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Neurocognitive functioning in first-episode Bipolar Disorder: Relationship with functional status

Alejandro G. Szmulewicz[a,b,*], Marina P. Valerio[c,d], Julieta Lomastro[d], José M. Smith[e], Virginia Chiappe[d], Diego J. Martino[a,c,f], Ana Igoa[a,d]

[a] Bipolar Disorder Program, Institute of Neurosciences, Favaloro University, Buenos Aires, Argentina
[b] Pharmacology Department, University of Buenos Aires School of Medicine, Buenos Aires, Argentina
[c] National Council of Scientific and Technical Research (CONICET), Argentina
[d] Psychiatric Emergencies Hospital Torcuato de Alvear, Buenos Aires, Argentina
[e] Psychiatric Department, Medical Education and Clinical Research Center Norberto Quirno, CEMIC, Buenos Aires, Argentina
[f] Institute of Cognitive and Translational Neuroscience (INCyT), INECO Foundation, Favaloro University, Buenos Aires, Argentina

ABSTRACT

Background: The aim of this study was to assess if an association between neurocognitive deficits and psychosocial functioning exists in first-episode BD patients.

Methods: Twenty-five euthymic first-episode BD patients and thirty-seven healthy controls were recruited. History of suicide attempts, psychiatric comorbidities, pharmacological exposure, and previous depressive episodes were investigated. Performances on neurocognitive domains (verbal memory, attention, processing speed, and executive functions) as well as a measure of psychosocial functioning were used as outcomes.

Results: First-episode BD patients showed medium-to-large size deficits on measures of attention, processing speed, and executive functions. A significant association between verbal memory and psychosocial functioning at the moment of BD diagnosis was detected (beta coefficient −3.9, IC 95% −6.7 to −1.2, $p < 0.01$).

Conclusions: A relationship between cognitive performance at the moment of BD diagnosis and psychosocial functioning was detected. Possible therapeutic implications of this finding are discussed.

1. Introduction

A broad number of reports have established that neuropsychological deficits are present in Bipolar Disorders (BD) even during periods of euthymia (Bourne et al., 2013; Mann-Wrobel et al., 2011). Moreover, these deficits have been widely reported in patients at the beginning of their disease (Hellvin et al., 2012; Lee et al., 2014; Torres et al., 2010). A recent meta-analysis evaluating neurocognitive deficits in first episode of mania (FEM) reported that patients presented medium-to-large size deficits in processing speed, attention, working memory, and cognitive flexibility, while smaller size deficits in verbal learning and memory tests were found (Lee et al., 2014), being these findings similar to those reported in patients in the midst of the disease (Bourne et al., 2013).

One of the most well-accepted associations between cognitive deficits and outcomes in BD is with psychosocial functioning. However, this association has been mostly studied in multiple-episode patients with cross-sectional (Rosa et al., 2014) and longitudinal designs (Martino et al., 2009; Tabarés-Seisdedos et al., 2008). Torres et al. (2011) could not detect a relationship between baseline functional outcomes and cognitive status but found that the latter predicted 6-month functional outcomes in FEM. However, a substantial proportion of patients experienced a depressive recurrence during the 6-month follow up period, thus blurring the direct relationship between cognitive and psychosocial functioning. Indeed, a recent study (Muralidharan et al., 2014) suggested that poorer cognitive outcomes in FEM predicted depressive recurrences and these might be the main drivers of poor psychosocial outcomes. Another possible explanation is that the authors evaluated baseline psychosocial functioning immediately after syndromic remission, which could have overestimated functional impairment of included patients. This relationship between baseline cognitive function and psychosocial outcomes is of major interest since it could better isolate whether if it is present from disease onset or instead, if patients with poorer cognitive status are predisposed to a higher rate of mood episodes, which, in turn, are the main drivers of declined psychosocial outcomes. This may have therapeutic implications in order to arrest psychosocial deterioration on BD patients early in their condition - either by preventing mood episodes or by focusing on cognitive

* Correspondence to: Gurruchaga 2463, 1°"C" (1425) Ciudad Autónoma de Buenos Aires, Argentina.
E-mail address: alejandroszm@gmail.com (A.G. Szmulewicz).

