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Long-term outcome predictors after functional remediation in patients with bipolar disorder‡

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Abstract

Background. Improving functioning in patients with bipolar disorder (BD) is one of the main objectives in clinical practice. Of the few psychosocial interventions that have been specifically developed to enhance the psychosocial outcome in BD, functional remediation (FR) is one which has demonstrated efficacy. The aim of this study was to examine which variables could predict improved functional outcome following the FR intervention in a sample of euthymic or subsyndromal patients with BD.

Methods. A total of 92 euthymic outpatients were included in this longitudinal study, with 62 completers. Partial correlations controlling for the functional outcome at baseline were calculated between demographic, clinical and neurocognitive variables, and functional outcome at endpoint was assessed by means of the Functioning Assessment Short Test scale. Next, a multiple regression analysis was run in order to identify potential predictors of functional outcome at 2-year follow-up, using the variables found to be statistically significant in the correlation analysis and other variables related to functioning as identified in the previous scientific literature.

Results. The regression model revealed that only two independent variables significantly contributed to the model ($F_{(6,53)}$: 4.003; $p = 0.002$), namely verbal memory and inhibitory control. The model accounted for 31.2% of the variance. No other demographic or clinical variable contributed to the model.

Conclusions. Results suggest that patients with better cognitive performance at baseline, especially in terms of verbal memory and executive functions, may present better functional outcomes at long term follow-up after receiving functional remediation.

Introduction

Patients with bipolar disorder (BD) exhibit neurocognitive deficits across distinct neuropsychological domains, such as attention, memory and the executive functions, which extend beyond the acute episodes (Bourne et al., 2013; Martínez-Arán et al., 2004). Although these deficits can be present from the onset of the disease, some cognitive deficits may improve in patients who maintain remission after the resolution of the first episode (Kozicky et al., 2014; Torres et al., 2014). It is also important to highlight the high heterogeneity in patient cognitive profiles, ranging from a normal to a severely affected cognitive performance (Burdick et al., 2014; Roux et al., 2017). Nowadays, there is no doubt about the marked impact of neurocognitive impairment on psychosocial functioning in BD (Depp & Mausbach, 2012; Iosifescu, 2012; Sanchez-Moreno, Martinez-Aran, & Vieta, 2017b). Recently Ehrminger and colleagues published a cross-lagged panel model supporting an upward causal effect of cognition on functioning in euthymic patients (Ehrminger et al., 2019). Different cognitive domains have been found to have an effect on overall functioning (Sanchez-Moreno et al., 2018). Moreover, a relationship has been demonstrated between neurocognition and quality of life, both in the early stages of the disease and in multiple episodes (Brissos, Dias, & Kapczinski, 2008; Mackala, Torres, Kozicky, Michalak, & Yatham, 2014). Hence, over the last decade, an interest in developing psychosocial treatments to improve or train cognitive functioning has emerged in the field, especially if we take into account that the drugs currently available do not seem to improve neurocognitive symptoms (Miskowiak, Carvalho, Vieta, & Kessing, 2016a; Salagre et al., 2017). Nonetheless, in contrast to schizophrenia, where the efficacy of this type of intervention is well established (Kahn et al., 2015; Penades et al., 2017), only a few studies have been conducted with samples exclusively composed of individuals

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with BD, and those have yielded mixed findings. Most of them showed positive results (Lewandowski et al., 2017; Torrent et al., 2013; Zyto, Jabben, Schulte, Regeer, & Kupka, 2016), although one randomized controlled trial (RCT) found no significant results, probably due to the fact that the intervention format was not long or intensive enough (Demant, Vinberg, Kessing, & Miskowiak, 2015). It is important to underscore the considerable variation between studies in terms of how cognitive interventions were delivered, their contents, the treatment duration, the intensity of each of them, and the primary outcome (cognition *v.* psychosocial functioning) (Solé et al., 2017).

