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Characteristics of non-verbal memory impairment in bipolar disorder: the role of encoding strategies

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ABSTRACT

Background. There is evidence that individuals with bipolar disorder exhibit neuropsychological impairments not only during episodes of depression or mania but also when they are euthymic. One of the most consistently reported cognitive problems in euthymic individuals with bipolar disorder is impairment in episodic memory. Learning and memory depend on individuals' ability to organize information during learning. A recent study by our group showed that verbal episodic memory impairments in euthymic patients with bipolar I disorder (BP-I) are mediated by difficulties in organizing verbal information appropriately during learning. The purpose of the present study was to determine whether memory impairments in euthymic individuals with BP-I extend to non-verbal memory and whether non-verbal memory impairments are mediated by difficulties in organizing non-verbal information during encoding.

Method. Study participants were 25 euthymic, remitted individuals with BP-I and 25 age, gender and education matched control participants. Participants completed the Rey-Osterrieth Complex Figure Test (RCFT), a well-established measure of non-verbal memory that enables assessment of organization during learning.

Results. Compared to control participants, BP-I participants showed impaired performance on the RCFT immediate recall. They also relied less on organizational strategies during encoding. Multiple regression modeling indicated that group differences between control and BP-I participants in long-delayed free recall did not remain statistically significant when effects of lower organization were partialled out.

Conclusions. Non-verbal memory problems in individuals with bipolar disorder, while euthymic, are mediated by poor use of non-verbal organization strategies during encoding, but do not appear to reflect deficits in retention of information.

INTRODUCTION

Bipolar disorder is characterized by recurrent episodes of depression and/or hypomania/mania interspersed with periods of recovery or remission. Neuropsychological studies in bipolar disorder have documented profound cognitive disturbances associated with episodes of depression and mania. This includes impairments in attention, executive functions and memory (Martinez-Aran *et al.* 2000; Bearden *et al.* 2001; Murphy & Sahakian, 2001). Over the past decade, evidence has accumulated that these neuropsychological impairments in bipolar disorder are not restricted to mood episodes but are found in euthymic (neither depressed nor manic) individuals with bipolar disorder as well (Dupont *et al.* 1990; McKay *et al.* 1995; Tham *et al.* 1997; Atre-Vaidya *et al.* 1998; van Gorp *et al.* 1998, 1999; Ferrier *et al.* 1999;

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Krabbendam *et al.* 2000; Rubinsztein *et al.* 2000; Cavanagh *et al.* 2002; Clark *et al.* 2002). One of the most consistently reported findings in euthymic individuals with bipolar disorder is an impairment in episodic memory – the ability to explicitly recollect information encountered in a previous study episode (Graf & Schacter, 1985). One of the processes that is known to enhance recollection is organization of information during encoding. Encoding refers to the processes that convert a perceived event into an enduring cognitive representation (Tulving, 1983). For example, learning a list of words which stem from different categories (e.g. fruits, tools) is facilitated if an individual groups these words into their categories during presentation of the word list. Likewise, organizing visuospatial information (e.g. a geometric figure) into meaningful perceptual units during encoding has been shown to enhance subsequent free recall from memory (Shorr *et al.* 1992, Savage *et al.* 1999, 2000). Presumably, more organized encoding of information (i.e. better visuospatial organization) leads to better structured memory representations which facilitate subsequent retrieval (Savage, 1998).

