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Research report

Cognitive performance and quality of life early in the course of bipolar disorder



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ABSTRACT

Background: Several studies have reported cognitive functioning as a significant predictor of quality of life (QoL) in patients with established bipolar disorder (BD), in addition to mood symptoms. However, it is unclear whether cognitive functioning predicts QoL early in the course of illness. The purpose of this study was therefore to evaluate the relationship between mood and neuropsychological variables and self-reported QoL early in the course of BD.

Methods: Patients with BD-I (n=54) completed a neuropsychological battery and clinical assessment within 3 months of resolution of their first manic episode. QoL was assessed 6 months later using the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). Cognitive predictors of QoL were assessed through Pearson correlations and hierarchical multiple regression.

Results: After accounting for mood rating scores at the time of cognitive testing (ΔR^2 =.27, p<.001), measures of sustained attention (ΔR^2 =.08, p<.05), verbal memory (ΔR^2 =.09, p<.01), working memory (ΔR^2 =.06, p<.05), and executive functioning (ΔR^2 =.08, p<.05) each predicted QoL when entered independently in separate regression models. When entered simultaneously, the cognitive domains explained 15% (R^2 =.42, p<.05) of the variance in QoL beyond mood.

Limitations: Some aspects of QoL that are particularly important in BD may be missing as a result of using the Q-LES-Q, because the measure was not specifically developed to assess QoL in BD.

Conclusions: In addition to mood symptoms, poorer cognitive functioning is a significant predictor of reduced QoL early in the course of BD. Recently diagnosed patients with BD may benefit from early cognitive-enhancing interventions to maintain or restore their QoL.

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1. Introduction

There is considerable interest in the assessment of quality of life (QoL) in bipolar disorder (BD) as an indicator of patient well-being and subjectively reported outcomes (Murray and Michalak, 2012). Traditionally, treatment for BD has focused on mood stabilization and symptom reduction; however, over the last decade, attention has also been directed toward addressing the impact of psychiatric illness on attaining optimal psychosocial functioning and subjective well-being (Awad et al., 1995; Fujii et al., 2004; Dias et al., 2008b). Thus, the target for effective treatment in psychiatric illness has shifted towards a biopsychosocial perspective placing emphasis on reduction of symptoms and

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concomitant optimization of the patient's QoL (Awad et al., 1995). QoL is a multidimensional concept that draws on a number of domains including physical, emotional, social, and spiritual wellbeing (World Health Organization, 1998). The assessment of QoL offers a subjective representation of one's well-being, which is distinct, at times, from external clinical judgment (Awad et al., 1995; Fujii et al., 2004; Dias et al., 2008b). Understanding the determinants of QoL in BD can provide insight into strategies for improving subjectively assessed outcomes, and potentially decreasing burden of the illness for the affected individuals and health care systems (IsHak et al., 2012).

A number of studies have found that patients with BD report lower QoL when experiencing symptoms of depression (Leidy et al., 1998; Vojta et al., 2001; Yatham et al., 2004; SanMighuel et al., 2005; Gazalle et al., 2006; Brissos et al., 2008a). Depressive symptoms have been associated with greater impairment in everyday functioning, and are clearly a primary determinant of impaired QoL in BD (Bauer et al., 2001; Vojta et al., 2001). The evidence concerning the relationship

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between mania and QoL is more mixed (Vojta et al., 2001; Zhang et al., 2006; Gazalle et al., 2007a, 2007b). Gazalle et al. (2007a, 2007b) suggested that the severity of manic symptoms may determine the direction in which QoL is affected. For instance, higher self-reports of QoL may be associated with more severe symptoms of mania (e.g., grandiose delusions) due to a patient's lack of awareness or insight of their own illness (Gazalle et al., 2007a), which can deteriorate with repeated manic episodes or if psychosis is present (Chand et al., 2004; Yen et al., 2007, 2009; Dias et al., 2008a). On the other hand, a patient with mild symptoms of mania may report lower QoL because he or she is aware of the consequences resulting from the illness (e.g., relationship conflicts, risky behavior, hospitalizations etc.; Gazalle et al., 2007a). However, data on the relationship between OoL and elevated mood states in patients with BD remains lacking. Diminished QoL appears to persist even in patients in remission (Robb et al., 1997; Michalak et al., 2005; SanMighuel et al., 2005; Gazalle et al., 2007b). Although mood symptoms are clearly a major driver of QoL in BD, studies in this area tend to find that mood symptoms, primarily depression, accounts for only a proportion (around 30-40%) of the variance in OoL scores (Bauer et al., 2001; Vojta et al., 2001; Zhang et al., 2006; Murray and Michalak, 2012; Michalak et al., 2013). Therefore, other factors such as cognitive functioning may serve as primary determinants of QoL in BD in addition to mood symptoms.

