Journal of Affective Disorders 210 (2017) 226–229

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Brief report

The effect of premorbid intelligence on neurocognitive and psychosocial functioning in bipolar disorder

Diego J. Martino[a,b,c,*], Marina P. Valerio[b,d], Alejandro G. Szmulewicz[a,d], Sergio A. Strejilevich[a,c]

[a] Bipolar Disorder Program, Institute of Neurosciences, Favaloro University, Buenos Aires, Argentina
[b] National Council of Scientific and Technical Research (CONICET), Argentina
[c] Institute of Cognitive and Translational Neuroscience (INCyT), INECO Foundation, Favaloro University, Buenos Aires, Argentina
[d] Psychiatric Emergencies Hospital Torcuato de Alvear, Buenos Aires, Argentina

ARTICLE INFO

Keywords:
Cognitive reserve
Premorbid IQ
Executive functions

ABSTRACT

Background: The aim of this study was to assess if premorbid IQ moderates the association between measures of clinical severity and neurocognitive or psychosocial functioning in euthymic patients with bipolar disorder.
Methods: One hundred and nineteen outpatients and forty healthy controls were included. The length of illness, number of previous hypo/manic and depressive episodes, episode density, and history of psychosis assessed clinical severity. Performances in verbal memory, attention, and executive functions, as well as level of psychosocial functioning were used as outcomes.
Results: The negative relationship between number of hypo/manic episodes and performance in executive functions decreased as a function of higher values of premorbid IQ. No other influences of premorbid IQ were found in the association between clinical severity measures and neurocognitive and psychosocial functioning.
Conclusions: Premorbid IQ might moderate the relationship between the number of hypo/manic episodes and executive functioning in bipolar disorder. Possible interpretations of this finding are discussed.

1. Introduction

The concept of reserve derives from the clinical observation that there is no direct association between the degree of brain pathology or damage and the clinical manifestations of such damage (Satz, 1993; Stern, 2002). Cognitive reserve (CR) is proposed as an active model in which the brain attempts to cope with brain damage by using pre-existing or compensatory cognitive processing approaches, and indices measures such as crystallized intelligence or years of education are frequently used as surrogates measures of this concept (Stern, 2002). Under this paradigm, premorbid intelligence can act as a moderator between pathology and clinical outcomes (Satz, 2011).

Although CR has been successfully used in Alzheimer disease and brain injury among others neuropsychiatric disorders, its potential utility in bipolar disorder (BD) is understudied (Barnett et al., 2006). In a small pilot study, premorbid IQ was an independent predictor of the number of cognitive domains affected in euthymic BD patients, leading the authors to suggest that such finding could be explained by the concept of CR, and that future studies were necessary to test this hypothesis (Martino et al., 2008). Two recent studies explored with similar methodologies the role of CR in psychosocial and neurocognitive functioning in BD (Anaya et al., 2016; Forcada et al., 2015). These studies used a composite score of CR -derived from measures of premorbid IQ, educational level, and occupational attainment- which was entered into several lineal regression models controlling for covariates such as age, chronicity, or bipolar subtype and using the performance in different domains of neurocognition and functional outcome as dependent variables. Overall, both studies reported a positive association between CR and performance in the different measures of neurocognition and psychosocial functioning suggesting that CR might influence BD outcomes (Anaya et al., 2016; Forcada et al., 2015). However, this interpretation must be taken with caution, since many studies have shown the positive association between intelligence and educational level with cognitive functioning or occupational status in the general population (Arffa et al., 2007; Bergman et al., 2014; Rapport et al., 1997). Thus, the findings of Anaya et al. (2016) and Forcada et al. (2015) might just mean that these relationships remain even after the onset of BD rather than suggesting that the CR moderates the impact of the illness in these outcomes. Therefore, the aim of this study was to assess if premorbid IQ moderates the association between clinical severity and neurocognitive or psychosocial functioning in BD.

* Corresponding author at: Bipolar Disorder Program, Institute of Neurosciences, Favaloro University, Buenos Aires, Argentina.
E-mail address: diejmartino@gmail.com (D.J. Martino).

http://dx.doi.org/10.1016/j.jad.2016.12.053
Received 7 December 2016; Accepted 31 December 2016
Available online 02 January 2017

Table 1
Demographical, clinical and neurocognitive characteristics of bipolar patients and healthy controls (values are expressed as mean, standard deviation is shown in brackets).