An example of this type of intervention is functional remediation (FR), a psychosocial program aimed at improving psychosocial functioning through training in different neurocognitive strategies targeted at the main neurocognitive deficits associated with BD, within an ecological 'real-life' framework which facilitates the transfer of learning to daily practice (Martínez-Arán et al., 2011; Torrent & Vieta, 2015). FR was shown to be effective at improving functioning (Torrent et al., 2013) in a RCT with three intervention arms, and its effects were maintained over time (Bonnin et al., 2016b). FR was also shown to improve the verbal memory domain in truly neurocognitively impaired patients (Bonnin et al., 2016a), and was also effective for patients with subsyndromal symptomatology (Sanchez-Moreno et al., 2017a).

Bearing in mind that therapies imply time and costs, and not all patients obtain benefit from them, it is important to identify the potential predictors of long-term maintenance response to specific therapies, so that specific patient profiles can be matched to appropriate treatments. In reality, some individuals respond well to FR while others do not, but currently, there is not enough information to be able to predict the outcome of FR for a given individual in advance. Whereas some studies have investigated potential predictors of response to cognitive remediation in schizophrenia and severe mental illnesses in general (Farreny et al., 2016; Fu et al., 2015; Kurtz, Seltzer, Fujimoto, Shagan, & Wexler, 2009; Lindenmayer et al., 2017; Medalia & Richardson, 2005; Reeder, Smedley, Butt, Bogner, & Wykes, 2006; Scheu et al., 2013; Twamley, Burton, & Vella, 2011; Vita et al., 2013), to the best of our knowledge, no studies have investigated so far which individual baseline characteristics may have an impact on the treatment response to cognitive interventions in BD.

Therefore, the current study was conducted to determine which baseline characteristics of a sample of patients with BD with functional impairment would predict psychosocial functioning at 2-year follow-up, after having received the FR program for 6 months.

Method

Participants

The 92 participants were outpatients with a diagnosis of BD (I or II) according to DSM-IV-TR diagnostic criteria, recruited from the Bipolar and Depressive Disorders Unit at the Hospital Clinic of Barcelona between September 2009 and February 2018. It is a program that provides integrated care for difficult-to-treat patients with mood disorders across Catalonia, including a specific catchment area in Barcelona (Vieta, 2011), and is also under the umbrella of the Center of Biomedical Research Network on Mental Health (CIBERSAM) (Salagre et al., 2019). The inclusion criteria were: (a) patients between 18 and 60 years old, (b) marked functional impairment assessed by means of the Functioning Assessment Short Test (Rosa et al., 2007) (FAST $\geqslant$18 score), (c) euthymic or with subthreshold clinical symptoms [Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) and Young Mania Rating Scale (YMRS) (Colom et al., 2002; Young, Biggs, Ziegler, & Meyer, 1978), both $\leqslant$14] for at least 3 months before study enrolment, and (d) to provide written informed consent to participate. The exclusion criteria were: (a) an estimated intelligence quotient (IQ) lower than 80, (b) any medical or comorbid psychiatric condition affecting neuropsychological performance, (c) substance abuse or dependence during the previous year, (d) having received electroconvulsive therapy within the past year and (e) participation in any structured psychological intervention, such as psychoeducation or cognitive remediation, within the past 2 years.

While functional impairment was one of the criteria for inclusion, the study design did not require a defined cognitive impairment at study entry. Hence, a number of patients showing functional but not cognitive impairment could be enrolled at the study.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice and approved by the Hospital Clinic Ethics and Research Board.