Previous research has established that cognitive performance is impaired in euthymic patients with BD (Martinez-Aran et al., 2007; Mur et al., 2007; Depp et al., 2007; Torres et al., 2007), and that cognitive deficits predict poor functional outcome in BD (Fujii et al., 2004; Bowie et al., 2010; Depp et al., 2012). Specifically, cognition has consistently been associated with objective functional outcome measures related to independent living, vocational success, and psychosocial skill acquisition (Green et al., 2000; Fujii et al., 2004; Dias et al., 2008a, 2008b; Brissos et al., 2008a, 2008b). The literature on the relationship between cognitive functioning and QoL, however, is comparatively lean. With some exception (Michalak et al., 2013), most studies in non-elderly euthymic patient samples with BD have reported attention/processing speed, verbal memory, and executive functioning to be significant predictors of QoL, in addition to mood symptoms (Fujii et al., 2004; Brissos et al., 2008a, 2008b; Sánchez-Morla et al., 2009; Pattanayak et al., 2012). Some of these studies, however, have not clarified whether cognitive deficits predict diminished OoL after controlling for the influence of mood symptoms. In other words, it is possible that the association between cognitive functioning and QoL may be driven exclusively by the presence of mood symptoms, which are also associated with cognitive functioning. In addition, these studies have all been conducted in multiple-episode patients with BD. However, cognitive deficits are recognized to occur at least by the time of initial diagnosis of BD (Hellvin et al., 2012; Torres et al., 2011). Thus, it is possible that cognitive impairments early in the course of illness may also predict diminished QoL in patients. This offers a potential "sweet-spot" in terms of early intervention; cognitive remediation strategies employed early in the course of BD to improve cognitive function hold potential to enhance QoL for patients with BD. Therefore, the purpose of the present study was to evaluate the relationship between mood and neuropsychological functioning and subjective OoL early in the course of BD. We hypothesized that cognition would predict QoL even after accounting for the effects of mood symptoms in patients who had recently experienced their first episode of mania.

2. Methods

2.1. Participants

Patients for this analysis were drawn from the Systematic Treatment Optimization Program for Early Mania (STOP-EM)

which recruited patients who met DSM-IV-TR criteria for Bipolar I Disorder (BD-I) from the University of British Columbia and other affiliated sites (Yatham et al., 2009a; Torres et al., 2010). These patients consisted of outpatients who were referred into the program by their psychiatrist or physician from the community or local hospitals. Diagnosis of BD-I and other Axis-I comorbidities was based on a comprehensive clinical interview by a fully qualified psychiatrist and confirmed with the Mini International Neuropsychiatric Interview (Sheehan et al., 1998). Patients were enrolled into the study within three months of resolution of their first manic/mixed episode. In order to capture a representative sample of patients with BD-I, the present naturalistic study allowed for the inclusion of patients with comorbidities such as prior substance abuse history or the presence of psychosis during their first manic episode. Enrolled patients were receiving treatments based on existing standards (CANMAT guidelines: Yatham et al., 2009b, 2013). For this report patients were required to be 17 years or older to be included in the study, and have an adequate understanding of the English language for cognitive testing purposes. In addition to having undergone neuropsychological evaluation, only those who completed the QoL ratings 6 months after cognitive testing were included in the present analysis. Ethics approval for the study was granted from the University of British Columbia Clinical Research Ethics Board, and written informed consent was obtained from all patients prior to participation. From a potential sample of 74 patients from the STOP-EM program, 54 final patients were included who had mood, cognitive, and QoL data.

2.2. Clinical assessment

Sociodemographic and clinical variables were obtained from the STOP-EM database compiled from the clinical interview and supplementary information from clinical charts (see Table 1). The Hamilton depression rating scale-29 items (HAM-D; Williams,

Table 1 Demographics and characteristics of the sample (n=54).