	Bipolar patients (n=119)	Healthy controls (n=40)	Test/df/p-value
Age	40.31 (11.34)	40.28 (12.03)	t=0.02; df=157; p=0.98
Gender (% female)	64.70	70.00	X^2=0.37; df=1; p=0.54
Years of education	14.39 (2.50)	13.88 (2.77)	t=1.09; df=157; p=0.28
Premorbid IQ (Z-score)	0.52 (0.56)	0.48 (0.58)	t=0.45; df=157; p=0.65
YMRS score	0.96 (1.49)	0.73 (0.93)	t=1.16; df=108.4; p=0.25
HDRS score	1.89 (1.92)	1.90 (1.81)	t=−0.26; df=157; p=0.98
GAF score	80.24 (9.59)	90.35 (5.58)	t=−8.10; df=117.1; p= < 0.001
Verbal memory (Z-score)	−0.57 (0.89)	0.00 (0.81)	t=−3.58; df=157; p= < 0.001
Attention (Z-score)	−0.28 (1.09)	0.31 (0.64)	t=−4.17; df=115.0; p= < 0.001
Executive functions (Z-score)	−0.36 (0.96)	0.44 (0.51)	t=−5.02; df=157; p= < 0.001
Length of illness	12.11 (7.61)		
N° of previous depressive episodes	3.59 (2.19)		
N° of previous hypo/manic episodes	3.25 (2.35)		
Episode density	0.81 (0.73)		
Clinical subtype (% type I)	49.6		
History of psychosis (%)	50.4		

BD: Bipolar disorder; IQ: Intelligence quotient; YMRS: Young Mania Rating Scale; HDRS: Hamilton Depression Rating Scale

2. Methods

One hundred and nineteen outpatients were consecutively selected with the following inclusion criteria: aged between 18 and 65; diagnosis of BD type I (BDI) or type II (BDII) according to DSM-IV using Structured Clinical Interview for DSM-IV (SCID); and being euthymic (defined by Hamilton Depression Rating Scale, HDRS, < 8 and Young Mania Rating Scale, YMRS, < 6) for at least 8 weeks. Exclusion criteria were: prior history of substance abuse, mental retardation, or neurological disease or presenting with any unstable clinical condition (like diabetes or hypothyroidism) that could affect cognitive performance. Additionally, forty healthy controls without prior neurological disease, affective or psychotic disorder, nor family history of psychotic/affective disorder in first-degree relatives, and without current psychotropic treatment were included. The study was approved by the Hospital Ethics Committee and all subjects gave written informed consent for their participation after receiving a complete description of the study.

2.1. Clinical assessment

All subjects were evaluated with the SCID, HDRS, and YMRS. Demographical information and clinical history was obtained from clinical charts and direct patient interview. Clinical severity was assessed by the length of illness, number of previous hypo/manic and depressive episodes, episode density (total number of previous episodes divided by length of illness), and history of psychosis. Psychosocial functioning was assessed with the General Assessment of Functioning (GAF). The rater was instructed to use the GAF to measure functioning in the last month but not symptoms since other measures of mood symptoms were obtained as part of the evaluation. Premorbid IQ as measured by the WAIS vocabulary subtest (Wechsler, 1995) was used as a proxy measure for CR.

2.2. Neurocognitive assessment

All subjects completed a neuropsychological tests described in detail in previous studies of our group (Martino et al., 2008). Briefly, it included the following tests: 1) Attention: Forward Digit Span, and Trail Making Test part A; 2) Verbal memory: Memory Battery of Signoret; 3) Executive functions: Wisconsin Card Sorting Test; Trail Making Test part B; and Phonological Fluency.

2.3. Statistical analysis

Raw-score of neurocognitive performance were transformed into Z-scores based on normative data for each test. A global score of attention, verbal memory and executive functions was calculated as an average of performance in each test of the corresponding cognitive domain. Between-group comparisons on clinical-demographical and neurocognitive variables were performed using t-test or chi squared tests as appropriate.

