

Research Article

Cognitive Trajectories in High Premorbid Social Functioning Bipolar Patients

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ABSTRACT

Introduction: This study aimed to describe the differences in global functioning in BD type I and type II patients with high premorbid functioning.

Methods: From a more extensive sample of 140 subjects, fifty euthymic bipolar outpatients with high level of premorbid social functioning measured by Premorbid Adjustment Scale were enrolled. 90 BD were excluded because they had a low premorbid social functioning. Current social and neuropsychological functioning was assessed.

Results: Cluster analysis showed that some BD patients maintain a high functioning, while other patients suffer of a loss of global functioning. Multivariate analysis showed that a lower social functioning, independently from premorbid social functioning, can be associated with a loss of executive functions ($p = .009$). In this analysis the effects of bipolar type (I or II), age at onset, current social roles and duration of illness were absent or not significant ($p > .05$).

Discussions: This is the first study to distinguish levels of global functioning in euthymic BD patients that had the same premorbid social functioning. These important differences in the course of the BD can be assessed through psychosocial and neuropsychological assessment tools for a more appropriate management of the variables able to modify the course of disorder, also in euthymic phase. This practice becomes crucial in the definition and implementation of specific psychosocial treatments in the short and long-term course of disease, providing a new and specific area of intervention for bipolar disorder: the cognition.

MeSh Headings/keywords: Bipolar disorder; Social functioning; Premorbid social functioning; Neuropsychological functioning; Executive functions; Age at onset; Community treatment

Introduction

Bipolar disorder (BD) is a severe and disabling disease in which patients experience episodes of recurrent depression and mania [1]. Although early reports of prolonged impairment in the psychosocial functioning of BD patients do exist [2], the course of the disorder has traditionally been viewed as episodic, with symptomatic and functional recovery between mood episodes [3].

This view has recently been challenged by clinical and epidemiological studies that document how, despite symptomatic improvements, many BD patients experience difficulties in

social and vocational functioning (functional recovery) during recovery following mood episodes (clinical recovery); these findings could explain the higher rates of unemployment and disability found among BD patients compared with non-affected subjects [4-6], in addition to their lack of individual psychological adaptation to the disorder (personal recovery) [7]. Distinguishing between different types of recovery contributes to clarifying that the term 'recovery', which refers not only to overcoming the negative consequences of the disorder, but also the positive goals of attaining a sense of agency and a meaningful life [8].

The classic Kraepelinian view of schizophrenia notes that chronic, long-lasting cognitive impairments should be expected in schizophrenia but not in BD; this view may currently be considered partially wrong given recent evidence showing that BD patients often present cognitive impairments (in memory, verbal fluency, planning and set-shifting domains), even during the euthymic phase of the disease, thus representing trait-dependent rather than state-dependent characteristics of the disorder [9-14]. In addition, cognition is known to play an important role in modulating patients' social functioning [15]; the persistence of chronic cognitive disturbances in BD patients could therefore negatively affect their outcomes in daily and professional activities [16].

Low social functioning appears to be longitudinally predictive of clinical outcomes [17] consequently, measures of functioning have recently been proposed as reliable tools for assessing BD patients' clinical conditions, even when full symptomatic recoveries from mood episodes of both polarities have been achieved [18].

Social functioning has been defined as "the ability to construct representations of the relations between oneself an others, and to use those representations flexibly to guide social behavior" [19]. Successful psychosocial functioning comprises many components, such achieve and maintain social roles, taking care of yourself, to work, go to school, forming relationships, etc. Generally, scales with high scores indicating better social functioning (achieving of roles, adequate behaviour at school, at job, good relations peer, etc.,), while, lower scores indicating a worse social functioning (social withdrawal, maladaptive behaviours, non compliance with the rules, failure to achieve personal autonomy and/or goals, etc.,) [20].

In some naturalistic studies on BD patients, a low premorbid social functioning characterized by a poor family functioning and low social support, have each been shown to be predictive of subsequent mood and of episode of recurrence [17]. Therefore, the possibility to distinguish between high and low functioning can help to identify the possible target of treatment to reduce relapses and improving clinical outcomes.