The prefrontal cortex, which has also been implicated in bipolar disorder, supports the ability to utilize organizational strategies that enhance encoding of episodic memories (Öngür *et al.* 1998; Strakowski *et al.* 1999; Rajkowska *et al.* 2001; Savage *et al.* 2001; Wagner *et al.* 2001; Bowley *et al.* 2002; Cotter *et al.* 2002). For example, individuals with lesions of the frontal lobes or with disorders affecting frontal-striatal system function (e.g. Parkinson's disease, Huntington's disease) have been shown to exhibit difficulties with organizational processes crucial for efficient encoding of information associated with impairments in learning and free recall (e.g. Shimamura *et al.* 1991; Bondi *et al.* 1993; Grossman *et al.* 1993; Pillon *et al.* 1993; Buytenhuijs *et al.* 1994; Gershberg & Shimamura, 1995; Savage, 1997). This pattern of memory problems can be differentiated from episodic memory problems associated with medial temporal system dysfunction, in which participants have difficulty storing and consolidating new memories (Squire, 1992). In bipolar disorder, it remains unclear whether previously reported episodic memory impairments stem from difficulties organizing information during encoding, impairments in storing and consolidating new memories, or both. A recent study in euthymic individuals with bipolar I disorder by our group (Deckersbach *et al.* 2002) suggests that impairments in long-delayed recall were mediated by difficulties organizing verbal information during learning (encoding). Furthermore, studies investigating episodic memory functioning in euthymic, remitted individuals with bipolar disorder have almost exclusively focused on the verbal domain. Thus, the purpose of the present study was to investigate the pattern of non-verbal episodic memory performance in euthymic individuals with BP-I. More specifically, we investigated (1) whether euthymic individuals with BP-I exhibit impairments in non-verbal memory and (2) whether such impairments are mediated by impairments in organization strategies during encoding. Previous neurobiological studies in bipolar disorder have shown structural abnormalities in regions of prefrontal cortex that are implicated in strategic memory processes (Fletcher *et al.* 1998; Öngür *et al.* 1998; Strakowski *et al.* 1999; Rajkowska *et al.* 2001; Savage *et al.* 2001; Wagner *et al.* 2001; Bowley *et al.* 2002; Cotter *et al.* 2002). Therefore, we hypothesized that non-verbal memory impairment in euthymic patients with bipolar disorder is mediated by difficulties in using organizational strategies during encoding.

METHOD

Subjects

Study participants were 25 euthymic, remitted participants meeting DSM-IV criteria for bipolar I disorder (BP-I; APA, 1994) and 25 healthy control participants. Participants were recruited through the Harvard Bipolar Research Program at the Massachusetts General Hospital. Normal control participants were recruited through bulletin board notices at the Massachusetts General Hospital. All participants provided written informed consent prior to participation. Diagnoses of BP-I participants and status of healthy control participants were determined by the Structured Clinical Interview for DSM-IV (SCID; First *et al.* 1995). BP-I participants were only included in the study if they met DSM-IV remission criteria (APA, 1994).

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Five BP-I participants were non-medicated. Twenty BP-I participants were taking mood stabilizer medications [lithium ($n=11$); anticonvulsants ($n=9$), including valproic acid, lamotrigine and gabapentin]. In addition to mood stabilizers, nine patients were selective serotonin reuptake inhibitor antidepressant medication (fluoxetine, fluvoxamine, sertraline and paroxetine). Three patients were taking atypical antipsychotics (risperidal, olanzapine) in addition to mood stabilizers. Seven participants had comorbid diagnoses in addition to bipolar disorder. These included panic disorder ($n=4$), obsessive-compulsive disorder ($n=2$), post-traumatic stress disorder ($n=1$) and social phobia ($n=1$). In all cases bipolar I disorder was the primary diagnosis. All participants were right-handed as determined by the Edinburgh Handedness Inventory (Oldfield, 1971). Participants with neurologic conditions and/or current and past drug or alcohol abuse were not included in the sample. Table 1 summarizes the demographic data and clinical characteristics of the sample. Both BP-I and control participants did not differ with regard to gender, age, education and handedness (all $p>0{\cdot}05$). BP-I and control participants completed the Beck Depression Inventory (BDI; Beck & Steer, 1987, see Table 1). For BP-I participants, the Hamilton Depression Inventory (HAM-D; Hamilton, 1960) and Young Mania Rating Scale (YMRS; Young *et al.* 1978) scores indicated low residual affective symptoms (see Table 1). BP-I and control participants completed the Rey-Osterrieth Complex Figure Test (RCFT; Osterrieth, 1944) which provides measures of organization during encoding and memory. Nine BP-I participants also completed a measure of verbal learning and memory in the same testing session. Results of the verbal memory test are reported elsewhere (T. Deckersbach *et al.* unpublished observations).

