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Impact of depressive episodes on cognitive deficits in early bipolar disorder: data from the Systematic Treatment Optimization Programme for Early Mania (STOP-EM)

Kesavan Muralidharan, Ivan J. Torres, Leonardo E. Silveira, Jan-Marie Kozicky, Joana Bücker, Nadeesha Fernando and Lakshmi N. Yatham

Background
Although manic episodes reportedly contribute to cognitive deficits in bipolar I disorder, the contribution of depressive episodes is poorly researched.

Aims
We investigated the impact of depressive episodes on cognitive function early in the course of bipolar I disorder.

Method
A total of 68 patients and 38 controls from the Systematic Treatment Optimization Programme for Early Mania (STOP-EM) first-episode mania programme were examined. We conducted (a) a cross-sectional analysis of the impact of prior depressive episodes on baseline cognitive function and (b) a prospective analysis assessing the contribution of depression recurrence within 1 year following a first episode of mania on cognitive functioning.

Results
The cross-sectional analysis showed no significant differences between patients with past depressive episodes compared with those without, on overall or individual domains of cognitive function (all $P>0.09$). The prospective analysis failed to reveal a significant group × time interaction for cognitive decline from baseline to 1 year ($P=0.99$) in patients with a recurrence of depressive episodes compared with those with no recurrence. However, impaired verbal memory at baseline was associated with a depression recurrence within 1 year.

Conclusions
Although deficits in all domains of cognitive function are seen in patients early in the course of bipolar disorder, depressive episodes do not confer additional burden on cognitive function. However, poorer verbal memory may serve as a marker for increased susceptibility to depression recurrence early in the course of illness.

Declaration of interest
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Neuropsychological deficits have been documented in patients with bipolar I disorder in manic, hypomanic, depressive as well as euthymic phases.[1,2] Deficits in the cognitive domains of verbal memory, executive functions and sustained attention have been consistently reported in remitted bipolar disorder[3–5] as well as in remitted first-episode mania/bipolar disorder, although the magnitude of impairment is smaller in remitted first-episode mania.[6,7] Although recurrent episodes of mania and depression are the hallmark of bipolar disorder, the impact of mood episodes on cognitive function is poorly researched. Studying mood episodes may help us understand the temporal evolution of cognitive deficits in bipolar disorder, the contribution of mood states to these deficits, and potentially the interaction between neurocognitive deficits and progression of the disorder.[8] Although episodes of illness have been proposed to be more closely associated with cognitive impairment than the total duration of illness,[9] the contribution of the specific type of mood episodes to cognitive deficits, however, has received limited attention. Neuropsychological deficits in the domains of verbal memory, executive function, sustained attention and visual memory are reportedly associated with more lifetime manic episodes.[7,8] The relationship of cognitive deficits in bipolar disorder with depressive episodes, however, is less clear.[8] A significant negative correlation between the number of previous depressive episodes and performance on some tests of executive functions,[10,11] verbal learning and memory,[12] non-verbal memory[13] and attention[14] has been reported in a few retrospective analyses, which are potentially confounded by the effects of age, illness duration, antipsychotic medications and multiple manic episodes. However, many other studies did not find a correlation between depressive episodes and cognition.[15–18]

Thus, whether depressive episodes contribute to cognitive deficits in bipolar disorder remains unclear. In this study we investigated the relationship between depressive episodes and neuropsychological functioning in a sample of clinically stable patients with bipolar disorder who were within 3 months of recovery from a first episode of mania. Studying a first-episode mania sample would address some of the methodological limitations of earlier studies by overcoming the confounds of age, illness duration, chronicity, effects of medication and multiple manic episodes, thus allowing us to evaluate more directly the impact of depressive episodes on cognitive function. Using a cross-sectional strategy, we compared cognitive functioning in remitted patients with and without a history of depressive episodes. We hypothesised that the former group would show more severe deficits in cognitive functioning compared with patients with first-episode mania without past depressive episodes and healthy controls. In a prospective longitudinal analysis, we

also evaluated whether depressive recurrence in the first year after diagnosis would be associated with cognitive decline. We hypothesised that patients with first-episode mania who experience a recurrence of depressive episode within 1 year following the first manic episode would show more cognitive decline than those who did not have a recurrence. Such a finding within the context of a prospective design would provide further support that the recurrent depressive episodes might be causing any observed decline in cognitive functioning

Method

Participants

Cross-sectional analysis

Sixty-eight patients meeting DSM-IV-TR[19] criteria for bipolar I disorder were initially recruited from the Systematic Treatment Optimization Program for Early Mania (STOP-EM) at the University of British Columbia and affiliated sites. Details of the STOP-EM study have been published previously.[20] Diagnosis of bipolar disorder was established by clinical interview and a Mini International Neuropsychiatric Interview[21] (MINI) conducted by a research psychiatrist. Patients who experienced their first manic or mixed episode in the preceding 3 months were enrolled in the study. Those with possible medical or neurological basis for the manic symptoms were excluded. Of the 68 patients recruited, 33 had a history of past depressive episodes (FEMD) and 35 had no history of depressive episodes (FEM). Demographics and clinical characteristics of the sample are summarised in Table 1.