Intervention

After the baseline assessment, all participants received the FR program for 6 months, with no control group. The efficacy of FR in improving psychosocial functioning was proven in a large multicenter RCT trial conducted in Spain (Torrent et al., 2013). The contents and structure of the program are described in more detail in the latter paper and in the manual for FR (Vieta, Torrent, & Martinez-Arán, 2014). Briefly, as previously mentioned, the intervention is focused on providing training in neurocognitive strategies and techniques, within a highly ecological context, in order to improve daily functioning. It consists of 21 weekly 1.5 h sessions delivered in a group format. The primary cognitive targets are attention, memory and executive functions, although the program also includes a segment providing education about cognition and another addressed at enhancing communication skills and autonomy. All participants received pharmacological treatment according to guidelines for the management of BD, without any restrictions, in order to capture a representative sample of patients. Criteria for discontinuation during the intervention were: missing more than five sessions, hospitalization for any type of episode, or clinically meaningful affective relapse.

Measures

All relevant demographic and clinical data were gathered through a clinical interview based on the Structured Clinical Interview for DSM-IV (SCID) and the revision of medical records (First, 1997). The variables collected were: age, gender, education level, occupation, marital status, diagnosis, number and type of episodes, chronicity (years of illness), age at onset, number of hospitalizations, lifetime history of psychotic symptoms and rapid cycling, family history of affective and psychiatric disorders and pharmacological treatment. The number of relapses during the 2-year follow-up, separated into the type of episode (manic, hypomanic or depressive), was collected through revision of medical records.

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In addition, all participants were evaluated at baseline, after finishing the FR program, and at 24-month follow-up with the following instruments and scales:

- Functional outcome was measured with the FAST (Rosa et al., 2007), an interviewer-administered tool that assesses the main functional difficulties presented by psychiatric patients in six functional domains (autonomy, occupational functioning, cognitive functioning, interpersonal relationships, financial issues and leisure time), evaluated through a total of 24 items. This tool may not be completely independent of neurocognitive performance since it includes a domain of neurocognitive functioning. However, this domain is based on the clinician appraisal obtained from information provided by the patient, so there is a subjective compound, and additional information from relatives and clinical criteria. Moreover, according to several studies, there is only partial correspondence between objective and subjective cognitive measures (Miskowiak et al., 2016b). The FAST scores range from 0 to 72, with higher scores indicating poorer functioning, i.e. greater disability.
- Clinical symptoms were assessed by means of the HDRS for the depressive features and the YMRS for manic ones.
- A comprehensive neuropsychological battery was administered to estimate the IQ and evaluate the following 6 cognitive domains:
  (1) The Wechsler Adult Intelligence Scale (WAIS-III) Vocabulary subtest to estimate the IQ (Wechsler, 1997).
  (2) Processing speed (PS), with the PS index of the WAIS-III (Wechsler, 1997) which comprised two subtests: the Digit-symbol coding and the Symbol search.
  (3) Attention, tested with the Continuous Performance Test–II (CPT-II) version 5 (Conners, 2000), and the Trail Making Test-part A (TMT-A) (Reitan, 1958).
  (4) Working memory (WM), with the WM index which includes the Arithmetic, Digits and Letter-number sequencing subtests of the WAIS-III (Wechsler, 1997).
  (5) Verbal learning and memory, assessed with the California Verbal Learning Test (CVLT) (Delis, Kramer, Kaplan, & Ober, 1987).
  (6) Visual memory, evaluated by means of the Rey-Osterrieth Complex Figure (ROCF) (Rey, 1997).
  (7) Executive functions, tested by several tasks assessing set-shifting, planning and response inhibition, namely, the computerized version of the Wisconsin Card Sorting Test (Heaton, 2003), the Stroop Color-Word Interference Test (SCWT) (Golden, 1978), the TMT-B (Reitan, 1958) and Semantic fluency (Animal naming) and Phonemic fluency (FAS) components of the Control Oral Word Association test (Benton & Hamsher, 1976).