The association between the cognitive domain and global functioning has been confirmed by the results of some recent studies [21,22]. Martino et al. [23] reported that 40-62% of euthymic BD patients presented some sort of impairment (from 1 to 5 affected cognitive domains), and similar prevalence rates of disability were found in a subsequent study in which psychosocial impairment was assessed (30-60% patients failed to achieve functional recovery, measured by impairments in employment and social functioning) [5,13,18,24]. These similar prevalence rates may indicate that cognitive dysfunction and functional outcomes could be somehow linked [4,25] suggesting that neurocognition could play an important role in the functional outcomes of BD patients [15] and explaining why not all bipolar patients develop some level of function loss during the course of their illness. Some studies showed small neuropsychological differences between BDI and BDII [25], suggesting different psychosocial outcomes as well. However, there has not yet been any investigation of reliable variables for the prediction of clinical, neuropsychological and functional outcomes among BD patients with high premorbid social functioning.

Given the above information, euthymic BD type I and BD type II patients with high premorbid social functioning were enrolled in the present study in order to retrospectively observe their clinical, neuropsychological and functional evolutions and to identify predictive factors of neuropsychological and functional outcomes.

Methods

Participants

The clinical sample of patients was consecutively recruited at the Bipolar Disorder Outpatient Clinic of Policlinico Umberto I University Hospital, Sapienza University of Rome.

The inclusion criteria were a diagnosis of BD type I or II according to the Structured Clinical Interview for DSM-IV TR Axis I Disorders (SCID-I) [26]; adequate premorbid functioning assessed with the Premorbid Adjustment Scale (PAS) [20,27], with patients being euthymic for at least six months (Young Mania Rating Scale < 5 and Hamilton Depression Rating Scale < 7 [28]. Only subjects with all three of these characteristics entered in the study.

The exclusion criteria were the presence of another Axis I diagnosis; a diagnosis of NOS BD [29]; absence of euthymia (HDRS > 7 or YMRS > 5) [28]; presence of low or borderline IQ (premorbid IQ < 70) measured by Progressive Matrices of Raven [30]; regular substance or alcohol abuse; and lifetime presence of neurological disease or injury.

A total of 140 BD patients were referred to our centre during the study period (98 BD type I, 42 BD type II). Among these, 90 patients did not meet the inclusion criteria, but 50 patients (22 males, 28 females; 33 BD type I, 16 BD type II; age range: 20-59 years) met the criteria and were enrolled. All patients were under stabilised pharmacological treatment with lithium (n = 12) and/or mood stabilisers (n = 17) and/or atypical antipsychotics (n = 17) and/or benzodiazepines (n = 10) and/or antidepressants (n = 5), which had been prescribed according to international treatment guidelines with worldwide acceptance [31]. Socio-demographic and clinical data of the participants are given in Table 1.

A total of 20 healthy control (HC) subjects were voluntarily recruited (8 males, 12 females). They had no antecedent neurological disease and no personal or family history of mental illness, and they were not taking psychotropic medications. The same proportion of healthy samples, but a different number, was used in the study by Martino et al. [32].

The local ethics committee approved the study protocol, and all subjects gave written informed consent to participate in the study before their enrolment.

Measures

Cognitive assessment: All participants completed a comprehensive neuropsychological battery administered by a senior neuropsychologist to assess their cognitive functioning.

Table 1: Socio-demographic Description of Professionals.

Variables	Categories	Questionnaires completed by managers/ Coordinators of primary care MH teams (N=33)	Questionnaires completed by respondent-psychiatrists (N=29)	Interviews (individual and focus groups) (N=102)	Total:164
Average age [Mean (SD)]		42.2 (9.4)	49.5 (10.9)	50.7 (8.8)	47.34 (11.6)
Gender [n (%)]	Female	25 (75.7)	11 (37.9)	69 (67.6)	105 (4.0)
	Male	7 (21.2)	18 62.1)	33 (42.4)	58 (35.4)
Current position [n (%)]	Psychiatrists	-	29 (100)	7 (6.9)	36 (22.0)
	General practitioners (GP)	-	-	10 (9.8)	10 (6.1)
	Psychosocial clinicians	7 (21.2)	-	4 (3.9)	20 (12.2)
	Regional managers		-	4 (3.9)	4 (2.4)
	Directors	-	-	35 (34.3)	38 (21.3)
	Program administrators/ Coordinators	26 (78.8)	-	42 (41.1)	113(40.1)
Years of experience [Mean; SD]	In current position	5.7 (8.6)	4.0 (4.7)	7.9 (6.2)	5.9 (7.7)
	In psychiatry	-	16.9 (9.9)	-	16.9 (9.9)
	In health and social services	-	-	23.1 (12.5)	23.1 (12.5)
	In MH*	-	-	19.4 (14.1)	19.4 (14.1)
	With adult populations (MH)	-	-	19.5 (12.6)	19.5 (12.6)
Organizations [n; %]	Regional agencies			10 (9.8.)	10 (6.1)
	Psychiatric hospitals (PHs)	-	6 (20.7)	20 (19.6)	26 (15.9)
	General hospitals (GHs)	-	3 (10.3)	13 (12.7)	16 (9.8)
	Health and social service centers	33 (100)	20 (69.0)	34 (33.3)	87 (53.7)
	Medical clinics	-	-	7 (6.9)	7 (4.3)
	Community organizations	-	-	18 (17.6)	18 (11.0)
Types of territories[n;%]	With a PH	15 (45.4)	6 (20.7)	37 (36.3)	58 (35.4)
	Without specialized MH services	2 (6.1)	1 (3.4)	16 (15.7)	19 (11.6)
	>200 000 inhabitants, with a psychiatric department in a GH	12 (36.4)	11 (37.9)	21 (20.6)	44 (26.8)
	<200 000 inhabitants, with a psychiatric department in a GH	4 (12.1)	11 (37.9)	28 (27.4)	43 (26.2)