Continuous variable	М	SD
Age	23.2	4.3
Education	14.0	2.3
Premorbid IQ	105.1	8.8
Age at illness onset	20.0	5.1
Global assessment of functioning	66.7	13.0
Categorical variable	N	%
Gender		
Female	28	51.9
Ethnicity		
Caucasian	42	77.8
Non-Caucasian	12	22.2
Primary language		
English	49	90.7
Other	5	9.3
Employment status		
Student	18	33.3
Employed	9	16.7
Unemployed	12	22.2
Disability	15	27.8
Medications		
On mood stabilizers	48	88.9
On antipsychotics	45	83.3
On antidepressants	5	9.3
On anxiolytics	4	7.4
History of depressive episode	28	51.9
Substance/alcohol abuse or dependence (lifetime)	25	46.3

Demographics at baseline. Premorbid IQ=North American Adult Reading Test

1988) and the Young Mania Rating Scale (YMRS; Young et al., 1978) were administered by a trained psychiatrist to assess depressive and manic symptoms, respectively, at baseline. The proximity of mood ratings to cognitive testing was a median of 2.5 days.

2.3. Neuropsychological assessment

As part of the STOP-EM study, subjects completed a 2.5 h cognitive battery that consisted of standardized clinical neurop-sychological measures (see Torres et al. (2010)). The specific measures drawn from the baseline cognitive battery and used in the present analysis were selected a priori based on previous research that used similar tests to evaluate the effects of cognition on QoL in BD (Fujii et al., 2004; Brissos et al., 2008a, 2008b; Sánchez-Morla et al., 2009; Pattanayak et al., 2012); measures were available for all patients. The individual measures used and their respective cognitive domains are presented below.

Sustained attention: the Rapid Visual information Processing (RVIP) discriminability score from the Cambridge Neuropsychological Test Automated Battery (Robbins et al., 1994).

Verbal memory: the California Verbal Learning Test-2nd edition (CVLT-II; Delis et al., 2000) recall trials 1 through 5 score.

Executive functioning: the Trailmaking Test trial B (TMT-B; Reitan and Wolfson, 1985) score for completion time.

Working memory: the Letter/Number Sequencing (LNS) total score from the Wechsler Memory Scale-3rd edition (Wechsler, 1997).

2.4. Quality of life assessment

The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q; Endicott et al., 1993) is a generic (as opposed to 'healthrelated') self-report questionnaire that has been validated for use in patients with BD (Ritsner et al., 2002). The Q-LES-Q evaluates QoL across eight broad domains including: physical health, subjective feelings, leisure time activities, social relationships, and general activities, as well as, work, household duties, and school/course work, if applicable. For this study the short form of the Q-LES-Q was used, which is synonymous with the 'general activities' domain of the scale (not including the last two items assessing satisfaction with medication and life overall). The short form has been reported to have good construct validity and high internal consistency (Cronbach's α =.89-.95; Ritsner et al., 2002; Rapaport et al., 2005). For a summary score of the Q-LES-Q the percentage of the maximum possible score (MPS; range from 14-70) is obtained from the 14 items in the short form, each rated on a scale from 1 to 5. The mean score for the short form was 83% of the MPS for the community sample reported in the Q-LES-Q validation paper (Endicott et al., 1993). Based on Schechter et al. (2007) scoring convention for the O-LES-O, respondents who fall within 10% of the mean score (i.e., 83%) are within the average range for healthy individuals. For this study, subjects completed the Q-LES-Q during a follow-up visit 6 months after their baseline visit to avoid biased effects of residual mood symptoms on QoL following their first manic episode.

2.5. Statistical analysis

Demographic-corrected z-scores were obtained from normative data for each of the cognitive measures, and the distributions were examined for normality and outliers. The distributions for YMRS and HAM-D for the remaining patients were positively skewed. Thus, the HAM-D and YMRS scores were transformed using square-root and inverse transformations, respectively. The HAM-D and YMRS scores marginally improved after statistical transformations, and since the results were identical using both transformed and untransformed variables the untransformed mood scores were presented for ease of

Table 2 Pearson correlations (r) and mean scores at baseline (n=54).