Table 1. *Demographic and clinical characteristics and RCFT scores of BP-I and control participants*

	BP-I		Controls		
Gender					
Female	15		15		
Male	10		10		
	M	S.D.	M	S.D.	*p*
Age	39·9	(13·3)	37·7	(10·5)	0·63
Education	15·8	(2·1)	15·4	(2·7)	0·54
BDI	5·8	(4·6)	3·8	(4·5)	0·12
HAM-D (17)	3·3	(2·5)	—		
YMRS	1·2	(1·5)	—		
Age of onset	16·9	(5·1)			
Duration of illness	22·6	(13·4)			
Depressive episodes	10·8	(7·9)			
Manic episodes	4·8	(4·8)			
RCFT accuracy scores*					
Copy accuracy	32·8	(4·2)	33·0	(2·4)	0·81
Immediate recall	14·0	(8·2)	20·0	(6·5)	0·006
Delayed recall	14·1	(7·4)	19·1	(6·8)	0·02
Retention	114·2	(56·8)	96·4	(19·9)	0·15
Recognition†	83·5	(9·2)	84·3	(6·5)	0·71
RCFT organization scores*					
Copy	2·7	(2·0)	4·5	(1·2)	<0·001

* See text for ANOVA results for omnibus tests.
† Recognition, Recognition discriminability score.

Materials

The RCFT (Osterrieth, 1944; Meyers & Meyers, 1995) is a widely-used measure of non-verbal learning and memory that requires participants to copy and recall a complex geometric figure. The RCFT figure is presented on a sheet of paper presented in landscape fashion. Immediately after copying the figure as well as after a 20-min delay, participants are asked (without prior notice) to redraw the design from memory. The delayed recall performance is followed by a recognition test in which participants are to discriminate between 12 of the original RCFT elements (e.g. the circle with dots; see Fig. 1) and 12 distractors (Meyers & Meyers, 1995). For copy and recall, participants were provided with colored pencils that were changed every 10–15 s to allow quantification of organizational strategies, based on whether organizational elements were constructed as unfragmented units.

Construction accuracy

Copy and recall drawings were scored for accuracy of construction (correctly copied or recalled elements). Construction accuracy was assessed using the Meyers & Meyers (1995) scoring system. In this system, the figure is subdivided into 18 components. Each piece is evaluated with respect to its drawing accuracy (1 point) and its correct placement (1 point) resulting in a range of scores per element from 0 to 2 and a total range of scores from 0 to 36. As demonstrated by Meyers & Meyers (1995), inter-rater reliability is high ($r>0{\cdot}90$). To ensure

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sufficient reliability of copy and recall accuracy scores, all copy and recall drawings were scored by two independent raters blind to group membership. As indicated by intra-class correlations, inter-rater reliability in the current study was high for copy accuracy scores ($r = 0{\cdot}88$, $p < 0{\cdot}001$), immediate recall ($r = 0{\cdot}97$, $p < 0{\cdot}001$) and delayed recall accuracy scores ($r = 0{\cdot}97$, $p < 0{\cdot}001$).

Recognition

Participants' ability to discriminate between the original 12 RCFT elements and the 12 distractor items was calculated using the non-parametric approach described by Underwood (1974). Discriminability was calculated according to the following formula: $[1 - (\text{false positives} + \text{false negatives})/24] \times 100$, where False Positives is the number of distractors incorrectly classified as RCFT elements and False Negatives is the number of RCFT elements that are incorrectly classified as distractors by a participant (Underwood, 1974).

Organization

Organization during copy was assessed using the Savage Organization Scale (SOS; Savage *et al.* 1999, 2000; Deckersbach *et al.* 2000). Briefly, the SOS divides the RCFT figure into five core configural elements: base rectangle, two diagonals, vertical midline, horizontal midline and the vertex of the triangle on the right (see Fig. 1).