*MH: mental health:

All neuropsychological tests had been translated and validated in the Italian language. All had well-documented norms and excellent estimates of reliability and validity [33]. The choice of neuropsychological tests was guided by an extensive review of the scientific literature [34,35].

Memory abilities were assessed using the Rey Auditory Verbal Learning Test (RAVLT) for verbal learning and recall [36]; the Digit Span Test (SDT) forward (WAIS subtest) for memory span [37]; and the Rey Complex Figure Test (RCFT) immediate and delay recall (IR and DR) for visuospatial learning and recall [38-40]. Executive functions were assessed using the Wisconsin Card Sorting Test (WCST) [40] for abstraction and flexible thinking; the Trail Making Test (TMT) Part B [41] for set shifting; phonetic fluency [trials F, P, L (FPL)] [38]; the Rey Complex Figure Test (RCFT) copy [39] for planning abilities; and the Digit Span Test (SDT) Backward for working memory [37]. Attention was assessed with Visual Search (VS) [42] for sustained attention and accuracy of visual scanning [37].

Raw cognitive scores were corrected and based on normative data from Italian normative samples. On some tests (RAVLT, DST, RCFT, FPL and VS), lower values reflected poorer performance.

Social functioning assessment: The Premorbid Adjustment Scale (PAS) was used to assess patients' premorbid social

functioning. The PAS has been translated and validated in the Italian language [27]. It is a rating scale designed to evaluate premorbid functioning across four age ranges: childhood (up to 11 years), early adolescence (12-15 years), late adolescence (16-18 years) and adulthood (19 years and above). The adulthood subscale was excluded because some patients had already experienced disease onset, but we considered the General Section. Subscale scores were obtained for major areas at multiple periods in the person's life: social isolation, peer relationships, ability to function outside the family and ability to form socio-sexual ties [20]. Each item is assigned a score from 0 (perfect adjustment) to 6 (severe impairment).

Current psychosocial functioning was assessed using two clinician-rated scales: the Life Skills Profile (LSP) [43] and the World Health Organization Disability Assessment Schedule-II (WHODAS-II) [44]. The LSP is a 39-item measure, translated into Italian [45] that is specifically designed to assess general levels of functioning and disability in psychotic patients (range by 39 to 156). It is based on five key dimensions (self-neglect, turbulence, seclusion, inappropriateness, and irresponsibility) and a total score [43]. The interviewer assigns a score ranging from 0 (no difficulty) to 4 (extreme difficulty); each dimension provides a partial score: the self-neglect score ranges from 10 to 40; turbulence ranges from 12 to 48; seclusion ranges from 6 to 24; inappropriateness ranges from 6 to 24; and irresponsibility ranges from 5 to 20.

The WHODAS-II is a measure of social functioning, translated into Italian [46], that was developed to assess the different areas of real-world functioning. In the present study, only the "impairment in social roles" (10 items) subtest was considered because it is specifically involved in the loss of daily functioning. The items (participation; social contacts; job performance; working interests; interests and information) are scored from 0 (no impairment) to 5 (extreme impairment). We decided to disregard the following items: marriage/ties; marriage/sexuality; parenting; sexuality; and emergency situations. Items were scored for the three months prior to evaluation [44].