First, in order to compare results in our sample with those of previous studies (Anaya et al., 2016; Forcada et al., 2015), we performed the same regression models with the three-neurocognitive scores (verbal memory, attention, and executive functioning) as dependent variables and using IQ, age, chronicity, and bipolar subtype as covariates. Likewise, another linear regression model was conducted using GAF as dependent variable and IQ, age, chronicity, bipolar subtype, HDRS, and verbal memory performance as covariates.

To address our research question, we run bivariate analyses between measures of clinical severity with neurocognitive and psychosocial functioning. Then, we performed several linear regression models with neurocognitive and psychosocial outcomes as dependent variables and measures of clinical severity, premorbid IQ, and an interaction term as covariates. Based on previous literature, bipolar subtype, subclinical symptoms, and exposure to antipsychotic medications were included as covariates in regression models. Homoscedasticity and normality of residuals of the multiple linear regression models were assessed with graphical (scatter plot of studentized residual by predicted values, as well as Normal Q-Q plot and Box Plot of studentized residual) and analytical (Kolmogorov–Smirnov test) approaches. The presence of multicollinearity in the multiple regression model was assessed by means of the variance inflation factor (values below 10 were considered adequate).

3. Results

Demographical, clinical, and neurocognitive features of patients and healthy controls are shown in Table 1. All patients were receiving mood stabilizers at the time of testing; additionally 37% were receiving antidepressants, 52% benzodiazepines, and 57% antipsychotics.

Using the regression models employed in previous studies, we found a statistically significant relationship between premorbid IQ and performance in attention (β=0.53; p=0.003) and executive functions (β=0.41; p=0.005) as well as between IQ and psychosocial functioning (β=4.16; p=0.008). The same pattern of association between premorbid IQ and attention (β=0.57; p= < 0.001), executive functions

Table 2
Bivariate analyses between measures of clinical severity and neurocognitive and psychosocial functioning.

	N° previous Hypo/manic episodes	N° previous depressive episodes	Length of illness	Episode density	History of psychosis
GAF score	**β=−1.10**	β=0.40	β=−0.095	β=0.24	**β=−6.03**
	p=0.005	p=0.36	p=0.43	p=0.85	**p=0.001**
Memory performance	β=0.012	β=0.058	β=0.009	β=−0.031	**β=−0.36**
	p=0.74	p=0.13	p=0.57	p=0.79	**p=0.027**
Attention performance	β=−0.084	β=0.000	β=−0.002	β=−0.032	β=−0.34
	p=0.057	p=0.99	p=0.87	p=0.82	p=0.088
Executive performance	**β=−0.078**	β=−0.010	β=0.007	β=0.19	β=−0.006
	p=0.032	p=0.81	p=0.50	p=0.12	p=0.97

(β=0.49; p= < 0.001), and GAF (β=5.73; p= < 0.001) was found among healthy controls using the same covariates (except chronicity and bipolar subtype).

Results of bivariate analyses between measures of clinical severity and neurocognitive/psychosocial functioning are shown in Table 2. Among the four regression models performed, using the significant results of bivariate analysis, the only significant interaction found (β=0.11; p=0.033) was that relating the number of previous hypo/manic episodes (β=−0.13; p=0.004) with executive functioning. A subsequent analysis showed that the association between number of previous hypo/manic episodes and executive function performance was significant for patients with a premorbid IQ below (−1 SD: β=−0.19; p=0.0027) or at level of the mean (0 SD: β=−0.13; p=0.0053) but not in those with higher values (+1 SD: β=−0.07; p=0.092).

4. Discussion

It is well known that there is a relationship between intelligence and educational level with cognitive functioning or occupational status in the general population (Arffa et al., 2007; Bergman et al., 2014; Rapport et al., 1997). Similarly to previous studies (Anaya et al., 2016; Forcada et al., 2015) we found a relationship between measures of CR and neurocognitive and psychosocial functioning in both euthymic BD patients and healthy controls. The regression models build in our and in previous studies might just mean that these relationships found in general population remain significant in subjects after the onset of BD type I or II at any age and chronicity (as well as for any level of subclinical symptoms and memory performance for psychosocial functioning). Therefore, it may be inaccurate to infer that CR moderates bipolar outcomes from such findings as has been suggested in previous studies (Anaya et al., 2016; Forcada et al., 2015).