Participants receive points for constructing (drawing) each element as an unfragmented unit. Construction (drawing) accuracy is not considered in this score. The large rectangle is assigned two points to reflect its importance to the fundamental organization of the figure. All other elements are assigned one point, resulting in a range of scores from 0 to 6. An organizational element is considered to be drawn as an unfragmented unit whenever (1) each side comprising a unit (e.g. each of the four sides of the rectangle) is drawn as a continuous line without interruption, and (2) all sides are drawn one after another. The order in which the sides of a unit are drawn is not taken into account as long as they are drawn one after another. For instance, if a given participant draws each of the organizational units without interruption, this yields a score of 6, reflecting good organization.

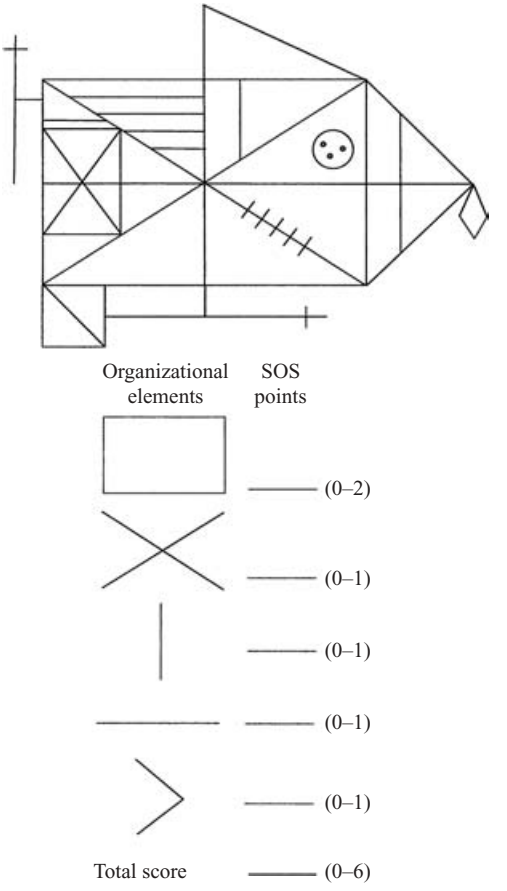

FIG. 1. The Savage Organizational Scale (SOS, Savage *et al.* 1999, 2000). The SOS divides the RCFT figure into the above shown core configural elements: base rectangle (2 points), diagonals (1 point), vertical midline (1 point), horizontal midline (1 point) and the vertex of the triangle on the right (1 point).

Conversely, if completion of most of the organizational elements is interrupted by drawing unrelated details (e.g. drawing the triangle on top of the large rectangle before completing the rectangle, see Fig. 1), this yields a low score, reflecting poor organization. To ensure sufficient reliability of copy organization scores, all copy drawings were scored by two independent raters blind to group membership. As indicated by intra-class correlations inter-rater reliability was high in the current study ($r = 0{\cdot}93$, $p < 0{\cdot}001$).

Statistical analyses

RCFT accuracy, recognition and organization scores were evaluated by analysis of variance (ANOVA) followed by independent *t* tests.

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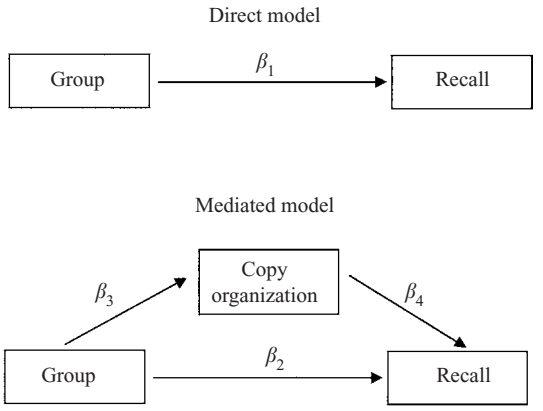

FIG. 2. Two alternate path models explaining group differences in immediate free recall in the RCFT. In the direct model (1) the effects of group (BP-I/controls) are expressed directly in differences in recall. In the mediated model (2) group differences are also expressed indirectly ('mediated') through copy organization. Standard coefficients (β) for each path are listed in the text. The direct effects of group are reduced in absolute size and statistical significance when the effects of copy organization are partialled out, supporting the validity of the mediated model.