Statistical analyses

Statistical analyses were performed using Statistical Package for the Social Sciences Version 20.0 (SPSS 20.0) for Windows (SPSS Inc., Chicago, Ill). Demographic and clinical variables were characterised with descriptive statistics. Data are shown as the mean (M) ± standard deviation (SD). Distributions of the continuous measures were examined prior to analysis. The chi-square test (X^2) for categorical variables was used to compare frequencies (Table 1). One-way between-group ANOVAs were used to compare neuropsychological functioning in BD I and BD II (Table 2) and to verify differences between these and the

Table 2: Respondent-psychiatrist Practice Profile (N=29).

		Mean	SD
Hours approximately allocated per month for	Telephone consultations with general practitioners (GP) in medical clinics	3.1	5
	Telephone consultations with mental health (MH) teams/one-stop service	5.1	15.3
	Visits to medical clinics	2.7	6.3
	Meetings with adult MH* team/one stop service	8.2	6.8
	Patient meetings with GPs in medical clinics	3.1	8.5
	Patient meetings with professionals from MH teams/one stop service	2	3.4
	Patient meetings without GP or MH team/one stop service, but within the scope of duties as respondent psychiatrists	0.7	1.4
	Coordination with specialized MH services	2.4	5.6
	Supplementary clinical activities (preparing meetings, case notes, etc.) with GP or MH team/one stop service	2.4	5.5
	Training activities other than case discussions (as included above) with MH team/ At one stop service or with GPs	1.2	2.2
	Travel	1.8	1.9
% of time allocated per month for	**With GPs :**	**%**	**SD**
	Case discussions/knowledge transfer on MH issues and problems	37.1	21.9
	Supplementary clinical activities (preparing meetings, case notes, etc.)	6.3	4.4
	Case recommendations and diagnoses	17.8	11.8
	Pharmaceutical recommendations	28.6	17.3
	Exploration of treatment avenues	16.6	8.2
	With MH professionals on the MH teams/one stop service:	**%**	**SD**
	Case discussions/knowledge transfer on MH issues and problem	54.5	20.4
	Supplementary clinical activities (preparing meetings, case notes, etc.)	5	3.6
	Case recommendations and diagnoses	11.7	6.7
	Pharmaceutical recommendations	8.7	6.5
	Exploration of treatment avenues	20.8	10.7

*MH: mental health:

HC. Given the number of tests used, a conservative alpha of $p < 0.01$ was set. Age and years of education were included as covariates in the statistical models for tests that had no Italian normative data (Digit Span Backward).

To exclude possible links between illness duration and neuropsychological functioning, Spearman correlations were calculated. In order to obtain the precise characterisation of all subjects in our sample as high (HSF-BD) or low social functioning (LSF-BD) based on methodology that had been adopted in studies on samples of schizophrenics [47,48], LSP and WHODAS-II scores were entered into a *K*-means cluster analysis (Table 3). This was specified for two groups to identify individuals with "high" or "low" functional outcomes.

Means and standard deviations were calculated for each LSP, WHODAS-II and PAS domain. The *T*-test and chi-square test were used to compare means and proportions between high and low social functioning groups.

One-way ANOVA was used to compare neuropsychological performance between high and low social functioning BD patients and healthy controls. Means, standard deviations and effect sizes, calculated as partial eta squares, are reported in Table 4. ANOVA, covaried for age and years of education, was used to analyze raw scores on tests with no normative Italian data. Effect sizes were calculated using Cohen's *d*.

To better understand whether the assumption of a social role is related to cognitive impairment, one-way ANOVA was used. We considered whether the patient was employed/not employed/student and married/not married [4]. For all statistical analyses, a conservative alpha of $p < 0.01$ was set or Bonferroni adjusted where multiple comparisons necessitated.

A stepwise multiple regression model' was also conducted to examine whether cognition predicted social functioning in BD patients with high premorbid social functioning, measured by total LSP score. Only neuropsychological variables that were significantly different between HSF-BD and LSF-BD patients were included in this model.

Table 3: Practice Assessment according to Respondent-psychiatrists (N=29).