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remediation -.

Accordingly, the aim of this study is to characterize neurocognitive and psychosocial functioning in FEM at baseline in order to gain some insights into the onset and implications of psychosocial deficits in BD.

2. Methods

2.1. Participants

Twenty-five patients meeting Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for Bipolar Disorder type I – presenting their FEM - were recruited from emergency service as a part of a program to assess longitudinal evolution of this disease at the Torcuato de Alvear Psychiatric Emergencies Hospital, in Buenos Aires, Argentina: FEPA program. Diagnosis of BD was performed by trained psychiatrists using the MINI-International Neuropsychiatric Interview (MINI) and reassessed by the treating physicians through medical records. MINI was also employed to assess the presence of psychiatric comorbidities. Patients with mental retardation, neurological illness, or unstable medical illness were excluded.

Patients received treatment under naturalistic conditions and were assessed weekly for symptomatic remission (Young Mania Rating Scale $\leq$ 6 and Hamilton Depressive Rating Scale $\leq$ 8 for 2 consecutive months). Once achieved, patients underwent neurocognitive assessment.

Thirty-seven healthy participant subjects matched on age, education, and premorbid IQ were recruited. Controls were also assessed to discard family history of psychiatric disorders and a personal history of psychotropic medication use.

Ethics approval was received and all patients included provided written informed consent.

2.2. Clinical, pharmacological, and functional assessment

Patients were assessed weekly for clinical status using YMRS and HDRS. The presence of suicide attempts – as a measure of illness severity - was evaluated by direct patient interviewing. All clinical information was also confirmed by revision of the medical chart. When possible, attempts were made to verify this data with a family record.

Pharmacological load was assessed by means of the Clinical Scale of Intensity, Frequency, and Duration of Psychopharmacological Treatment (IFD) that provides a quantitative measure of exposure to psychotropic agents in a 0–5-point range (Peralta and Cuesta, 2002).

Baseline functional and social status was evaluated using the Functional Assessment Short Test (FAST) (Rosa et al., 2007). Patients were asked to respond to this scale on the basis of their functioning immediately previous to the manic episode and/or hospitalization.

2.3. Neurocognitive assessment

Neurocognitive tests were selected on the basis of previous literature on cognitive deficits associated with euthymic BD type I and performed by non-blinded trained evaluators.

1. *Premorbid verbal IQ* was assessed by using the WAIS vocabulary subtest
2. *Attention and Processing Speed* was assessed using the Trail Making Test part A (TMT-A) time to completion, the direct span digit test, the Stroop test word and color naming trials number correct, and the Rey Auditory Verbal Learning Test (RAVLT) trial 1 words recalled.
3. *Cognitive Flexibility* was evaluated using the Trail Making Test part B (TMT-B) time to completion, and through the quotient between phonological and semantic fluency.
4. *Response inhibition* was assessed by means of the Stroop Interference test
5. *Working Memory* was evaluated with the inverse SPAN digit test
6. *Learning / Memory* was evaluated using the RAVLT recall trials 1–5, delayed free recall and the recognition test.

2.4. Statistical analysis

Quantitative variables are presented as mean and standard deviation. Baseline differences in demographical and cognitive measures between FEM patients and controls were assessed using chi-square test for categorical variables and student's T test for continuous variables. For each cognitive measure, raw scores were transformed to Z-scores ranging from -4 to $+4$ based on normative data constructed locally for each test. Patient-control differences in cognitive performance were evaluated through Student's T test.

To evaluate the effect of neurocognitive measures on functional status in the FEM group, a multiple lineal regression analysis was conducted using FAST total score as the dependent variable and measures of the six cognitive domains evaluated separately as covariates adjusting by education and premorbid IQ.