Effects of RCFT copy organizational strategies on recall were evaluated with multiple regression (Baron & Kenny, 1986; described in detail in Savage *et al.* 1999) comparing two path models separately for each test (see Fig. 2).

In the direct model (see Fig. 2), group differences in recall are expressed directly without mediation by organization during encoding (copy). In the mediated model (see Fig. 2), group differences in recall are expressed indirectly ('mediated') through organization during encoding (i.e. organization 'mediates' the 'effect' of group). A multiple regression solution was calculated for each model. For the direct model (β_1), group (BP-I = 1 *v.* control = 0) was the independent variable. The number of RCFT elements recalled was the dependent variable in the regression equation (see Fig. 2). For the mediated model, to investigate whether group differences in recall were mediated by group differences in organization, copy organization scores and group (BP-I = 1 and control = 0) were simultaneously entered as independent variables into a multiple regression equation as predictors for RCFT recall (mediated model; β_2, β_4). The beta coefficient from group to copy organization in the mediated model (β_3; see Fig. 2) was obtained by computing a simple regression with group as the independent and copy organization as the dependent variable. Full mediation is thought to occur if group significantly predicts recall only through copy organization (i.e. β_3, and β_4 are statistically significant, but not β_2; see Fig. 2).

To investigate the role of co-morbidity and medication effects, group comparisons and multiple regression analyses were repeated, excluding BP-I participants with co-morbid psychiatric disorders. Effects of medications were also evaluated using multiple regression analysis.

RESULTS

Mean RCFT copy and recall accuracy scores, recognition discriminability scores and organization scores are presented in Table 1. RCFT copy and recall accuracy scores were evaluated in a two-factor (Group × Condition) analysis of variance (ANOVA) with condition (Copy, Immediate Recall, Delayed Recall) as the repeated measures factor and group as the between group factor. This analysis yielded significant effects for group [$F(1,48) = 6{\cdot}53$, $p = 0{\cdot}014$] and condition [$F(2,96) = 312{\cdot}32$, $p < 0{\cdot}001$], as well as a significant Group × Condition interaction [$F(2,96) = 6{\cdot}88$, $p = 0{\cdot}012$]. *Post-hoc* analysis of simple main effects (t tests) indicated that BP-I and control participants did not differ in their copy accuracy [$t(48) = 0{\cdot}23$, $p = 0{\cdot}82$], but BP-I participants recalled fewer elements of the figure than control participants on the Immediate Recall condition [$t(48) = 2{\cdot}87$, $p = 0{\cdot}006$] and the Delayed Recall condition [$t(48) = 2{\cdot}52$, $p = 0{\cdot}015$]. BP-I participants also organized the RCFT figure to a lesser extent than control participants when copying the RCFT figure [$t(48) = 3{\cdot}84$, $p < 0{\cdot}001$; see Table 1]. However, both groups showed preserved abilities to retain information between the immediate and delayed recall condition as calculated by the following formula: (delayed recall/immediate recall) × 100 [$t(48) = -1{\cdot}47$, $p = 0{\cdot}15$; see Table 1]. BP-I participants also did not differ from control participants and in their ability to discriminate between the original RCFT elements and distractor items on the recognition test [$t(48) = 0{\cdot}37$, $p = 0{\cdot}71$].

Multiple regression analysis

The impact of impairments in RCFT organization during encoding (copy) on immediate recall was tested via multiple regression analysis,