Thirty-eight age-, gender-, ethnicity- and premorbid IQ-matched healthy individuals were recruited from the community. Healthy controls were also assessed with MINI. The exclusion criteria included a personal or family history of major psychiatric disorder in first- or second-degree relatives, or major medical or neurological illness affecting cognition.

Prospective analysis

Of the 68 patients included in this study, 48 patients had completed 1-year follow-up. Of these, 3 patients had experienced a manic recurrence and 6 patients had experienced both manic and depressive recurrence in the first year after enrolment, and were thus excluded. The remaining 39 patients were selected for the prospective analysis; of these 39, 24 did not have a recurrence (NR group) and 15 had a depressive episode (DR group) within the first year following enrolment in the study. Demographics and clinical characteristics of the sample are summarised in Table 2.

The study was approved by the University of British Columbia Clinical Research Ethics Board. Written informed consent was obtained from all participants.

Procedures

As part of the larger STOP-EM study,[20] all patients received a comprehensive baseline clinical evaluation including the MINI, Young Mania Rating Scale (YMRS),[22] 29-item Hamilton Rating Scale for Depression (HRSD-29),[23] Positive and Negative Syndrome Scale (PANSS),[24] and the Global Assessment of Functioning Scale (GAF).[25] Patients received individualised open-label treatment based on CANMAT guidelines for treatment of bipolar disorder.[26–28] All patients recruited into the STOP-EM programme received treatments that were naturalistic and

Table 1 Cross-sectional analysis: comparison of sociodemographic and illness variables between the three groups

	First-episode mania ($n=35$)	First-episode mania with past depression ($n=33$)	Healthy controls ($n=38$)	F or χ^2	P
Age, years: mean (s.d.)	22.5 (4.6)	23.4 (4.1)	23.3 (4.9)	$F=0.216$	0.81
Female, *n* (%)	19 (52.8)	18 (51.4)	22 (57.9)	$\chi^2=0.484$ d.f. = 2	0.76
Ethnicity, White, *n* (%)	26 (81.3)	25 (71.4)	24 (63.2)	$\chi^2=2.34$ d.f. = 2	0.31
Education, years: mean (s.d.)	14.1 (2.1)	14.6 (2.4)	15.0 (2.4)	$F=1.54$	0.22
Overall age at illness onset, years: mean (s.d.)	22.1 (4.4)	17.3 (5.9)		$F=14.165$	0.000
Age at mania onset, years: mean (s.d.)	22.5 (4.4)	23.1 (4.1)		$F=0.416$	0.52
Number of past depressive episodes, mean (s.d.)		2.2 (1.6)			
Duration of illness at intake, years: mean (s.d.)	0.3 (1.3)	5.2 (4.9)		$F=29.161$	0.000
Any history of substance misuse/dependence, *n* (%)	15 (48.4)	17 (48.6)		$\chi^2=2.391$ d.f. = 2	0.30
Psychotic symptoms in the first manic episode, *n* (%)	24 (72.7)	24 (70.0)		$\chi^2=0.038$ d.f. = 1	0.84
Medication, *n* (%)					
Lithium	19 (52.8)	13 (37.1)		$\chi^2=2.072$ d.f. = 1	0.15
Valproate	12 (34.3)	20 (57.1)		$\chi^2=3.684$ d.f. = 1	0.06
Mood stabiliser + antipsychotic	24 (68.6)	26 (74.3)		$\chi^2=0.28$ d.f. = 1	0.59
Antipsychotic	25 (69.4)	26 (74.3)		$\chi^2=1.296$ d.f. = 1	0.25
North American Adult Reading Test for premorbid IQ: mean (s.d.)	107.4 (7.3)	106.2 (7.6)	107.6 (6.6)	$F=0.372$	0.69
YMRS score, mean (s.d.)	1.1 (1.9)	1.6 (3.6)		$F=0.551$	0.46
HRSD-29 score mean (s.d.)	4.1 (5.2)	8.6 (8.4)		$F=7.435$	0.008

HRSD-29, 29-item Hamilton Rating Scale for Depression; YMRS, Young Mania Rating Scale.