Variable	1	2	3	4	5	6	7	M	SD
1.Q-LES-Q ^a 2.YMRS 3.HAM-D 4.RVIP ^c 5.CVLT 6.TMT 7.LNS	43**b 36**b .35* .37* .29* .35*	- .15 21 11 08 27	- .03 09 .07 03	- .31° .27 .47°	- .43** .49**	- .32*	_	64.55 .89 5.89 44 .06 03 13	20.42 1.81 6.78 1.03 1.14 1.13

Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire (Max Possible Score %). YMRS=Young Mania Rating Scale. HAM-D=Hamilton Depression Rating Scale (29). RVIP=Rapid Visual Information Processing. CVLT=California Verbal Learning Task (Trials I-V). TMT-B=Trail Making Test (Trial B). LNS=Letter Number Sequencing.

- ^a Q-LES-Q at 6 month follow-up.
- ^b Spearman correlations were also significant (p < .05).
- c RVIP (n = 52).
- * *p* < .05.
- ** p < .01.

interpretation. Pearson correlations were used to assess the relationship between clinical and neuropsychological variables and QoL (Table 2). Relevant predictors were entered into multiple hierarchical regression models with QoL as the dependent variable (Table 3). The first step included entry of HAM-D and YMRS scores to account for the influencing effects of mood symptoms on QoL. The second step included forced-entry of cognitive measures (after accounting for the influence of mood symptoms). Cognitive measures of sustained attention, verbal memory, executive functioning, and working memory, were entered both simultaneously (Table 3, Model 1) and individually in the final step (Table 3, Models 2–5). All statistical tests were 2-tailed (α =.05) and were performed using SPSS version 21.0 (SPSS Inc, Chicago, Illinois, 2012).

3. Results

Of the 20 eligible subjects who were excluded from analysis, one subject had extreme values (>3 SDs) on several of the cognitive measures and showed poor effort based on clinical observation. Another subject was also excluded from the analyses because of extremely high scores on the mood rating scales. The other 18 subjects who were excluded from the analysis did not have QoL data at 6-months for the following reasons: 3 were recently enrolled and only had baseline data; 9 remained in the study but had not completed the Q-LES-Q at 6-months due to scheduling reasons; and 6 had dropped out of the study after baseline. Overall, there were no significant (p > .05) differences in mood ratings and cognitive variables between subjects who remained in the study and those who had dropped out.

Overall, patients were clinically stable, with minimal symptoms of depression (mean=5.9, SD=6.8) and mania (mean=.89; SD=1.81) at the time of cognitive testing, and reported relatively high QoL (mean Q-LES-Q MPS=64.6, SD=20.4) at the 6 month follow-up visit. Despite this, the mean Q-LES-Q MPS were below the normal range for healthy individuals with no medical or mental illness (Endicott et al., 1993; Schechter et al., 2007). Mean z-scores for cognitive variables are presented in the right panel of Table 2.

As expected, HAM-D (r= -.36, p < .01) and YMRS (r= -.43, p < .01) correlated negatively with Q-LES-Q MPS. Cognitive measures of sustained attention (r= .35, p < .05), verbal memory (r= .37, p < .01), executive functioning (r= .29, p < .05), and working memory (r= .35, p < .01) were observed to be positively correlated with Q-LES-Q MPS (Table 2).