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comparing two path models separately for each test (Baron & Kenny, 1986 and described in detail in Savage *et al.* 1999; see Fig. 2). In the direct model, when group was used as a single predictor for immediate free recall, the direct model accounted for 15% of the total variance in immediate recall [$R^2 = 0{\cdot}15$, $F(1, 48) = 8{\cdot}23$, $p = 0{\cdot}006$; $\beta_1 = -0{\cdot}38$, $t = -2{\cdot}87$, $p = 0{\cdot}006$]. In the mediated model, as hypothesized, introducing copy organization as a mediator significantly increased explained variance to 37% [$R^2 = 0{\cdot}37$, $F(2, 47) = 13{\cdot}60$, $p < 0{\cdot}001$; $\Delta R^2 = 0{\cdot}22$, $p < 0{\cdot}001$]. Direct group effects on immediate recall were reduced to non-significance when effects of organization were partialled out ($\beta_2 = -0{\cdot}12$, $t = -0{\cdot}92$, $p = 0{\cdot}36$). On the other hand, the indirect pathway from group through organization to immediate recall was statistically significant ($\beta_3 = -0{\cdot}49$, $t = 3{\cdot}84$, $p < 0{\cdot}001$), $\beta_4 = -0{\cdot}54$, $t = -4{\cdot}04$, $p < 0{\cdot}001$). Thus, the comparison of the two path models indicated that impairments in immediate recall in the BP-I group were fully mediated by difficulties in applying organizational strategies during copy of the RCFT figure.

Residual affective symptoms, co-morbidity and medication

Residual affective symptoms

To test the effect of residual depression symptoms we entered BDI scores in addition to group and copy organization simultaneously as predictors for immediate recall into the multiple regression equation. In comparison to the mediated model, this did not change the amount of explained variance [$R^2 = 0{\cdot}37$, $F(3, 47) = 8{\cdot}49$, $p < 0{\cdot}001$; BDI: $\beta = -0{\cdot}05$, $t = -0{\cdot}38$, $p = 0{\cdot}70$]. HAM-D scores in the BP-I group were neither significantly correlated with copy organization scores ($r = -0{\cdot}19$, $p = 0{\cdot}37$) nor with immediate recall scores ($r = 0{\cdot}09$, $p = 0{\cdot}67$). We also evaluated the role of residual manic symptoms in the BP-I group by correlating YMRS scores with copy organization and immediate recall (YMRS scores were not available for control participants). YMRS was not significantly correlated with either copy organization ($r = 0{\cdot}11$, $p = 0{\cdot}59$) or immediate recall ($r = 0{\cdot}04$, $p = 0{\cdot}87$).

Co-morbidity

The current sample included seven patients with co-morbid disorders. To investigate potential effects of co-morbidity we excluded the participants with co-morbid diagnoses and repeated the previous statistical analysis. In short, results obtained with this reduced sample resembled the results with the full sample. The groups remained well matched with respect to age, education and gender (all $p > 0{\cdot}55$). There were no group differences in construction accuracy [$t(41) = -0{\cdot}50$, $p = 0{\cdot}62$] whereas group differences in immediate recall [$t(41) = 2{\cdot}31$; $p = 0{\cdot}03$], delayed recall [$t(41) = 2{\cdot}03$, $p = 0{\cdot}05$] and copy organization [$t(41) = 3{\cdot}50$, $p = 0{\cdot}001$] remained significant after exclusion of participants with co-morbid conditions. In the direct model, this corresponded to 12% explained variance when group was entered as a single predictor for immediate recall in a multiple regression equation [$R^2 = 0{\cdot}12$; $F(1, 41) = 5{\cdot}34$; $p = 0{\cdot}03$]. In the mediated model, simultaneous introduction of group and copy organization as independent predictors for long-delayed free recall significantly increased the percent of explained variance to 25% [$R^2 = 0{\cdot}25$, $F(2, 40) = 6{\cdot}73$, $p = 0{\cdot}003$, $\Delta R^2 = 0{\cdot}13$, $p < 0{\cdot}01$]. Only copy organization ($\beta = 0{\cdot}42$, $t = 2{\cdot}70$, $p < 0{\cdot}01$), but not group ($\beta = -0{\cdot}14$, $t = -0{\cdot}89$, $p = 0{\cdot}38$) explained significant portions of the immediate free recall variance. Thus, despite exclusion of participants with co-morbid conditions, copy organization still mediated group differences in immediate recall in the RCFT.