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Table 2 Prospective analysis: comparison of the sociodemographic and illness variables between the two FEM patient groups

	FEM no recurrence ($n = 24$)	FEM depressed recurrence ($n = 15$)	Test	P
Age, years: mean (s.d.)	21.7 (3.5)	24.9 (3.8)	$F = 6.902$	0.01
Female, *n* (%)	13 (54.2)	9 (60)	$\chi^2 = 0.128$ d.f. = 1	0.72
Ethnicity, *n* (%)				
White	16 (72.7)	13 (86.7)	$\chi^2 = 1.023$ d.f. = 1	0.31
Other	6 (27.3)	2 (13.3)		
Education, years: mean (s.d.)	13.9 (2.1)	14.7 (1.3)	$F = 1.768$	0.19
Overall age at illness onset, years: mean (s.d.)	18.9 (4.2)	21.4 (5.7)	$F = 2.318$	0.13
Age at mania onset, years: mean (s.d.)	21.6 (3.4)	24.7 (3.8)	$F = 6.895$	0.01
Age at onset of depression, years: mean (s.d.)	16.3 (3.6)	20.7 (6.5)	$F = 3.483$	0.07
Number of past depressive episodes, mean (s.d.)	1.0 (1.5)	1.07 (0.9)	$F = 0.026$	0.87
Duration of illness at intake, years: mean (s.d.)	2.7 (3.4)	3.3 (5.1)	$F = 0.504$	0.6
Any history of substance misuse/dependence, *n* (%)	9 (39.1)	9 (60)	$\chi^2 = 1.586$ d.f. = 1	0.20
Medication, *n* (%)				
Lithium	7 (31.8)	5 (33.3)	$\chi^2 = 0.009$ d.f. = 1	0.92
Valproate	11 (50)	7 (46.7)	$\chi^2 = 0.040$ d.f. = 1	0.84
Mood stabiliser + antipsychotic	6 (27.3)	10 (66.7)	$\chi^2 = 5.639$ d.f. = 1	<0.05
Antipsychotics	7 (31.8)	10 (71.4)	$\chi^2 = 5.386$ d.f. = 1	<0.05
North American Adult Reading Test for premorbid IQ, mean (s.d.)	106.2 (8.9)	106.9 (6.0)	$F = 0.077$	0.78
YMRS baseline: mean (s.d.)	0.8 (1.6)	2.4 (5.0)	$F = 2.206$	0.14
YMRS year 1: mean (s.d.)	0.5 (1.6)	2.0 (5.7)	$F = 1.597$	0.21
HRSD-29 baseline: mean (s.d.)	5.2 (6.7)	11.2 (10)	$F = 4.868$	0.03
HRSD-29 year 1: mean (s.d.)	1.5 (2.9)	4.4 (5.4)	$F = 4.332$	0.04

FEM, first-episode mania; HRSD-29, 29-item Hamilton Rating Scale for Depression; YMRS, Young Mania Rating Scale.

determined by the individual treating psychiatrist: treatments typically consisted of either mood stabiliser monotherapy (lithium or valproate) or combination therapy (mood stabiliser and an atypical antipsychotic) as recommended by CANMAT guidelines. If patients became depressed during the follow-up period, they were typically treated with the addition of lamotrigine or a selective serotonin reuptake inhibitor, or bupropion or quetiapine, if the patient has not already been taking quetiapine. The details of the treatments in both the cross-sectional and prospective analyses are detailed in Tables 1 and 2.

Neuropsychological assessment

Patients were clinically stable at the time of neuropsychological testing, and mean symptom ratings are presented in Table 1. The neuropsychological tests were administered in a quiet room following standard procedures. Subtests from the Cambridge Neuropsychological Test Automated Battery (CANTAB)[29] were selected based on demonstration of their relevance to bipolar disorder.[30,31] The grouping of tasks into cognitive domains was based on the approach taken with the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Cognitive Consensus Battery (MCCB),[32] given the overlap of cognitive deficits observed in schizophrenia and bipolar disorder.[33] Moreover, the use of the resulting six MCCB cognitive domains has been shown to have utility in bipolar disorder.[34] The specific tasks included in each cognitive domain are outlined in the Appendix. For the subset of patients included in the prospective analysis, patients were retested with the same cognitive battery 1 year after the baseline assessment. Practice effects, if present, may have been present in both groups of patients and would unlikely be a major confound.

Statistical analysis

Analyses were conducted using SPSS for Windows, Version 20.0 (SPSS Inc, Chicago, Illinois, USA). For analysis of cognitive data, raw scores for each measure were converted to demographics-corrected *z*-scores based on norms published in accompanying testing manuals. The *z*-scores for all measures contained within a cognitive domain were averaged to obtain a mean cognitive domain score. Based on prior work,[35] test–retest reliabilities for domain scores in healthy volunteers were as follows: processing speed, $r = 0.93$; attention, $r = 0.71$; verbal memory, $r = 0.68$; non-verbal memory, $r = 0.73$; working memory, $r = 0.71$; and executive functions, $r = 0.77$.