How adequate is the number of hours (3.5/month per 50 000 inhabitants) provided for meeting the following needs in your territory?	**Inadequate/ Very inadequate impact**	**Neutral**	**Adequate/Very adequate**
	N (%)	**N (%)**	**N (%)**
Needs of general practitioners (GP) in medical clinics	8 (27.6)	5 (17.2%)	11 (55.2)
Needs of professionals on the MH* Teams/one stop service	2 (6.9)	7 (24.1)	20 (69.0)
As a respondent-psychiatrist, how do you rate your satisfaction with the following aspects of care?	Unsatisfactory/ Very unsatisfactory	Neutral	Satisfactory/ Very Satisfactory
Aspects related to GPs in medical clinics:	**N (%)**	**N (%)**	**N (%)**
Number of telephone consultations	14 (48.3)	7 (24.1)	8 (27.5)
Duration of telephone consultations	6 (20.7)	8 (27.6)	15 (51.7)
Pertinence of consultations/collaboration	2 (6.8)	4 (13.8)	23 (79.3)
Level of collaboration	4 (13.8)	7 (24.1)	18 (62.0)
Assessment of your contributions	5 (17.2)	8 (27.6)	16 (55.1)
Aspects related to the MH Teams/one stop service:	**N (%)**	**N (%)**	**N (%)**
Number of telephone consultations	6 (20.7)	1 (3.4)	22 (75.9)
Duration of telephone consultations	3 (10.3)	4 (13.8)	22 (75.9)
Pertinence of consultations/collaboration	2 (6.9)	3 (10.3)	24 (86.2)
Level of collaboration	1 (3.4)	2 (6.9)	26 (89.7)
Assessment of your contributions	3 (10.3)	1 (3.4)	25 (86.2)
Other aspects:	**N (%)**	**N (%)**	**N (%)**
Clarity of your role/mandate	5 (17.2)	10 (34.5)	14 (48.2)
Clarity of civil responsibility connected to your role	4 (13.7)	18 (62.1)	7 (24.1)
Support among hospital psychiatrists for your role	4 (13.7)	9 (31.0)	16 (55.1)
Opportunities for exchanges with other respondent-psychiatrists	14 (48.2)	9 (31.0)	6 (20.7)
Degree of involvement in choosing therapeutic for case discussed	0 (0.0)	4 (13.8)	25 (86.2)
Degree of involvement in deciding about patient orientation for cases discussed	1 (3.4)	6 (20.7)	22 (75.9)
Margin of maneuver for improving MH services in your territory	7 (24.1)	11 (37.9)	11 (37.9)

*MH: mental health:

Table 4: Patient Profiles in Case Discussion with Primary Care Mental Health (MH) Teams or GPs According to Respondent-psychiatrists (N=29).

		Minimum	Maximum	Mean (%)	SD
Age	18-30 years old	20	50	33.8	9.6
	31-64 years old	30	98	49.4	13.2
	65 years old and older	0	40	18.7	10.8
Civil status	Single, widowed, divorced	0	90	50.2	18.9
	married/common law	0	80	46	18,6
Income level	High	0	20	6.7	5
	Medium	9	8	35.6	18.6
	Low (poverty level)	15	90	59.2	19.9
MH diagnosis	Personality disorder	10	90	38.7	18.4
	Substance use disorder	5	70	31.9	19
	Depression	5	60	30.5	15.4
	Anxiety disorder	5	60	27.1	13.5
	Bipolar disorder	0	40	12.7	8.6
	Adjustment disorder	10	60	27	12.3
	Psychotic disorder (e.g. schizophrenia, delusional disorder etc.)	1	40	11.7	8.7
	Attention deficit disorder or hyperactivity	0	25	8.4	6.4
	Chronic pain disorder/syndrome	0	20	6.8	5.4
	Intellectual disorder/pervasive developmental disorder	0	15	5	4.1
	Eating disorder	0	10	3.8	3.1
MH Episodes	One episode	5	75	25.5	18.3
	Two or more episodes	0	60	35.7	14.1
	Multiple or chronic episodes	10	80	38.9	20.6
Psychosocial issues	Social isolation	10	70	32.7	14.3
	Problems involved with activities of daily living	5	75	32.4	16.3
	Physical health problems (chronic illness)	10	50	26.1	10.4
	Housing insecurity	5	50	15.8	9.9
	Elevated risk of suicide	0	40	12.9	11.3
	Elevated risk of aggressive behavior	0	40	10	8.4
Service utilization	Sees a primary care clinician on the MH team	10	100	62	31.7
	Has a general practitioner	0	80	49.3	19.5
	Participates actively in a community organization for MH	0	75	21.1	16.3
	Qualifies as a heavy user of MH services overall	0	60	20.4	14.3
	Receives service for substance use disorder	5	50	17.3	10.7
	Sees a private psychologist	0	50	11.2	11.8

*MH: Mental Health

Results

Similar to other studies [48,49], BD I diagnosis was mostly representative; illness duration averaged 12.5 ± 10.4 years, and a small number (8%) of BD patients were late-onset cases. Of the 50 DSM-IV BD study participants, 56% were female.