Medication

Medication effects were evaluated in two ways. First, we included medication ('yes' = 1; 'no' = 0) as a predictor for immediate recall in addition to group and copy organization scores in the multiple regression analysis. This did not significantly increase the amount of immediate recall variance explained compared to the mediated model with group and organization as predictors [$R^2 = 0{\cdot}39$, $F(3, 47) = 9{\cdot}9$, $p < 0{\cdot}001$, $\Delta R^2 = 0{\cdot}02$, $p > 0{\cdot}05$]. Only organization ($\beta = 0{\cdot}56$, $t = 4{\cdot}23$, $p < 0{\cdot}001$) but neither group ($\beta = -0{\cdot}09$, $t = -0{\cdot}46$, $p = 0{\cdot}64$), nor medication ($\beta = -0{\cdot}26$, $t = -0{\cdot}14$, $p = 0{\cdot}16$) explained significant portions of the immediate recall variance. Secondly, we investigated the role of different medication regimens in the BP-I group by entering lithium ('yes' = 1; 'no' = 0), anticonvulsant ('yes' = 1; 'no' = 0), antidepressant ('yes' = 1; 'no' = 0) and antipsychotic ('yes' = 1;

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'no' = 0) simultaneously as predictors for immediate recall into the multiple regression equation. This explained only 9% of the immediate recall variance in the BP-I group [$R^2 = 0{\cdot}09$, $F(4, 20) = 0{\cdot}50$, $p < 0{\cdot}73$]. In summary, controlling for residual depressive symptoms, neither co-morbidity nor medication changed the pattern of results, indicating that BP-I participants' impairments in immediate recall were mediated by impairments in organization during encoding.

Age of onset/duration of illness

Finally, in order to explore whether BP-I participants with earlier onset, longer duration of illness and more manic or depressive episodes were more impaired in organization and recall, we correlated age of onset, duration of illness, and the number of manic and depressive episodes with organization during copy and immediate recall scores. There was no significant correlation between age of onset and copy organization ($r = 0{\cdot}26$, $p = 0{\cdot}21$) or immediate recall ($r = 0{\cdot}09$, $p = 0{\cdot}69$). Duration of illness was also not significantly correlated with organization ($r = -0{\cdot}16$, $p = 0{\cdot}45$) or immediate recall ($r = -0{\cdot}28$, $p = 0{\cdot}17$). The number of depressive and manic episodes were significantly negatively correlated with both organization (depressive episodes: $r = -0{\cdot}44$, $p = 0{\cdot}03$; manic episodes: $r = -0{\cdot}42$, $p = 0{\cdot}04$) and immediate recall (depressive episodes: $r = -0{\cdot}52$, $p = 0{\cdot}01$; manic episodes: $r = -0{\cdot}50$; $p = 0{\cdot}01$).

DISCUSSION

Results indicate that individuals with BP-I in our study had difficulties recalling the complex RCFT figure, whereas copy and recognition abilities and the ability to retain information once learned were preserved. The finding of memory impairment in euthymic individuals with bipolar disorder is consistent with findings in previous studies showing learning and long-term memory impairments in this patient cohort (Atre-Vaidya *et al.* 1998; van Gorp *et al.* 1998, 1999; Ferrier *et al.* 1999; Krabbendam *et al.* 2000; Rubinsztein *et al.* 2000; Cavanagh *et al.* 2002; Clark *et al.* 2002). The current results extend the findings of previous studies by documenting that episodic memory difficulties are not restricted to the verbal domain, but encompass non-verbal learning and memory as well. Our study was specifically designed to investigate whether such impairments in free recall are attributable to difficulties in organizing the RCFT figure during encoding. Individuals with BP-I organized the RCFT figure to a lesser extent than control participants. Path-analytic modeling revealed that group differences in immediate recall were fully mediated by group differences in organization during encoding. This suggests immediate free recall impairments in BP-I participants in the present study were secondary to difficulties organizing non-verbal information and that difficulties arise early, during the stage of learning/encoding rather than reflecting impairments in retention. It is unlikely that group differences in age, gender or education contributed to the observed findings, since our participants were well matched on these variables. Furthermore, repetition of our analyses with exclusively co-morbidity-free patients did not change the pattern of results, suggesting that our findings do not reflect effects of co-morbid disorders. The pattern of results also held up when BDI scores were included in the multiple regression analysis. This finding is in contrast to at least two other studies which previously found associations between residual depressive symptoms and impaired memory performance (Ferrier *et al.* 1999; Clark *et al.* 2002). However, overall, residual depression symptoms of BP-I participants in the present study were very low. Thus, it is most parsimonious to consider that the small range of BDI scores (shrunken variance) may account for the lack of association between residual depression symptoms and organizational and memory performance in the present study. This may also account for the lack of correlation between residual manic symptoms and RCFT performance, although it cannot be ruled out that this reflects a lack of sensitivity of the YMRS for residual manic symptoms. Similar to previous studies, most patients with bipolar I disorder in our study were taking mood stabilizers, such as lithium, or anticonvulsants. Including medication into the multiple regression analysis did not change the pattern of results. Likewise, within the BP-I group, different medication regimens only accounted for a small percentage of the immediate recall variance. The lack of medication effects is surprising in the light of