In this study, we used regression models with interaction terms, which allow testing whether premorbid IQ moderates the association between the measures of clinical severity and the examined outcomes. The main finding of our study was that the negative relationship between number of hypo/manic episodes and executive functions, which was consistently reported in literature (for a review see Robinson and Ferrier (2006)), decrease as a function of higher values of premorbid IQ. The interpretation of this finding requires caution since the longitudinal course of cognitive impairments in BD is not yet clearly understood (Martino et al., 2016). In fact, based on the cross-sectional studies reported above, some authors have proposed that cognitive impairments increase as a function of successive affective episodes (Berk et al., 2011; Kapczinski et al., 2014). However, this view contrasts with the findings of neurocognitive studies in elderly patients (for a review see Samamé et al., 2013) and from the few longitudinal studies available (for a review see Samamé et al. (2014)) suggesting that the evolution of such deficits would be static rather than progressive. Therefore, further longitudinal studies with larger follow-up periods are needed to clarify the longitudinal course of cognitive impairments in BD.

If future longitudinal studies prove that executive dysfunction progressively worsens throughout the disease with successive episodes, then the result of this study might be interpreted from the CR paradigm. CR hypothesis proposes that, in a patient population, for any level of brain pathology, clinical severity would be lower in those individuals with high CR. That is, patients with BD with greater CR would have higher ability to cope with illness in terms of number of hypo/manic episodes before executive dysfunctions appear. On the contrary, if future longitudinal studies show that executive function impairments are stable along the course of BD, the main finding of this study may be interpreted in terms of physiopathological differences between subgroups of patients. For example, a recent study has been suggested the existence of a subgroup of BD patients with neurodevelopmental deviance characterized by low premorbid IQ, poor premorbid adjustment and neurological signs (Arango et al., 2014). Likewise, some of the largest cohort studies showed that both low and high levels of intelligence and school performance in youth are associated with an increased risk of developing BD, which also supports the view of pathophysiological subgroups (Gale et al., 2013; MacCabe et al., 2010). Therefore, we could hypothesize about the existence of a subgroup of patients in whom there is a factor (i.e. neurodevelopmental abnormalities) that will predispose to a lower premorbid IQ and that could act as a common cause for the joint occurrence of hypo/manic episodes and executive dysfunction. In contrast, another subgroup of patients without such factor might have a higher premorbid IQ and, in them, the occurrence of hypo/manic episodes may be relatively independent of executive functioning. If this were the case, future studies should focus on the identification of these subgroups of patients.

Certain limitations of our study should be considered. First, although premorbid IQ has been widely used in previous studies, the validity of CR measures is subject to controversy (Satz et al., 2011). Likewise, psychosocial functioning was assessed with the GAF which is a single item score and does not cover multiple domains of functioning. Additionally, all patients included in the study were taking psychotropic medication and we cannot discount the influence of these drugs on cognitive functioning.

Notwithstanding these limitations, our results show that premorbid IQ might moderate the relationship between the number of hypo/manic episodes and executive functioning in BD. The precise interpretation of this finding requires future longitudinal studies.

References

Anaya, C., Torrent, C., Caballero, F.F., Vieta, E., Bonnin, C.M., Ayuso-Mateos, J.L., CIBERSAM Functional Remediation Group, 2016. Cognitive reserve in bipolar disorder: relation to cognition, psychosocial functioning and quality of life. Acta Psychiatr. Scand. 133 (5), 386–398.

Arango, C., Fraguas, D., Parellada, M., 2014. Differential neurodevelopmental trajectories in patients with early-onset bipolar and schizophrenia disorders. Schizophr. Bull. 40 (Suppl 2), S138–S146.

Arffa, S., 2007. The relationship of intelligence to executive function and non-executive function measures in a sample of average, above average, and gifted youth. Arch. Clin. Neuropsychol. 22 (8), 969–978.

Barnett, J.H., Salmond, C.H., Jones, P.B., Sahakian, B.J., 2006. Cognitive reserve in neuropsychiatry. Psychol. Med. 36 (8), 1053–1064.

