed findings suggest anomalies of medial temporal function, the vast majority of studies have not reported hippocampal volume abnormalities in patients with bipolar disorder (e.g., Monkul et al., 2003). In contrast, in patients with unipolar depression, a relationship between declarative memory deficits and hippocampal volume reduction has been noted, an effect thought to result from hippocampal neuronal loss secondary to glucocorticoid-induced neurotoxicity (McEwen and Magarinos, 2001). Nevertheless, recollection memory impairment has also been reported in first episode, never-treated depressed patients with no evidence of morphological changes in the hippocampus, suggesting that hippocampal dysfunction may precede measurable structural changes (MacQueen et al., 2003). These investigators additionally detected a logarithmic association between decreased hippocampal size and length of illness in patients with major depression; it may be that illness course plays a

similar role in bipolar disorder, with increasing hippocampal structural pathology developing over the course of illness. While at present it is unclear whether similar mechanisms underlie declarative memory impairment in bipolar disorder, schizophrenia and unipolar depression, it is possible that a combination of structural and neurophysiologic anomalies may underlie the observed functional deficits, and that neurochemical and neurophysiologic changes may precede structural anatomic deficits.

Although caution is needed when relating neuropsychological results to underlying brain circuitry without concurrent neuroimaging data, it is possible that the observed findings do not reflect dysfunction in one isolated brain area, but rather a dysregulation of cortical modulation of subcortical networks. In particular, a neuroanatomic model of mood regulation comprising the prefrontal cortex, amygdala–hippocampal complex, thalamus, basal ganglia, and their inter-connections has been proposed to be implicated in the pathophysiology of primary and secondary mood disorders (Soares and Mann, 1997). However, the majority of neuroimaging studies of affective disorders to date have focused on neuroanatomy, resting-state brain physiology, or receptor physiology (Drevets, 1998; Mayberg, 1997), without assessing cognitive function. Further investigations of the interaction of biochemical, neuroanatomic, and functional changes in cortical systems during symptomatic exacerbation and in remission, within the same individuals, may be a particularly useful strategy for advancing our understanding of the neural system disturbances underlying the cognitive deficits observed in bipolar disorder.

Certain limitations of the current study should be noted. Although groups were similar with regard to parental education and socioeconomic status, the control participants themselves were better educated than the participants with bipolar disorder. However, statistically controlling for educational attainment had no effect on verbal memory performance, indicating that level of education does not account for group differences. In addition, few of the patients in this sample were euthymic at the time of testing. However, the wide range of clinical symptomatology in this large sample allows us to compare the degree of impairment across mood states; notably, we found that even severe mood symptomatology had no significant effect on performance.

In conclusion, our findings of declarative memory dysfunction that is not attributable to current mood symptoms, medication usage, or comorbid psychiatric disorders, suggest that impairment in this cognitive domain may represent a trait abnormality in bipolar disorder. Nonetheless, further investigation of the characteristics, causes, course, and treatment of neurocognitive deficits associated with various phases of bipolar disorder is clearly warranted. In addition, longitudinal within-subjects studies examining the course and persistence of neurocognitive deficits in bipolar illness will be necessary to differentiate state- and trait-related deficits, and also to determine whether there is any accelerated cognitive decline over the lifespan associated with the occurrence of more frequent or severe episodes of illness, whether achieving prolonged states of remission is associated with a gradual recovery of cognitive abilities, and whether different treatments have differential benefits for cognitive functioning.

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