Cross-sectional analysis

Demographic and clinical variables of the three groups were compared using one-way analysis of variance (ANOVA) for continuous variables and chi-squared for categorical variables. Overall performance on the six domains of cognitive function was compared across the three groups using multivariate analysis of variance (MANOVA), followed by *post hoc* Tukey tests to identify between-group differences. Further, the two patient groups were compared using MANCOVA, covarying for potential confounding variables, to identify potential differences in cognitive performance. Bivariate correlational analysis was conducted to assess the correlation between the number of past depressive episodes and neuropsychological performance in the FEMD group.

Prospective analysis

Demographic and clinical variables of the FEM group with no recurrence (NR group) and the FEM group with depression

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recurrence (DR group) were compared using one-way ANOVA for continuous variables and chi-squared for categorical variables. The change in performance on neurocognitive domains over time was compared between the two groups using repeated measures analysis of variance, with a focus on the group × time interaction. The time and group main effects were also evaluated. Effect sizes were calculated using Cohen's *d*.

Results

Cross-sectional analysis

Demographics and clinical characteristics

The three groups – FEM ($n=35$), FEMD ($n=33$) and healthy controls ($n=38$) – were comparable on age, gender, handedness, education, ethnicity, premorbid IQ and age at onset of the first manic episode (all $P>0.17$). The FEMD group had an average of 2.2 (s.d. = 1.6) depressive episodes prior to the first manic episode. The onset of illness was, as expected, earlier in the FEMD group compared with the FEM group. Of the 33 patients in the FEMD group, only 4 received antidepressants for the prior depressive episode. The FEMD group showed a significantly higher score on the HRSD-29 compared with the FEM group (mean 8.7 (s.d. = 8.4) *v.* mean 4.1 (s.d. = 5.2); $F=7.4$, $P<0.05$). There was a trend for more patients in the FEMD group to be treated with valproate than in the FEM group ($\chi^2=3.7$; $P=0.055$). A comparison of the demographic and clinical variables is provided in Table 1.

Neurocognitive domains

On MANOVA, there was a significant group effect on overall cognitive functioning (Wilks lambda = 0.758, $F=2.430$, $P=0.006$). On individual cognitive domains, there was a significant difference between the three groups on five of the six domains ($P<0.05$), and there was a trend for significance in the domain of processing speed ($P=0.08$). On *post hoc* pair-wise comparison of between-group differences, both FEM and FEMD groups performed significantly poorer than healthy controls on domains of verbal memory, non-verbal memory, working memory and executive function. Only the FEMD group and not the FEM group had significantly poorer performance on tests of attention ($P=0.024$) compared with healthy controls. However, there was no significant difference between the two patient groups in attention ($t=0.983$; $P=0.32$) The results are shown in Table 3.

To directly test the hypothesis of poorer cognitive function in the FEMD group relative to the FEM group, the two groups were compared using MANOVA to test for overall differences in cognitive functions. There was no significant difference between the two groups (Wilks lambda = 0.924; $F=0.842$; $P=0.54$). Also, there was no difference between the two groups on individual domains of neurocognitive functioning (all $P>0.09$). Effect size differences between the two patient groups on individual cognitive domains were as follows: processing speed, $d=0.01$; attention, $d=0.21$; verbal memory, $d=-0.06$; non-verbal memory, $d=0.1$; working memory, $d=0.37$; and executive functions, $d=-0.01$.

The two patient groups were further compared using MANCOVA, covarying for HRSD-29 scores and treatment with valproate, as there was a significant difference between the two groups on these variables and hence, they may have confounded the potential impact on cognitive functioning. However, as in the first analysis, there was no difference between the FEM and FEMD groups on overall performance in cognitive functions (Wilks lambda = 0.925, $F=0.779$, $P=0.59$) or on individual domains of cognitive function (all $P>0.2$). Excluding the four patients on treatment with antidepressants in the FEMD group also showed no difference between the FEM and FEMD groups on overall (Wilk's lambda = 0.932, $F=0.639$, $P=0.69$) or individual domains of cognitive functioning (all $P>0.2$).

On bivariate correlation analysis, there was no correlation between the number of past depressive episodes and performance on any of the neurocognitive domains in the FEMD group. The Spearman correlation coefficients between number of depressive episodes and respective cognitive domains were: processing speed, $r=-0.09$, $P=0.63$; attention, $r=0.10$, $P=0.95$; verbal memory, $r=-0.16$, $P=0.35$; non-verbal memory, $r=0.11$, $P=0.51$; working memory, $r=-0.05$, $P=0.78$; and executive functions, $r=-0.25$, $P=0.15$. We also did not find any correlation between the duration of illness and performance on cognitive domains in the FEMD group (all $P>0.24$).