Finally, the proportion of FEM patients with clinically significant neurocognitive impairment (defined as at least one neurocognitive score below 2 SD the control group) was calculated.

3. Results

3.1. Patient sample

All patients included presented with a manic episode with psychotic features and were medication-free. Thirteen patients of the total sample (52%) were hospitalized due to the severity of their manic episode. Five patients presented a previous depressive episode (20% of the sample) and three of those did not receive medication while two did received but abandoned such treatment. One patient was hospitalized in his/her previous depressive episode (Table 1).

Median time from manic episode to mood-stabilizing treatment was 2 months with an inter-quartile range from 2 to 4 months. Median time from episode to neuropsychological assessment was 4 months.

Patients meeting criteria for comorbid substance abuse (n = 9, 36% of the sample) presented with poorer functional status (mean FAST total score 22.4 vs. 15.3, p = 0.04). Also, these patients had a non-significant lower education (11.5 years vs. 13.1, p = 0.18) and younger age at onset (19.2 years vs. 23.7, p = 0.06).

All of the patients were treated with either a mood stabilizer and/or an antipsychotic drug.

3.2. Neurocognitive results

Mean cognitive scores in Z-scores and all group differences are displayed in Table 1. Medium-to-large effect sizes (Cohen's $d > 0.60$) were observed on measures of attention, processing speed, and cognitive flexibility, while small effect sizes (Cohen's $d \leq 0.59$) were found on response inhibition and delayed memory.

No significant correlations between any of the cognitive measures and the time elapsed in symptomatic remission were observed. Finally, no significant correlations between mood symptomatology scores and cognitive measures were found (all R's P > 0.10).

3.3. Relationship with functional status

The only cognitive domain associated with a poorer baseline functional status in the regression analysis was verbal memory – delayed recall – after adjusting by education and premorbid IQ (beta coefficient -3.9, IC 95% -6.7 to -1.2, p < 0.01) (Table 2). Also, a measure of cognitive flexibility – performance on TMT-B – was marginally associated with a poorer functional status (beta coefficient -2.1, IC 95% -4.3 to 1.02, p = 0.05).

Table 1
Demographic, clinical and cognitive characteristics of control and patient sample.

Characteristic	Patient sample (N = 25)	Healthy controls (N = 37)	p value[1]
Age - years (mean, SD)	23.2 (7.4)	25.7 (4.4)	0.13
Male sex – (%)	72	47	0.07
Premorbid IQ (mean Z-score; SD)	0.1 (0.7)	−0.1 (0.8)	0.25
Education, years (mean; SD)	12.7 (2.6)	13.8 (2.7)	0.11
Clinical features			
Age at illness onset, years (mean, SD)	22.0 (6.9)		
Age at mania onset, years (mean, SD)	23.2 (7.4)		
Previous depressive episodes (mean, SD)	0.5 (0.64)		
YMRS score (mean, SD)	2.2 (2.1)		
HDRS score (mean, SD)	0 (0)		
Suicide attempt (%)	16		
Substance abuse (%)	36		
Pharmacological features			
IFD score –mood stabilizers- (mean, SD)	2.3 (1.3)		
IFD score –antipsychotics- (mean, SD)	2.2 (1.2)		
IFD score –benzodiazepines- (mean, SD)	0.6 (1.3)		
% Patients receiving lithium (%)	64		
Functional features			
Autonomy sub-scale score (mean; SD)	3.3 (2.4)		
Working status sub-scale (mean; SD)	4.5 (2.7)		
Cognitive status sub-scale (mean; SD)	4.6 (3.2)		
Finance status sub-scale (mean; SD)	1.5 (1.5)		
Leisure status sub-scale (mean; SD)	1.2 (1.2)		
Cognitive performance			
Memory domain			
RAVLT total score (Z score; SD)	−0.22 (1.12)	0.58 (0.96)	< 0.01
RAVLT delayed recall (Z score; SD)	0.03 (1.06)	0.48 (0.99)	0.10
RAVLT recognition (Z score; SD)	−0.47 (1.34)	0.13 (0.69)	0.05
Attention / Processing speed			
Direct Digit Span (Z score; SD)	−0.53 (1.32)	0.38 (1.14)	< 0.01
Trail-Making test A (Z score; SD)	0.76 (0.86)	1.37 (0.70)	< 0.01
Stroop Word naming (Z score; SD)	−0.92 (0.92)	0.02 (0.73)	< 0.01
Stroop Color naming (Z score; SD)	−1.26 (0.92)	−0.26 (0.87)	< 0.01
Executive functions			
Inverse Digit Span (Z score; SD)	0.36 (1.20)	0.48 (1.25)	0.71
Stroop Interference (Z score; SD)	−0.10 (0.53)	0.25 (0.84)	0.07
Trail Making Test B (Z score; SD)	−0.37 (1.41)	0.98 (1.06)	< 0.01
Phonological/Semantic fluency (Z score; SD)	−0.53 (0.82)	0.27 (0.84)	< 0.01