Table 3 Hierarchical regression models.^a

Model #1 (n=52) Step 1: HAM-D		В	SE	р	R ²	ΔR^2			
HAM-D	Model #1 (n=52)								
YMRS -4.32 1.39 .00 Step 2:	Step 1:								
Step 2:	HAM-D		.37	.02	.27	.27***			
HAM-D95	YMRS	-4.32	1.39	.00					
YMRS									
RVIP 3.57 2.64 .18 CVLT 2.95 2.50 .24 TMT 2.67 2.31 .25 LNS 1.54 4.36 .73 Model #2 (n=52) Step 1: HAM-D91 .37 .02 .27 .27 YMRS -4.32 1.39 .00 Step 2: HAM-D96 .36 .01 .35 .08 YMRS -3.61 1.36 .01 RVIP 5.82 2.40 .02 Model #3 (n=54) Step 1: HAM-D90 .36 .02 .28 .28 YMRS -4.39 1.36 .00 Step 2: HAM-D83 .34 .02 .37 .09 YMRS -4.05 1.29 .00 CVLT 5.55 2.04 .01 Model #4 (n=54) Step 1: HAM-D90 .36 .02 .28 .28 YMRS -4.39 1.36 .00 Step 2: HAM-D91 .35 .00 .00 Model #4 (n=54) Step 1: HAM-D90 .36 .02 .28 .28 YMRS -4.39 .36 .00 Step 2: HAM-D90 .36 .00 .20 Model #4 (n=54) Step 1: HAM-D90 .36 .00 .22 Model #4 (n=54) Step 1: HAM-D90 .36 .00 .00 TMT 5.12 .2.06 .00 Model #5 (n=54) Step 2: HAM-D91 .35 .01 .36 .00 Step 2: HAM-D91 .35 .01 .34 .06					.42	.15			
CVLT 2.95 2.50 .24 TMT 2.67 2.31 .25 LNS 1.54 4.36 .73 Model #2 (n=52) Step 1: HAM-D91 .37 .02 .27 .27 YMRS -4.32 1.39 .00 Step 2: HAM-D96 .36 .01 .35 .08 YMRS -3.61 1.36 .01 RVIP 5.82 2.40 .02 Model #3 (n=54) Step 1: HAM-D90 .36 .02 .28 .28 YMRS -4.39 1.36 .00 Step 2: HAM-D83 .34 .02 .37 .09 YMRS -4.05 1.29 .00 CVLT 5.55 2.04 .01 Model #4 (n=54) Step 1: HAM-D90 .36 .02 .28 .28 YMRS -4.39 1.36 .00 Step 2: HAM-D83 .34 .02 .37 .09 YMRS -4.05 1.29 .00 CVLT 5.55 2.04 .01 Model #4 (n=54) Step 1: HAM-D90 .36 .02 .28 .28 YMRS -4.39 .136 .00 Step 2: HAM-D90 .36 .02 .28 .28 YMRS -4.39 .136 .00 Step 2: HAM-D97 .35 .01 .36 .08 YMRS -4.10 1.30 .00 TMT 5.12 2.06 .02 Model #5 (n=54) Step 1: HAM-D90 .36 .02 .28 .28 YMRS -4.39 .136 .00 TMT 5.12 2.06 .02 Model #5 (n=54) Step 2: HAM-D90 .36 .02 .28 .28 YMRS -4.39 .136 .00 Step 2: HAM-D91 .35 .01 .34 .06									
TMT									
LNS									
Model #2 (n=52) Step 1: HAM-D 91 .37 .02 .27 .27 YMRS -4.32 1.39 .00 .36 .01 .35 .08* YMRS -3.61 1.36 .01 .01 .08* .08* .00* .02 .08* .08* .00*									
Step 1: HAM-D 91 .37 .02 .27 .27" YMRS -4.32 1.39 .00	LNS	1.54	4.36	.73					
HAM-D	Model #2 (n	=52)							
YMRS	Step 1:								
Step 2: HAM-D 96 .36 .01 .35 .08* YMRS -3.61 1.36 .01 .02 .02 .02 .02 .02 .02 .02 .02 .02 .02 .02 .02 .02 .02 .02 .02 .02 .02 .02 .03 .00 .02 .03 .00 .02 .03 .00 .02 .03 .09* .00 .02 .03 .09* .09* .09* .00 .00 .00 .00* .00* .00* .00* .00* .00* .00* .00* .00* .00* .00* .00* .00* .00* .00* .00* .00* .00* .00* .00* <t< td=""><td>HAM-D</td><td>91</td><td>.37</td><td>.02</td><td>.27</td><td>.27</td></t<>	HAM-D	91	.37	.02	.27	.27			
HAM-D	YMRS	-4.32	1.39	.00					
YMRS									