Prospective analysis

Demographics and clinical characteristics

The two FEM groups – NR group ($n=24$) and DR group ($n=15$) – were comparable on gender ($\chi^2=0.128$; $P=0.72$), education ($P=0.19$), ethnicity (White; $\chi^2=1.023$; $P=0.31$), premorbid IQ ($P=0.82$) and on the number of depressive episodes prior to the first manic episode ($P=0.89$). Eleven patients from the FEMD group in the cross-sectional analysis were part of the DR group in the prospective analysis.

The NR group was slightly, although significantly, younger than the DR group (mean 21.8 years (s.d. = 3.6) *v.* mean 24.9 years (s.d. = 3.8); $F=6.902$, $P<0.05$) and had a younger age at onset of mania ($P<0.05$) and depression ($P=0.07$). The DR group had significantly higher scores on HRSD-29 at baseline ($P<0.05$) and at 1 year ($P<0.05$) compared with the NR group. There was no difference between the two groups on treatment with lithium ($P=0.26$) or valproate ($P=0.47$). Significantly more

Table 3 Cross-sectional analysis: comparison of performance on cognitive domains between the three groups, using multivariate analysis of variance

	FEMD ($n=33$) Mean (s.d.)	FEM ($n=35$) Mean (s.d.)	HC ($n=38$) Mean (s.d.)	*F*	d.f.	*P*	*Post hoc* Tukey
Processing speed	−0.49 (0.50)	−0.40 (0.75)	−0.13 (0.79)	2.510	2	0.09	
Attention	−0.31 (0.90)	−0.10 (0.84)	0.17 (0.73)	3.196	2	0.045*	FEMD < HC**
Verbal memory	−0.26 (1.16)	−0.24 (1.01)	0.60 (0.91)	8.446	2	0.000*	FEM & FEMD < HC
Non-verbal memory	−0.16 (0.59)	−0.32 (0.91)	0.36 (0.46)	5.901	2	0.004*	FEM & FEMD < HC
Working memory	−0.46 (0.96)	−0.09 (0.87)	0.40 (0.69)	8.141	2	0.001*	FEM & FEMD < HC
Executive functions	−0.15 (0.67)	−0.14 (0.79)	0.36 (0.66)	6.203	2	0.003*	FEM & FEMD < HC

FEM, first-episode mania without depression; FEMD, FEM with past depression; HC, healthy controls.
*$P<0.05$; **Differences between FEMD and HC (but not FEM and HC) showed statistical significance ($P=0.03$).

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patients in the DR group were on treatment with antipsychotics and a combination of antipsychotics and mood stabilisers than in the NR group. A summary of demographic and clinical variables is provided in Table 2.

Neurocognitive domains

Regarding the overall group main effect, there was no significant difference between the NR and DR groups on overall performance on neurocognitive tests (Wilks lambda = 0.774; $F = 1.510$; $P = 0.20$). Univariate tests of the group main effect, however, revealed a difference between the two groups on verbal memory ($F = 6.861$, $P = 0.01$), with the DR group showing poorer verbal memory compared with the NR group and a trend for significance on tests of non-verbal memory ($P = 0.06$).

There was a significant overall time effect (Wilks lambda = 0.306; $F = 11.706$ and $P < 0.001$) and univariate tests revealed a significant time effect on all cognitive domains except non-verbal memory ($P = 0.11$). However, there was no significant group × time interaction observed on overall neurocognitive functioning (Wilks lambda = 0.975; $F = 0.130$ and $P = 0.99$) or individual cognitive domains (all $P > 0.50$). The neuropsychological results are shown in Table 4.

Since the two groups were significantly different on HRSD scores both at baseline and at year 1, the potential confound of depressive symptoms was examined by comparing the groups using MANOVA with repeated measures controlling for HRSD-29 scores at baseline and year 1 separately. There was no significant group × time effect after controlling for HRSD-29 scores at baseline, on overall (Wilks lambda = 0.850; $F = 0.881$; $P = 0.52$) or individual domains of cognitive functioning (all $P > 0.60$); similar results were obtained after controlling for HRSD-29 scores at year 1, both on overall (Wilks lambda = 0.960; $F = 0.209$; $P = 0.97$) and performance on individual cognitive domains (all $P > 0.39$). Importantly, the univariate tests of the group main effect continued to show poorer verbal memory in the DR group compared with the NR group, both after controlling for HRSD-29 scores at baseline ($F = 6.454$; $P < 0.05$) and at a trend level at 1 year ($F = 3.835$; $P = 0.06$).