[1] Two sided p values. Means are compared with Student's T-test and proportions with the Chi squared test.

Table 2
Relationship between cognitive measures and functional status.

Cognitive measure	B coefficient (95% CI)	p value[a]
RAVLT total score	−2.4 (−5.4; 0.7)	0.12
RAVLT delayed recall	−3.9 (−6.7; −1.2)	< 0.01
RAVLT recognition	−2.1 (−4.4; 0.2)	0.07
Trail-Making test A	−1.5 (−5.4; 2.3)	0.41
Trail-Making test B	−2.1 (−4.2; 0.1)	0.05
Phonological/Semantic fluency	3.2 (−0.6; 7.0)	0.09
Stroop Interference	0.8 (−5.6; 7.1)	0.81

[a] Multiple lineal regression after adjusting for education and premorbid IQ.

3.4. Differences between cognitively impaired and cognitively intact first episode patients

Sixteen patients met the definition of cognitive impairment (64% of the sample) and 36% were cognitively intact at the moment of their FEM.

No significant differences regarding comorbid substance abuse, suicide attempts, education level, age at onset, nor pharmacological exposure emerged between cognitively impaired and intact patients. However, patients cognitively impaired presented with a poorer psychosocial functioning (FAST total score 21.0 vs. 14.8, p = 0.04).

4. Discussion

The main findings of the present study are that cognitive deficits are present in patients with BD at the beginning of the illness - which appeared to be of similar magnitude than those observed in multiple episode patients (Bourne et al., 2013) - and that some of these deficits are associated with functional status at the moment of disease onset. To the best of our knowledge, this is the first study showing a relationship between neurocognitive performance and psychosocial outcomes at the time of BD diagnosis.

Since patients and controls were successfully matched on age, sex, education, and premorbid IQ, these factors are unlikely to have influenced the outcomes observed. On the other hand, we found no significant correlations between mood symptoms scores or time elapsed in symptomatic remission and cognitive performance suggesting that these deficits were not due to subsyndromal symptoms. Also, since patients with BD presented a high prevalence of substance abuse, we evaluated whether this factor influenced cognitive outcomes in BD patients and found that there were no significant differences in substance abuse rates between patients with and without cognitive impairment.

Finally, we observed that the widely reported association between verbal memory and psychosocial functioning (Baş et al., 2015; Bonnín Cdel et al., 2014; Duarte et al., 2016; Torres et al., 2010) is also present in FEM patients. This result is at odds with that reported by Torres et al. (2011). One possible explanation is that patients in the present study were asked to inform their functional status prior to their hospitalization contrary to the method used in the study conducted by Torres et al. (2011). Our finding that cognitive performance is not associated with clinical outcomes (suicide attempts, substance abuse, age at onset, or pharmacological exposure) does concur with the findings in Torres et al. (2011), suggesting that cognitive performance is independent of proxies for clinical evolution.