RVIP 5.82 2.40 .02 Model #3 (n=54) Step 1: HAM-D					.35	.08			
Model #3 (n=54) Step 1: HAM-D 90 .36 .02 .28 .28 YMRS -4.39 1.36 .00 .37 .09° Step 2: HAM-D 83 .34 .02 .37 .09° YMRS -4.05 1.29 .00									
Step 1: HAM-D 90 .36 .02 .28 .28" YMRS -4.39 1.36 .00	RVIP	5.82	2.40	.02					
HAM-D90 .36 .02 .28 .28 .28	Model #3 (n	=54)							
YMRS	Step 1:								
Step 2: HAM-D 83 .34 .02 .37 .09* YMRS -4.05 1.29 .00	HAM-D	90	.36	.02	.28	.28			
HAM-D83	YMRS	-4.39	1.36	.00					
YMRS	Step 2:								
CVLT 5.55 2.04 .01 Model #4 (n=54) Step 1: HAM-D90 .36 .02 .28 .28 YMRS -4.39 1.36 .00 Step 2: HAM-D97 .35 .01 .36 .08 YMRS -4.10 1.30 .00 TMT 5.12 2.06 .02 Model #5 (n=54) Step 1: HAM-D90 .36 .02 .28 .28 YMRS -4.39 .136 .00 Step 2: HAM-D91 .35 .01 .34 .06 YMRS -3.62 1.37 .01					.37	.09**			
Model #4 (n=54) Step 1: HAM-D									
Step 1: HAM-D 90 .36 .02 .28 .28" YMRS -4.39 1.36 .00	CVLT	5.55	2.04	.01					
Step 1: HAM-D 90 .36 .02 .28 .28" YMRS -4.39 1.36 .00	Model #4 (n	=54)							
YMRS -4.39 1.36 .00 Step 2: HAM-D97 .35 .01 .36 .08* YMRS -4.10 1.30 .00 TMT 5.12 2.06 .02 Model #5 (n=54) Step 1: HAM-D90 .36 .02 .28 .28* YMRS -4.39 1.36 .00 Step 2: HAM-D91 .35 .01 .34 .06* YMRS -3.62 1.37 .01	,	ŕ							
YMRS -4.39 1.36 .00 Step 2: HAM-D97 .35 .01 .36 .08* YMRS -4.10 1.30 .00 TMT 5.12 2.06 .02 Model #5 (n=54) Step 1: HAM-D90 .36 .02 .28 .28* YMRS -4.39 1.36 .00 Step 2: HAM-D91 .35 .01 .34 .06* YMRS -3.62 1.37 .01	HAM-D	90	.36	.02	.28	.28***			
HAM-D97 .35 .01 .36 .08° YMRS -4.10 1.30 .00 TMT 5.12 2.06 .02 Model #5 (n=54) Step 1: HAM-D90 .36 .02 .28 .28° YMRS -4.39 1.36 .00 Step 2: HAM-D91 .35 .01 .34 .06° YMRS -3.62 1.37 .01	YMRS	-4.39	1.36	.00					
YMRS -4.10 1.30 .00 TMT 5.12 2.06 .02 Model #5 (n=54) Step 1: HAM-D90 .36 .02 .28 .28 YMRS -4.39 1.36 .00 Step 2: HAM-D91 .35 .01 .34 .06 YMRS -3.62 1.37 .01	Step 2:								
TMT 5.12 2.06 .02 Model #5 $(n=54)$ Step 1: HAM-D90 .36 .02 .28 .28 YMRS -4.39 1.36 .00 Step 2: HAM-D91 .35 .01 .34 .06 YMRS -3.62 1.37 .01	HAM-D	97	.35	.01	.36	.08*			
Model #5 (n=54) Step 1: HAM-D	YMRS	-4.10	1.30	.00					
Step 1: HAM-D 90 .36 .02 .28 .28************************************	TMT	5.12	2.06	.02					
Step 1: HAM-D 90 .36 .02 .28 .28 YMRS -4.39 1.36 .00 Step 2: .01 .34 .06 YMRS -3.62 1.37 .01 .34 .06	Model #5 (n	Model #5 $(n=54)$							
HAM-D90 .36 .02 .28 .28	,	,							
YMRS -4.39 1.36 .00 Step 2: .01 .34 .06* HAM-D 91 .35 .01 .34 .06* YMRS -3.62 1.37 .01		90	.36	.02	.28	.28***			
Step 2: HAM-D 91 .35 .01 .34 .06° YMRS -3.62 1.37 .01									
HAM-D91 .35 .01 .34 .06° YMRS -3.62 1.37 .01									
YMRS -3.62 1.37 .01		91	.35	.01	.34	.06			
LNS 7.18 3.39 .04	YMRS	-3.62		.01					
	LNS	7.18	3.39	.04					

Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire (Max Possible Score %). YMRS=Young Mania Rating Scale. HAM-D=Hamilton Depression Rating Scale (29). RVIP=Rapid Visual Information Processing. CVLT=California Verbal Learning Task (Trials I-V). TMT-B=Trail Making Test (Trial B). LNS=Letter Number Sequencing.

Table 3 illustrates the multiple hierarchical regression models that were conducted to assess whether cognitive domain measures predicted QoL (i.e., Q-LES-Q) after accounting for the variance explained by mood symptoms. Depression and mania symptoms were entered simultaneously in the first step of the regression model, represented by HAM-D (B=-.91, p<.05) and YMRS (B=-4.32, p<.001) scores, respectively, and were related to QoL ($R^2=.27, p<.001$). Individually, measures of sustained attention ($\Delta R^2=.08, p<.05$), verbal memory ($\Delta R^2=.09, p<.01$), executive functioning ($\Delta R^2=.08, p<.05$), and working memory ($\Delta R^2=.06, p<.05$), each explained additional variance in QoL (Models 2–5) after accounting for the effects of mood symptoms. However, the unique contribution of each cognitive measure was no longer significant when all the cognitive measures were entered simultaneously in step 2 of Model 1. Rather, the combined

impact of the cognitive variables significantly predicted QoL (ΔR^2 =.15, p < .05) beyond the influence of mood symptoms, and the predicting variables of the entire model explained 42% of the total variance in QoL (p < .05).

4. Discussion

Despite a growing body of research that has linked cognitive functioning to QoL in multiple-episode patients with BD, little is known about the relationship between cognition and QoL early in the course of illness. The current study investigated the effects of cognition on self-reported QoL in recently diagnosed BD-I patients, after controlling for mood symptoms. As expected, results revealed that both HAM-D and YMRS scores significantly correlated with Q-LES-Q in a negative direction, indicating that patients with BD who experienced greater symptoms of depression and mania exhibit impaired QoL. Therefore, the previously reported finding that mood symptoms are significant predictors of QoL was replicated in our first episode sample (Vojta et al., 2001; Yatham et al., 2004; SanMighuel et al., 2005; Gazalle et al., 2006, 2007b).

With regard to the primary hypothesis, results showed that cognitive measures of sustained attention, verbal memory, executive functioning, and working memory each correlated positively with Q-LES-Q, indicating that patients with BD who experience better cognitive functioning report higher QoL. Furthermore, each cognitive domain uniquely predicted QoL even after accounting for mood symptoms (see Models 2-5). However, when the cognitive domains were entered simultaneously to evaluate the effect of global cognition on QoL (Model 1), the unique predictive validity of each cognitive domain was no longer significant. Therefore, the results from Model 1 indicate that global cognition, rather than specific cognitive domains, is a significant predictor of OoL above that of mood symptoms. An earlier cohort from this sample was studied in a previous report (Michalak et al., 2013) that aimed to assess the relationship between various clinical predictors and QoL; however in that study we did not find an association between verbal learning (i.e., CVLT-II) and QoL (Q-LES-Q). This discrepancy may be due to the fact that the outcome variable used previously (mean of MPS for all Q-LES-Q subtests) differs from the one used in this study (MPS for Q-LES-Q short form), the latter of which follows the scoring convention reported in the Q-LES-Q validation paper (Endicott et al., 1993). Additionally, the discrepancy may be related to the fact that this was an earlier cohort, or to differences that were used in obtaining data for statistical analysis (i.e., multiple-imputation procedure for missing data was employed in the first study). Unfortunately, there is little consensus within the literature on how to measure QoL most accurately, and this underscores the need to establish optimal validated outcome measures for QoL within the field. Nevertheless, because the current study was specifically designed to assess the influence of multiple aspects of cognition, the general finding of an association between cognitive functioning and QoL, previously observed in multiple-episode patients with BD (Fujii et al., 2004; Brissos et al., 2008a, 2008b; Sánchez-Morla et al., 2009; Pattanayak et al., 2012), also appears to extrapolate to first episode mania patients based on the findings from this study.

Based on the pattern of findings, our data suggest that a general cognitive factor (common to all cognitive measures) is what predicts QoL in early BD. Previous research that assessed cognition and QoL in established BD showed similar patterns in their results (Depp et al., 2007). Pattanayak et al. (2012) proposed that impairments in executive functioning underlie psychosocial and functional deficits, as well as broad cognitive deficits, and thus that executive deficits may represent a central trait in BD. If this is the case, then deficits in executive skills such as effective problem

^a Dependent variable is Q-LES-Q at 6 month follow-up.