The average age and education did not differ significantly between the BD sample and the HC sample. Roughly half of the BD sample was employed (full or part-time), and a very small number were still students, whereas most of the HC sample was stably employed. More than half of the BD sample had never married or had ended a significant relationship, but there was no significant difference in the HC sample. Despite the BD sample having non-verbal IQ scores above 100, the HC sample scored significantly higher.

Current psychotropic drug treatments involve a median of 3.0 (2.0) agents/patient: 96% were taking SG antipsychotics with a mood stabiliser; 38% were receiving an antidepressant with or without a mood stabiliser or antipsychotic (Table 1).

Similar to Torrent et al. [50] significant differences distinguished BDI and BDII from HC on the immediate and delayed recall verbal learning test (measured in our sample with the RAVLTdr and Digit Forward) and in the higher number of perseverative errors. Similar to Harkavy-Friedman et al. [51] significant differences also distinguished BDI and BDII from the HC in phonetic fluency. As reported by Dittmann et al. [52] the visual memory performance of the BDI and BDII (RCFTir, dr) patients was worse than that of the HC. Similar to most other studies [53], BDI patients performed worse than the HC on all other administered neuropsychological tests. No correlation ($p > 0.05$) emerged between illness duration and neuropsychological function, as was previously shown in other studies [54], or between age at onset (early, intermediate and late) and neuropsychological functioning [48].

In accordance with cluster analysis (Table 3), the BD sample was divided into two groups, high current social functioning (HSF-BD) and low current social functioning (LSF-BD). Means, standard deviations and *t*-tests comparing the different functioning levels were calculated. There were no significant differences in PAS scores between any of the groups ($p = >$ 0.05), and the WHODAS-II showed significant difference only in social contacts ($p = < 0.013$); significant differences emerged in all LSP domains ($p = < 0.000$). When we compared neuropsychological functioning in the LSF-BD, HSF-BD and HC groups, we observed important differences.

As evidenced by post-hoc analysis, and as reported in a similar study by Martino et al. [55] the LSF-BD group demonstrated worse performance on all tests of executive functions, attention and memory than did the HC. The HSF-BD and HC groups showed similar performance in executive functions (WCST global score, RCFTc, Digit Span Backward) and attention (Visual Search) but differed significantly in set-shifting (TMT-B) and visual memory (RCFTir and RCFTdr). Measures of phonetic fluency, immediate and delayed recall of verbal information (RAVLTir and RAVLTdr) and span number (Digit Span Forward) were similar in LSF-BD and HSF-BD but significantly different from the HC. For all tests, effect sizes were large (Table 4).

To investigate in more detail the possible link between cognitive impairment and the loss of social functioning in BD with high premorbid social functioning, a comparison between cognitive functioning in the major classes of social roles (employed/unemployed/student and married/unmarried) was conducted, but no significant differences emerged ($p > 0.05$).

Lastly, all cognitive tests differed significantly between HSF-BD and LSF-BD; the WCST global, RCFT copy, Span Backward and Visual Search scores were used in a stepwise multiple regression analysis to predict global social functioning. All correlations, except for those between WSCT global score and Visual Search and between Span Backward and Visual Search, were statistically significant. The prediction model contained two of the four predictors and was reached in two steps with two variables removed (WSCT global score and Span Backward). RCFTc was entered in step 1, and Visual Search was entered in step 2. In the first step, RCFTc was entered into the model, and the *R*square with that predictor in the model was .240. In the second step, Visual Search was added to the model, and the *R*square with both predictors in the model was 0.300. The model was statistically significant, $F(2, 47) = 10.069$, $p < 0.0001$, and accounted for approximately 30% of the variance in global social functioning ($R^2 = .300$, adjusted $R^2 = .270$). Global social functioning was primarily predicted by higher RCFTc and Visual Search scores (Table 5).

Table 6 summarises the comparison between HSF-BD and LSF-BD in socio-demographic and clinical data. BDII patients are mostly represented in the HSF-BD group ($p < 0.05$). Although the years of education between the HSF-BD and LSF-BD patients were similar, in the LSF-BD group, a graduate education level was most common, whereas in the HSF-BD group, post-graduate education was more prevalent.

Discussion

We can attest that the first part of our results confirm previous assumptions that patients with BDII are generally less impaired than those with BDI [12,25,50-53].