Thus, based on the current findings, it seems reasonable to suggest that subgroups regarding cognitive functioning are present from disease onset and also that from disease onset such dysfunction is related to psychosocial outcomes - rather than being causally determined as the disease goes on -. If this result were confirmed with subsequent studies with larger sample sizes, efforts devoted to arrest cognitive dysfunction in BD patients would be valuable to improve psychosocial outcomes in this condition.

However, several limitations of this study should be acknowledged. First, small sample size should prompt a careful appraisal of the result presented. It is possible that broadening our sample size significant results in the delayed recall performance would appear, as reported in the literature (Chakrabarty et al., 2015). However, most of our cognitive results are in line with previous research in FEM (Daglas et al., 2015; Lee et al., 2014; Torres et al., 2010). Second, our sample of FEM was defined by meeting diagnostic criteria for a manic episode. This could introduce bias as some patients might have experienced a substance-induced psychotic episode with indistinguishable clinical features to those observed in manic episodes. However, as patients are all included in the FEPA program, longitudinal assessment of clinical and family history was obtained which helped us to ascertain patient

diagnosis. Third, although presence of psychotic symptoms was not an inclusion criterion, all the patients included presented these features. As there are some reports stating worse cognitive outcomes in BD with psychotic symptoms (Bora et al., 2007; Savitz et al., 2009), our results might not be generalized to all FEM.

Further studies with larger sample sizes are warranted to confirm the findings of this exploratory study.

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References

Baş, T.Ö., Poyraz, C.A., Baş, A., Poyraz, B.Ç., Tosun, M., 2015. The impact of cognitive impairment, neurological soft signs and subdepressive symptoms on functional outcome in bipolar disorder. J. Affect. Disord. 174, 336–341.

Bora, E., Vahip, S., Akdeniz, F., Gonul, A.S., Eryavuz, A., Ogut, M., Alkan, M., 2007. The effect of previous psychotic mood episodes on cognitive impairment in euthymic bipolar patients. Bipolar Disord. 9, 468–477.

Bonnín Cdel, M., González-Pinto, A., Solé, B., Reinares, M., González-Ortega, I., Alberich, S., Crespo, J.M., Salamero, M., Vieta, E., Martínez-Arán, A., Torrent, C., 2014. Verbal memory as a mediator in the relationship between subthreshold depressive symptoms and functional outcome in bipolar disorder. J. Affect. Disord. 160, 50–54.

Bourne, C., Aydemir, O., Balanzá-Martínez, V., Bora, E., Brissos, S., Cavanagh, J.T.O., Clark, L., Cubukcuoglu, Z., Dias, V.V., Dittmann, S., Ferrier, I.N., Fleck, D.E., Frangou, S., Gallaher, P., Jones, L., Kieseppä, T., Martínez-Aran, A., Melle, I., Moore, P.B., Mur, M., Pfennig, A., Raust, A., Senturk, V., Simonsen, C., Smith, D.J., Bio, D.S., Soeiro-de-, Souza, M.G., Stoddart, S.D.R., Sundet, K., Szöke, A., Thomson, J.M., Torrent, C., Zalla, T., Craddock, N., Andreassen, O.A., Leboyer, M., Vieta, E., Bauer, M., Worhunsky, P.D., Tzagarakis, C., Rogers, R.D., Geddes, J.R., Goodwin, G.M., 2013. Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. Acta Psychiatr. Scand. 128. pp. 149–162.

Chakrabarty, T., Kozicky, J.M., Torres, I.J., Lam, R.W., Yatham, L.N., 2015. Verbal memory impairment in new onset bipolar disorder: relationship with frontal and medial temporal morphology. World J. Biol. Psychiatry 16, 249–260.

Daglas, R., Yücel, M., Cotton, S., Allott, K., Hetrick, S., Berk, M., 2015. Cognitive impairment in first-episode mania: a systematic review of the evidence in the acute and remission phases of the illness. Int. J. Bipolar Disord. 3, 9. http://dx.doi.org/10.1186/s40345-015-0024-2.