Discussion

Main findings

This study represents one of the first attempts at investigating the contribution of depressive episode(s) to cognitive impairment in patients who are early in the course of bipolar disorder. A major strength of this study is the inclusion of both a cross-sectional and prospective analysis within the methodology, which allowed us to study the contribution of depressive episodes to cognitive deficits before and after a first episode of mania. The main findings of this study are that (a) in early bipolar disorder, following recovery from a first manic episode, past depressive episodes do not appear to have a substantial impact on cognitive deficits, and (b) recurrence of a depressive episode within the first year after diagnosis of bipolar disorder is not associated with further cognitive decline. We did, however, find that verbal memory deficit at baseline was associated with depression recurrence within the first year following a diagnosis of bipolar disorder.

Deficits in sustained attention,[7,36] processing speed,[7,37] learning and memory,[6] working memory and executive function[7] have been reported in first-episode bipolar disorder compared with healthy individuals. Our findings of impaired performance in both the patient groups vis-à-vis the healthy controls in almost all domains of cognitive functioning are consistent with other studies reporting cognitive deficits in early bipolar disorder. Based on the existing literature,[6,7]it is possible that cognitive deficits in early bipolar disorder, immediately after recovery from a first manic episode, are likely determined by the first manic episode and not depressive episodes.

We did not, however, find any significant difference between the two patient groups on overall or individual domains of cognitive function in our cross-sectional analysis. On tests of attention, the FEMD group performed poorly compared with the FEM group, although the difference was non-significant and the effect size was small (0.21). A meta-analysis of cognitive deficits in patients with remitted first-episode major depressive disorder and young patients with remitted major depressive disorder reported deficits in sustained attention relative to healthy controls.[38,39] It has been suggested that much like major depressive disorder, past depression may contribute to attention deficits in early bipolar disorder.[40] Even though we did not find this in the current sample, it is possible that with more depressive episodes, these differences on attention tasks may become more apparent.[9,41]

The prospective analysis did not reveal any further impact of depression recurrence in the first year after bipolar disorder diagnosis to the existing cognitive deficits at baseline. A study has suggested that cumulative duration of depressive episodes may be associated with more cognitive dysfunction in major depressive disorder.[41] An association between multiple depressive episodes and greater global cognitive decline has been reported previously, with no differences between unipolar depression and bipolar disorder.[9] Wekking *et al* highlight that cumulative deterioration in cognitive functioning after each new depressive episode has been poorly studied[39] since the idea was first proposed by Kessing in 1998. The current study which controlled for a number of confounds and used a prospective cohort design to assess the potential causative impact of depressive episodes does

Table 4 Prospective analysis: comparison of performance on cognitive domains from baseline to 1 year between the two first-episode mania (FEM) patient groups, using repeated measures analysis of variance

	FEM no recurrence, mean (s.d.)		FEM depression recurrence, mean (s.d.)		*F*			Group main effect baseline, effect size	Group main effect year 1, effect size
	Baseline	Year 1	Baseline	Year 1	Group	Time	Time × group		
Processing speed	−0.58 (0.63)	−0.09 (0.63)	−0.58 (0.65)	−0.20 (0.59)	0.089	22.357**	0.540	0.00	0.11
Attention	−0.03 (0.90)	0.47 (0.94)	−0.31 (0.65)	0.31 (0.65)	0.695	26.178**	0.593	0.28	0.16
Verbal memory	0.03 (0.93)	0.69 (1.06)	−0.78 (1.20)	−0.15 (1.04)	6.861*	18.393**	0.931	0.81	0.84
Non-verbal memory	0.12 (0.77)	0.39 (0.69)	−0.32 (0.68)	−0.10 (1.29)	3.668†	2.679	0.856	0.44	0.49
Working memory	−0.21 (0.81)	0.22 (0.78)	−0.37 (1.09)	0.12 (0.74)	0.236	16.038**	0.793	0.16	0.10
Executive function	−0.19 (0.62)	0.38 (0.65)	−0.31 (0.87)	0.21 (0.55)	0.449	37.080**	0.794	0.12	0.17

*$P<0.05$; **$P<0.001$; Trend for significance.

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not suggest that depressive episodes in bipolar disorder have significant deleterious effects on cognitive function at least in the early stage of the disorder.

Even though depressive recurrence did not associate with further cognitive decline, the DR group showed evidence of poorer verbal memory at baseline and at year 1 compared with the NR group. It is thus possible that impaired verbal memory may serve as a trait marker that makes patients more susceptible to depressive recurrence early in the course of illness, even though depressive recurrence per se may not cause cognitive decline early in the illness.