We assume that the most important difference between them is in executive functioning, specifically in cognitive control of attention, (planning, set-shifting and working memory) [56] and in memory, although this is less involved. In fact, low performance on the RCFT copy may influence low RCFT immediate and delayed recall scores, and attentional deficits may affect verbal memory scores [12,33].

As evidenced by Andreou and Bozikas [21] and Gilbert et al. [57], cognitive deficits were a significant predictor of psychosocial outcomes in patients with BD I and II. In the past two years, quite a number of studies have investigated the association between neuropsychological performance and various measures of functional outcome in BD [13,22,58]. In many of these [59] cognitive deficits were found to significantly predict social outcomes and functional status. In particular, Martino et al. [23] found significant associations between functional capacity and measures of attention and executive functioning. Pattanayak et al. [13] found significant associations between lack of social functioning and executive functioning, and Jabben et al. [60] described an association between reaction time and functional outcomes. Braw et al. [61] found that BD patients had deficits in psychomotor speed, sustained attention and cognitive planning, and this study also supports a strong correlation between loss of executive and social functioning in BD. The correlations between cognitive functioning and functional recovery were similar in BD I and BD II, confirming the hypothesis that both subtypes of bipolar disorder may result in loss of functioning that requires targeted intervention [4].

We attempted to understand whether socio-demographic variables could influence the course of BD with high premorbid social functioning, as did Wingo et al. [4], but there was no significant differences, likely because the simplistic categorisations of married/not married and employed/not employed variables were used. Patients were not considered if they were engaged, divorced, or widowed, or were housewives, volunteers, disabled, or employed. Maintaining social roles is

Table 5: Impact of Respondent-psychiatrists (N=29).

		No/weak impact	Average Impact	High/very high impact
		N (%)	N (%)	N (%)
On general practitioners (GP) working in the territory	Improved ability to make a diagnosis	9 (31.0)	14 (48.3)	6 (20.6)
	Improved quality of patient care	7 (24.1)	17 (58.6)	5 (17.2)
	Improved numbers of patients taken into care	9 (31.0)	14 (48.3)	6 (20.6)
	Improved capacity to orient patients to services	5 (17.2)	14 (48.3)	10 (34.5)
	Improved coordination with MH* teams/ one stop service	8 (27.6)	11 (37.9)	10 (34.5)
On professionals working on MH teams and one stop services	Improved ability to evaluate patients	3 (10.3)	12 (41.4)	14 (48.2)
	Improved quality of patient care	1 (3.4)	9 (31.0)	19 (65.5)
	Improved numbers of patients taken into care	6 (20.7)	13 (44.8)	10 (34.5)
	Improved capacity to orient patients to services	1 (3.4)	7 (24.1)	21 (72.4)
	Improved coordination with specialized services	3 (10.3)	7 (24.1)	19 (65.5)
Overall Impact	Increase in MH services provided in the territory	6 (20.7)	15 (51.7)	8 (27.5)
	Improved effectiveness of services to patients	5 (17.2)	12 (41.4)	12 (41.4)
	Improved health and wellbeing among patients	3 (10.3)	17 (58.6)	9 (31.0)

*MH: Mental Health

Table 6: Socio-demographic and clinical information in HSF-BD and LSF-BD.

Variables	Categories	HSF-BD	LSF-BD	Statistics	
				t, U, F or X^2	*p*-value
Diagnosis [n;%]	BD I	18 (56)	16 (89)	5.640*	.018*
	BD II	14 (44)	2 (11)		
Age of Onset [n;%]	Early (<22)	12 (37.5)	8 (45)	1.547	.461
	Intermediate (25-37)	16 (50)	6 (33)		
	Late (>40)	4 (12.5)	4 (22)		
Duration of illness [M;SD]		11.03 ± 2.030	14.52 ± 2.110	-1.438	.150
Sex [n;%]	Males	12 (37.5)	10 (56)	1.524	.217
	Females	20 (62.5)	8 (44)		
Age [M;SD]		39.94 ± 11.40	41.67 ± 11.85	-.516	.606
Education [n;%]	Primary [≤8 yy]	11 (34)	4 (22)	8.912	.012*
	Graduate [13yy]	8 (25)	12 (67)		
	Post Graduate [≥16yy]	13 (41)	2 (11)		
Employment [n;%]	Employment	19 (59)	8 (45)	1.188	.552
	Not employment	11 (35)	9 (50)		
	Student	2 (6)	1 (5)		
Married [n;%]	Married	12 (37.5)	6 (33)	.087	.768
	Not Married	20 (62.5)	12(67)		
Non Verbal IQ [M;SD]		105.19 ± 15,13	104.94 ± 14.55	-.055	.956

Notes: p*<.05; p**<.01
N = number of patients; M = mean score; SD = standard deviation; Non Verbal IQ (intelligence quotient) estimated from Raven Matrices (PM38)

very important in describing the evolution of social impairment in BD. Moreover, the data from this study can be explained by the fact that our sample consisted of BD subjects with high premorbid functioning who might have previously acquired high social roles and may have subsequently lost social functioning; the sample in Wingo's study, however, was not divided by a premorbid functioning class.