Bergman, L.R., Covoric, J., Ferrer-Wreder, L., Modig, K., 2014. High IQ in early adolescence and career success in adulthood: findings from a Swedish longitudinal study. Res. Hum. Dev. 11, 165–185.

Berk, M., Brnabic, A., Dodd, S., Kelin, K., Tohen, M., Malhi, G.S., Berk, L., Conus, P., McGorry, P.D., 2011. Does stage of illness impact treatment response in bipolar disorder? Empirical treatment data and their implication for the staging model and early intervention. Bipolar Disord. 13 (1), 87–98.

Forcada, I., Mur, M., Mora, E., Vieta, E., Bartrés-Faz, D., Portella, M.J., 2015. The influence of cognitive reserve on psychosocial and neuropsychological functioning in bipolar disorder. Eur. Neuropsychopharmacol. 25 (2), 214–222.

Gale, C.R., Batty, G.D., McIntosh, A.M., Porteous, D.J., Deary, I.J., Rasmussen, F., 2013. Is bipolar disorder more common in highly intelligent people? A cohort study of a

million men. Mol. Psychiatry 18 (2), 190–194.
Kapczinski, F., Magalhães, P.V., Balanzá-Martinez, V., Dias, V.V., Frangou, S., Gama, C.S., Gonzalez-Pinto, A., Grande, I., Ha, K., Kauer-Sant'Anna, M., Kunz, M., Kupka, R., Leboyer, M., Lopez-Jaramillo, C., Post, R.M., Rybakowski, J.K., Scott, J., Strejilevich, S., Tohen, M., Vazquez, G., Yatham, L., Vieta, E., Berk, M., 2014. Staging systems in bipolar disorder: an international society for bipolar disorders task force report. Acta Psychiatr. Scand. 130 (5), 354–363.
MacCabe, J.H., Lambe, M.P., Cnattingius, S., Sham, P.C., David, A.S., Reichenberg, A., Murray, R.M., Hultman, C.M., 2010. Excellent school performance at age 16 and risk of adult bipolar disorder: national cohort study. Br. J. Psychiatry 196 (2), 109–115.
Martino, D.J., Strejilevich, S.A., Scápola, M., Igoa, A., Marengo, E., Ais, E.D., Perinot, L., 2008. Heterogeneity in cognitive functioning among patients with bipolar disorder. J. Affect Disord. 109 (1–2), 149–156.
Martino, D.J., Samamé, C., Marengo, E., Igoa, A., Strejilevich, S.A., 2016. A critical overview about the clinical evidence supporting the concept of neuroprogression in bipolar disorder. Psychiatry Res. 23, 1–6.
Rapport, L.J., Axelrod, B.N., Theisen, M.E., Brines, D.B., Kalechstein, A.D., Ricker, J.H., 1997. Relationship of IQ to verbal learning and memory: test and retest. J. Clin. Exp. Neuropsychol. 19 (5), 655–666.
Robinson, L., Ferrier, N., 2006. Evolution of cognitive impairment in bipolar disorder: a systematic review of cross-sectional evidence. Bipolar Disord. 8, 103–116.
Samamé, C., Martino, D.J., Strejilevich, S.A., 2013. A quantitative review of neurocognition in euthymic late-life bipolar disorder. Bipolar Disord. 15 (6), 633–644.
Samamé, C., Martino, D.J., Strejilevich, S.A., 2014. Longitudinal course of cognitive deficits in bipolar disorder: a meta-analytic study. J. Affect Disord. 164, 130–138.
Satz, P., 1993. Brain reserve capacity on symptom onset after brain injury: a formulation and review of evidence for threshold theory. Neuropsychology 7, 273–295.
Satz, P., Cole, M.A., Hardy, D.J., Rassovsky, Y., 2011. Brain and cognitive reserve: mediator(s) and construct validity, a critique. J. Clin. Exp. Neuropsychol. 33 (1), 121–130.
Stern, Y., 2002. What is cognitive reserve? Theory and research application of the reserve concept. J. Int. Neuropsychol. Soc. 8, 448–460.
Wechsler, D., 1995. Wechsler Adult Intelligence Scale-Revised. Psychological Corporation, Cleveland.