The possible link between verbal memory and depression is also apparent when underlying brain substrates are considered. For example, verbal learning and memory have been correlated with hippocampal volume in various neuropsychiatric disorders.[42] The hippocampus is a regulator of prefrontal cortical function[43] and deficits in hippocampal functioning have been associated with attention and memory deficits observed in depression.[42] Smaller hippocampal volume has been associated with more than one depressive episode[44] and has been documented to predict future depressive episodes in high-risk studies in major depressive disorder.[45] Although the association between depression and smaller hippocampal volumes has been well documented, the relationship between bipolar disorder and hippocampal volume is less clear from structural imaging studies.[46] One study reported that smaller hippocampal volumes were correlated with poor performance on tests of verbal memory in bipolar disorder[47] compared with healthy individuals, but no information was provided on the impact of depressive episodes to this finding. There is also evidence of abnormal hippocampal activation during performance of attention and memory encoding tasks in bipolar disorder from functional magnetic resonance imaging studies.[46] Based on the poorer performance in the domain of verbal memory by the DR group vis-à-vis the NR group, and the recurrence of a depressive episode within 1 year of bipolar disorder onset, we can only speculate that the DR group may have had more impaired hippocampal functioning relative to the NR group. The number of depressive episodes in our sample was much lower than those cited in the meta-analysis by McKinnon *et al*.[44] Although our data suggest that depressive episodes do not appear to contribute to cognitive deficits early in the course of illness, we cannot rule out the possibility that further depressive episodes may occur with illness progression and could contribute to more deficits in hippocampus functioning and cognitive decline subsequently, as reported in the McKinnon study. However, imaging studies comparing these two groups, in drug-naive conditions, are required before such a hypothesis can be tested.

Deficits in verbal memory have been reportedly associated with other clinical features such as longer duration of illness and more manic episodes.[8] However, we were not able to study a similar association with manic recurrence because of the small number of patients with manic recurrence in our sample. Deficits in verbal memory have been reported both in patients with remitted bipolar disorder and in their first-degree relatives. Gourovitch *et al* reported deficits in verbal memory but not working memory in unaffected monozygotic twins discordant for bipolar disorder compared with unaffected control monozygotic twins;[48] another study reported similar findings in siblings of patients with bipolar disorder and schizophrenia relative to controls.[49] Robinson & Ferrier reported significant impairments in verbal memory and executive function in patients with bipolar disorder and modest impairments in their first-degree relatives.[8] This was reflected in the meta-analysis by Arts *et al*, who found large impairments in patients and intermediate impairments in first-degree relatives on tasks of executive function and verbal memory.[3] Another review on relatives of patients with bipolar disorder concluded that verbal learning and memory is the most likely candidate for a neurocognitive endophenotype for bipolar disorder.[50] A meta-analysis by Bora *et al* reported similar findings,[40] although the effect sizes in first-degree relatives were modest. In our prospective analysis, greater verbal memory deficits were observed in the DR group. In light of the above literature, it can be hypothesised that verbal memory deficits may represent a cognitive endophenotype of bipolar disorder, which may confer a greater risk of recurrence of a depressive episode within the first year of a first manic episode in bipolar disorder. However, the absence of premorbid memory testing limits the inferences that we can draw from this particular finding.

Strengths

The study has several strengths. It is a first attempt to examine the impact of past depression on cognitive deficits in early bipolar disorder. It is also the first to prospectively study the impact of new depressive episodes on existing cognitive deficits in early bipolar disorder. Prior manic episodes have served as a major confound in previous studies in bipolar disorder attempting to link depressive episodes to neuropsychological deficits, which we were able to overcome. Although the FEMD group had an earlier age at onset, it was a function of the inclusion criteria and we did not find any correlations between the duration of illness and performance on cognitive functions in this group. The potential confounding effect of current medications on cognitive performance was also controlled.

Limitations

Some limitations with the present study need to be mentioned. The FEMD and DR groups had more depressive symptoms on HRSD-29 than the FEM and NR groups respectively. Although this was controlled statistically, the potential influence of depressive symptomatology on performance cannot be ruled out completely.[51] The FEMD group also had more patients on valproate, which was also controlled for statistically as valproate is documented to have a possible negative impact on cognitive functions.[52] While assessing the impact of depressive episodes on neurocognitive dysfunction, we did not study the severity, duration and the presence of psychotic symptoms in the depressive episodes independently which have been shown to influence cognitive functions associated with depression.[41] The reason is that a large majority of our patients had a history of psychosis. Another limitation is that we only examined the impact of number of depressive episodes and not the duration of episode, which may also be an important variable to investigate. Further, as very few patients in the FEMD group had received prior treatment with antidepressants; the impact of treatment with antidepressants on cognitive function could not be assessed, although excluding those patients who received treatment with antidepressants did not change the results of our analysis.