Data analyses

All analyses were performed with the IBM Statistical Package for Social Sciences version 23. Firstly, a descriptive analysis of demographic, clinical, functional and neuropsychological characteristics was carried out, with means and standard deviations for continuous variables and frequencies for categorical variables. Secondly, in order to analyze potential associations between different type of variables at baseline (demographic, clinical and neurocognitive) and functioning at endpoint (FAST score at 2-year follow-up), partial correlations controlling for the influence of functioning at baseline (pre-intervention FAST score) were computed for the continuous variables. The association between binary variables and the FAST score at 2-year follow-up was examined using a *t* test, controlling again for the effects of the pre-intervention FAST score. Then, a multiple linear regression model was performed to investigate which of the baseline characteristics were potential predictors of psychosocial outcome, with the total FAST score at endpoint as the dependent variable. Those variables which were statistically significant in the correlation analyses and *t* tests were entered into the regression model, as were some further clinical variables previously reported in the literature to influence functioning. To avoid multicollinearity, we required all variables in the model to have variance inflation factor values below 5. For these analyses, the last observation carried forward was used to minimize the effect of attrition rates at 24-month follow-up (18 months after finishing the FR program). Lastly, differences at baseline between completers and dropouts were examined using *t* tests and chi-squared tests. Statistical significance was set at $p < 0.05$ in all analyses.

Results

Patient flow

The patient flow chart is shown in Fig. 1, from screening through to final follow-up. Ninety-two out of 117 screened patients started the intervention, 69 of whom (75%) were considered to be completers (finished the intervention), while 23 (25%) discontinued the intervention. Twenty-two completers (31.9%) were BD-II and 47 (68.1%) were BD-I. Seven of these patients did not complete the endpoint follow-up. Common reasons for dropping out are specified on the flow chart (Fig. 1). An analysis comparing completers and non-completers revealed that both groups did not differ in baseline characteristics (demographic and clinical), with the exception of years of education ($t = 0.345$, $p = 0.021$); where the completers had more years of education (mean = 14.12; S.D. = 3.43) compared to the non-completers (mean = 12.22; S.D. = 3.13).

Descriptive characteristics of the sample

The sample consisted of mostly females ($n = 63$, 68.5%), patients who ranged in age from 19 to 60 (mean = 46.7, S.D. = 8.73), mostly unemployed (76.1%) and the mean years of education was 13.64 (S.D. = 3.44) years (see Tables 1 and 2 for more details). Thirty-seven out of the 62 patients that finished the follow-up (59.7%) experienced an affective episode of some kind: 5 (13.5%) had a manic relapse, 22 (59.4%) suffered from a hypomanic relapse and 29 (78.3%) had a depressive episode during the 2-year follow-up. With regard to affective symptomatology, the HDRS mean score at baseline was 6.24 (S.D. = 3.17) and 5.73 (S.D. = 4.94) at the endpoint, and 1.65 (S.D. = 1.78) and 2.46 (S.D. = 3.42) for the YMRS. Concerning neurocognitive performance at 24-month follow-up, we found an improvement in different neurocognitive variables such as PS index ($p = 0.033$), WM index ($p = 0.022$), TMT-A ($p = 0.011$), all CVLT measures ($p \leqslant 0.001$), recall of ROCF ($p = 0.002$), Interference Stroop ($p < 0.001$), CPT-II commission errors ($p = 0.015$), CPT-II reaction time ($p = 0.018$) and CPT-II d' attentiveness ($p = 0.002$).

Relationship between baseline variables and the outcome variable

The FAST total score average at baseline was 33.57 (S.D. = 8.12), whereas this score was reduced by more than 5 points at endpoint