^{*} p < .05.

^{**} *p* < .01.

^{***} p < .001.

solving may be the common factor that can account for the relationship between cognition and QoL. Our results also suggest that a general cognitive ability might be an important determinant of QoL, although we are unable to specify further whether executive functioning might be the core feature at play. A further contributor to why general cognitive functioning was observed to predict QoL in our sample is that our QoL measure was a composite measure of functioning in numerous domains. Given the use of this broad QoL outcome measure, it follows that general, rather than specific cognitive ability, might be expected to associate with QoL. On the other hand, there is some evidence that cognitive measures assessing individual cognitive domains may associate with individual aspects of QoL (Fujii et al., 2004; Brissos et al., 2008a, 2008b; Sánchez-Morla et al., 2009; Pattanayak et al., 2012).

Although the connection between cognition and QoL is present, the mechanisms underlying how cognition links to QoL are less clear. The link between cognition and QoL is potentially straightforward. For example, those individuals who have better cognitive ability may achieve more success at work/school or at home, and this may lead to increased subjective well-being and happiness. On the other hand, those with cognitive impairments may struggle to complete tasks efficiently or effectively, which in turn can jeopardize success in their various roles and lead to subjective dissatisfaction. The link between cognition and QoL may also be mediated by other variables. For instance, better insight and self-awareness is associated with better self-reported QoL (Dias et al., 2008b). Impairments in self-awareness can negatively affect an individual's insight into their mental, emotional, and cognitive states, thus disrupting their ability to accurately judge their everyday experience and their sense of self (Lysaker et al., 2005). It is evident that patients with more severe manic symptoms have significantly reduced insight and disrupted self-awareness (Dias et al., 2008a), which may not fully improve with the resolution of mood symptoms (David et al., 1992; Amador et al., 1993; Dias et al., 2008a). In addition, decreased insight may be associated with reduced cognitive functioning. Indeed, there is some evidence that suggests preserved insight to be partially dependant on intact executive functioning (Amador and David, 2004; Varga et al., 2006). Therefore, one variable underlying the relationship between cognition and QoL may be insight/self-awareness. Regarding other potential mediators, Bowie et al. (2010) suggest that the relationship between cognition and objective functional outcome (i.e., real-world psychosocial outcome) may be mediated by variables including: daily living skills, social competence, social cognition, psychiatric symptoms, motivation, and metacognition. Therefore, further research is needed to determine whether such variables may also mediate the relationship between cognition and QoL.

4.1. Limitations

Some limitations of this study must be taken into account. First, the Q-LES-Q is not a self-report QoL measure developed specifically for BD; therefore, it may be possible that some aspects of QoL may be missed that are particularly important in BD (Michalak and Murray, 2010). Further research assessing the affects of cognition on QoL may benefit from using BD-specific QoL measures such as the Quality of Life- Bipolar Disorder questionnaire (QoL.BD), developed by Michalak and Murray (2010), to capture a more accurate representation of QoL in BD. Also, given the modest sample size and therefore the limitations in our ability to use multiple predictors in our regression models, this study did not assess the influence of other potential psychosocial and clinical predictors of QoL, including but not limited to: social support, stress management, comorbid substance use, and medication affects. Therefore, in light of these limitations, further research is

needed to assess the predictive validity of cognition and other variables on QoL early in the course of BD.

4.2. Conclusion

The purpose of this study was to evaluate the relationship between mood and neuropsychological variables and self-reported QoL following a first manic episode in patients with BD. Based on our findings, cognitive functioning is a significant predictor of QoL in addition to mood symptoms, even in the early stages of the illness. Therefore, cognitive-enhancing interventions may be important for restoring or maintaining QoL among BD patients early in the course of this disorder.

Conflict of interest

EEM has been a speaker for and sat on advisory boards for Lundbeck. IJT has received research funding from the Canadian Institutes of Health Research (CIHR) and consulted for Lundbeck. LNY has received research grant funding from, has been a member of advisory boards for, and has been a speaker for AstraZeneca, Janssen, Eli Lilly & Co., GlaxoSmithKline, Bristol-Myers Squibb, Novartis, Servier, Lundbeck, Merck, and Pfizer. JK and SAM have no conflicts of interest to disclose.

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