Duarte, W., Becerra, R., Cruise, K., 2016. The relationship between neurocognitive functioning and occupational functioning in bipolar disorder: a literature review. Eur. J. Psychol. 12, 659–678.

Hellvin, T., Sundet, K., Simonsen, C., Aminoff, S.R., Lagerberg, T.V., Andreassen, O.A., Melle, I., 2012. Neurocognitive functioning in patients recently diagnosed with bipolar disorder. Bipolar Disord. 14, 227–238.

Lee, R.S., Hermens, D.F., Scott, J., Redoblado-Hodge, M.A., Naismith, S.L., Lagopoulos, J., Griffiths, K.R., Porter, M.A., Hickie, I.B., 2014. A meta-analysis of neuropsychological functioning in first-episode bipolar disorders. J. Psychiatry Res. 57, 1–11.

Mann-Wrobel, M.C., Carreno, J.T., Dickinson, D., 2011. Meta-analysis of neuropsychological functioning in euthymic bipolar disorder: an update and investigation of moderator variables. Bipolar Disord. 13, 334–342.

Martino, D.J., Marengo, E., Igoa, A., Scápola, M., Ais, E.I., Perinot, L., Strejilevich, S.A., 2009. Neurocognitive and symptomatic predictors of functional outcome in bipolar disorders: a prospective 1 year follow-up study. J. Affect. Disord. 116, 37–42.

Muralidharan, K., Torres, I.J., Silveira, L.E., Kozicky, J.M., Bücker, J., Fernando, N., Yatham, L.N., 2014. Impact of depressive episodes on cognitive deficits in early bipolar disorder: data from the systematic treatment optimization programme for early mania (STOP-EM). Br. J. Psychiatry 205, 36–43.

Peralta, V., Cuesta, M., 2002. Escala Clínica de Intensidad, Frecuencia y Duración del Tratamiento Psicofarmacológico (Escala IFD). Virgen del Camino Hosp, Pamplona, Spain.

Rosa, A., Magalhães, P.V.S., Czepielewski, L., Kapczinski, F., 2014. Clinical staging in bipolar disorder: focus on cognition and functioning. J. Clin. Psychiatry 75, e450–e456.

Rosa, A.R., Sánchez-Moreno, J., Martínez-Aran, A., Salamero, M., Torrent, C., Reinares, M., Comes, M., Colom, F., Van Riel, W., Ayuso-Mateos, J.L., Kapczinski, F., Vieta, E., 2007. Validity and reliability of the functioning assessment short test (FAST) in bipolar disorder. Clin. Pract. Epidemiol. Ment. Heal. 3, 5.

Savitz, J., van der Merwe, L., Stein, D., Solms, M., Ramesar, R., 2009. Neuropsychological status of bipolar I disorder: impact of psychosis. Br. J. Psychiatry 194, 243–251.

Tabarés-Seisdedos, R., Balanzá-Martínez, V., Sánchez-Moreno, J., Martinez-Aran, A., Salazar-Fraile, J., Selva-Vera, G., Rubio, C., Mata, I., Gómez-Beneyto, M., Vieta, E., 2008. Neurocognitive and clinical predictors of functional outcome in patients with schizophrenia and bipolar I disorder at one-year follow-up. J. Affect. Disord. 109, 286–299.

Torres, I.J., DeFreitas, C.M., DeFreitas, V.G., Bond, D.J., Kunz, M., Honer, W.G., Lam, R.W., Yatham, L.N., 2011. Relationship between cognitive functioning and 6-month clinical and functional outcome in patients with first manic episode bipolar I disorder. Psychol. Med. 41, 971–982.

Torres, I.J., DeFreitas, V.G., DeFreitas, C.M., Kauer-Sant'Anna, M., Bond, D.J., Honer, W.G., Lam, R.W., Yatham, L.N., 2010. Neurocognitive functioning in patients with bipolar I disorder recently recovered from a first manic episode. J. Clin. Psychiatry 71, 1234–1242.