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studies documenting effects of mood-stabilizers and antipsychotic medication on cognitive functioning. For example, lithium and anticonvulsants have been found to slow cognitive processing, and are associated with impairments in concentration and memory (Judd *et al*. 1977; Ananth *et al*. 1987; Goldberg *et al*. 2001). Most patients in our study had been taking mood stabilizer medications for several years. Thus, it is possible that development of tolerance to the cognitive effects of lithium and anticonvulsants accounts for the lack of association in our study. Support for this possibility comes from studies investigating memory performance in long-term benzodiazepine users (a drug that also increases CNS inhibitory tone), which have repeatedly failed to find memory impairments that are typically found after more acute benzodiazepine intake (Lucki *et al*. 1986; Cowley *et al*. 1995; Toenne *et al*. 1995).

In summary, the results of the current study suggest that previously reported impaired recall in euthymic individuals with bipolar disorder is attributable to an impairment in organizing of non-verbal information during encoding. This makes it more difficult to subsequently retrieve stored information even though the storage/retention of information itself appears to be preserved. These difficulties do not appear to be domain specific. That is, a recent study by our group using the California Verbal Learning Test showed, that euthymic individuals with bipolar disorder are also impaired in using verbal organizational strategies during learning (Deckersbach *et al*. 2002). Overall, the processes which lead to impaired organization and episodic memory in bipolar disorder as well as their neurobiological underpinnings are not well understood. It is possible that increased impulsivity even in the euthymic phase of bipolar illness (Swann *et al*. 2003) may account for difficulties in organization (i.e. bipolar patients start drawing rather than 'analyzing' the material to be drawn first). Episodic memory impairments during mood episodes may reflect a decrease in motivation and effortful processing in depressed individuals with bipolar disorder and increased thought disorganization in manic patients. Although not in this study, in some instances, residual symptoms appear to account at least in part for the impairments observed in euthymic individuals with bipolar disorder. There is converging evidence from functional neuroimaging studies and studies in brain damaged patients that intact organizational strategies depends on the integrity of frontal regions of the brain (Gershberg & Shimamura, 1995; Fletcher *et al*. 1998; Savage *et al*. 2001; Baldo *et al*. 2002). The effect of mood stabilizer medications/anticonvulsants on encoding strategies has, to our knowledge, not yet been investigated. Furthermore, consistent with previous studies, our study suggests that cognitive difficulties of euthymic patients with bipolar disorder reflect 'neurotoxic' effects of repeated affective disturbances (Altshuler, 1993; van Gorp *et al*. 1998; Cavanagh *et al*. 2002; Clark *et al*. 2002). That is, in our study the number of depressive and/or manic episodes, but not the duration of the disorder itself, was associated with impairments in organizational abilities and memory. However, longitudinal studies are needed to corroborate the cross-sectional findings from this and previous studies. From a clinical perspective, it is important to recognize that episodic memory impairments may have an impact on daily functioning (e.g. ability to work, functioning at work). Memory impairments may also require appropriate and flexible adjustments of psychosocial treatments for bipolar disorder (e.g. cognitive-behavior therapy, family therapy, interpersonal therapy) which substantially rely on a patient's ability to learn and to remember.

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