Although the sample size in this study was modest, it is not likely that this factor had a major impact on findings. For example, the effect sizes for the group differences in cognitive functioning in the cross-sectional analysis were generally small: processing speed, $d = 0.01$; attention, $d = 0.21$; verbal memory, $d = -0.06$; non-verbal memory, $d = 0.1$; working memory, $d = 0.37$; and executive functions, $d = -0.01$. Considering the largest effect ($d = 0.37$), a sample size of approximately 115 per group would have been necessary to detect a difference of that magnitude with power of 0.8. Thus, a considerably larger sample

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size would have been necessary to detect an effect of that magnitude.

Clinical implications

In conclusion, although deficits in all domains of cognitive function are observed in patients early in the course of bipolar disorder, the additional burden and impact of depressive episodes in the early stages is not significant. Despite this, presence of poorer verbal memory may serve as a marker for increased susceptibility to depressive recurrence early in the course of bipolar disorder.

Kesavan Muralidharan, MD, Mood Disorders Centre, Department of Psychiatry, University of British Columbia, Vancouver, Britich Columbia, Canada, and Department of Psychiatry, National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, India; **Ivan J. Torres**, PhD, Mood Disorders Centre, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia, Canada; **Leonardo E. Silveira**, MD, Mood Disorders Centre, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia, Canada, and Laboratory of Molecular Psychiatry, Centro de Pesquisas Experimentais, Hospital de Clínicas de Porto Alegre, and INCT for Translational Medicine, Porto Alegre, and Programa de Pós-Graduação em Medicina: Psiquiatria, Universidade Federal do Rio Grande do Sul, UFRGS, Rua Ramiro Barcelos, Porto Alegre, Brazil; **Jan-Marie Kozicky**, BSc, Mood Disorders Centre, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia, Canada; **Joana Bücker**, PsyD, Mood Disorders Centre, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia, Canada, and Laboratory of Molecular Psychiatry, Centro de Pesquisas Experimentais, Hospital de Clínicas de Porto Alegre, and INCT for Translational Medicine, Porto Alegre, and Programa de Pós-Graduação em Medicina: Psiquiatria, Universidade Federal do Rio Grande do Sul, UFRGS, Porto Alegre, Brazil; **Nadeesha Fernando**, Mood Disorders Centre, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia, Canada; **Lakshmi N. Yatham**, FRCPC, MRCPsych, Mood Disorders Centre, Department of Psychiatry, University of British Columbia, Vancouver, British Columbia, Canada

Correspondence: Dr Lakshmi N. Yatham, Professor of Psychiatry, Department of Psychiatry, University of British Columbia, Regional Head, Vancouver Coastal Health Authority/Providence Healthcare, 2255 Wesbrook Mall, Vancouver, BC, Canada V6T 2A1. Email: yatham@mail.ubc.ca

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Appendix

Cognitive domains and the neuropsychological tests included in each domain

Cognitive domain	Neuropsychological tests included
Processing speed	Trailmaking Test – time to complete part A Stroop Test – Word and Color Naming trials, number correct Letter Fluency – number correct
Attention	CANTAB – Rapid Visual Information Processing (RVIP) discriminability score RVIP latency score
Verbal memory	California Verbal Learning Test 2nd edition (CVLT-II) recall trials 1–5 CVLT-II delayed free recall trial
Non-verbal memory	CANTAB Spatial Recognition Memory (SRM) per cent correct CANTAB Pattern Recognition Memory (PRM) per cent correct CANTAB Paired Associate Learning total errors adjusted score
Working memory	Wechsler Memory Scale 3rd edition (WMS-III) (24) Letter/Number Sequencing CANTAB Spatial Working Memory (SWM) between errors
Executive function	Trailmaking Test B time Stroop C/W trial, number correct CANTAB Intra Extra Dimensional (IED) set shifting task number of extra-dimensional shifting (EDS) errors CANTAB Stockings problems solved in the minimum number of moves

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100 words

Randomised controlled trials

John Geddes

A randomised controlled trial (RCT) is an experiment in which the outcomes are compared between participants who have been allocated to comparator treatments or interventions unpredictably and randomly. Properly done, an RCT provides a fair test of treatments, avoiding bias due to treatment selection according to initial patient characteristics. Masking minimises biases due to clinical management or outcome assessment being influenced by the allocated treatment. Including all randomised patients in the analysis avoids bias due to differential drop-out. The trick for the trialist is to ensure that all this control does not make the results unusable in the real world.

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