In their study, Bellivier et al. [62] suggested different classes of age of onset defined by clinical variables. We used these classes, and, similar to Aminoff et al. [48], we found that age of onset was not related to current cognitive functioning in our high premorbid social functioning sample.

We hypothesised that patients with high premorbid social functioning may be less impaired in the global functioning at the onset's age of the disease than BD patients with a not high premorbid social functioning, and that they can maintain their high levels of functioning.

The two different neurodevelopmental trajectories of current functioning have highlighted that BD patients with high premorbid social functioning may have a different disease courses and outcomes in terms of global functioning [63,64].

In more detail, a subset of the sample had achieved or had maintaining high levels of social functioning, which is related to high cognitive functioning, whereas the other subset had lost global functioning.

As reported by Rietschel et al. [65], poor premorbid adjustment may be associated with the poor neuropsychological performance widely observed in schizophrenia. In BD patients, even though they may show cognitive impairment in premorbid states, these impairments may not necessarily be mirrored in poor premorbid functioning as defined by the PAS. This is in accordance with the notion that BD may represent a perturbation in regulatory systems that is not expressed until a later stage of development [66].

An important matter for consideration is that during the euthymic phase, there were important differences in cognition and social functioning despite the fact that all enrolled patients had shown adequate premorbid functioning characterised additionally by good premorbid intellectual functioning.

Therefore, regarding cognitive and social functioning, we could hypothesise two possible neurodevelopmental trajectories of BD, one more favourable than the other. As highlighted by Wingo et al. [4], even our high premorbid social functioning sample showed that a high level of education can offset loss of functioning and likely facilitate recovery.

Conclusions

To the best of our knowledge, this is the first study to compare neuropsychological functioning in BD patients with high premorbid social functioning. For clinicians, it may be very important to know a BD patient's "neurocognitive destiny" to understand the impact of BD on the individual's recovery. Because of numerous studies, it is possible to affirm that these conditions are often promoted by the presence of non-protective factors (for example, genetic factors) that with the onset of BD and the presence of additional precipitating factors (for example, oxidative stress or circadian rhythm disorders) may help to determine a loss of overall functioning [67-69]. It is also possible that different factors exist during the disease course, genetic and/or epigenetic, that may either protect or worsen social and cognitive functioning [68,69].

Therefore, it is useful to identify neuropsychological indicators of BD separate from its symptoms in order to predict social functioning. Indeed, these indicators may themselves be targets of early cognitive remediation interventions.

This study contributes to the identification specific targets for treatment or remediation in BD. Severe cognitive deficits exist in the euthymic phase of BD [9-14,48,50-53], and these patients also show personal and social functioning impairment [4-6]. A number of implications become apparent in light of these data. First, we recommend accurate periodic assessments of cognitive and social functioning in everyday BD clinical practice, especially in primary care setting that it should be considered a front line of care for patients with bipolar disorder [70]. Second, specific treatment focused on cognitive deficits should be used in BD patients for optimal functional outcomes in the real world. From this perspective, cognitive remediation interventions should be understood as protective factors. Additional investigations are required in order to better understand the losses in cognitive and social functioning that characterize these patients.

This study was limited by a small and heterogeneous sample, and methodological limitations preclude more specific inferences. Certain limitations should be considered for studies in which self-report measures of functional outcome are used, because they may have questionable validity and might be affected by mood state [2]. The same limitations should be considered for those studies in which psychosocial function is assessed using categorical milestones such as employment or living alone, because these measures can be influenced by contextual factors such as social support, availability of jobs, ethnicity, and disability compensation legislation [13,17]. However, the occurrence of significant associations across a number of studies that have investigated patients with BD during various stages of their illness and the use of different outcome measures (self-rated VS observer-rated scales, general functional capacity VS specific function domains) lends credibility to the notion of neuropsychological deficits as significant predictors of functional outcome in these patients. Moreover, information about onset characteristics was collected retrospectively, with the possibility of error.

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