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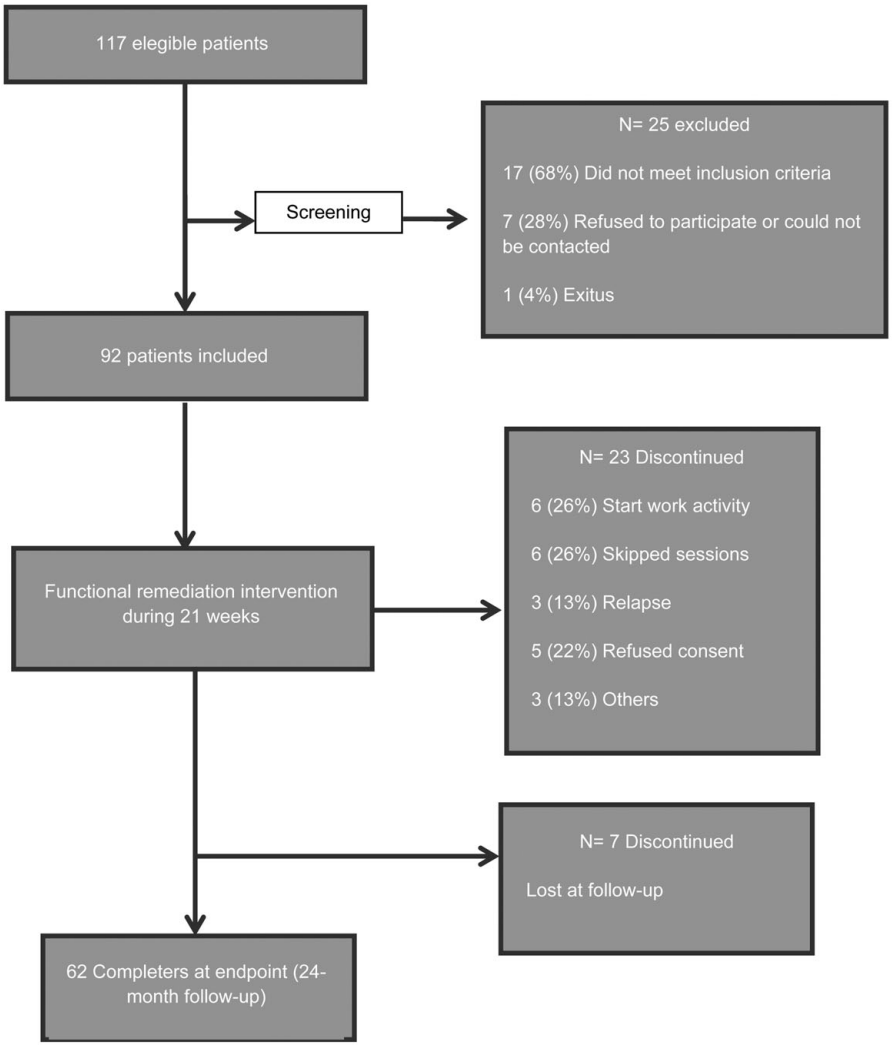

Fig. 1. Patients' flow chart.

(mean = 28.04; S.D. = 9.65). To investigate potential baseline variables associated with functioning at 24-month follow-up, partial correlations (controlling for functioning at baseline) between FAST total score at endpoint and baseline characteristics were run. Significant negative correlations were found with: total number of episodes ($r = -0.385$, $p = 0.008$), hypomanic episodes ($r = -0.368$, $p = 0.011$), PS ($r = -0.327$, $p = 0.025$), CVLT short cued recall ($r = -3.25$, $p = 0.026$), CVLT delayed free recall ($r = -0.312$, $p = 0.033$), CVLT delayed cued recall ($r = -0.308$, $p = 0.035$), recall of Rey figure ($r = -0.323$, $p = 0.027$), and Interference Stroop ($r = -0.399$, $p = 0.005$). Concerning categorical variables, there was an association with employment status, specifically, as expected, patients who were not working at baseline had higher scores on FAST total score at endpoint ($t = 2.393$, df = 65, $p = 0.020$). No other demographic or clinical variables were associated with our principal outcome.

Regression model

A standard multiple regression analysis was used to assess the ability of different baseline variables to predict the functional outcome at 2-year follow-up of a group of patients who had received the FR program, after controlling for the influence of functioning at baseline (FAST total score). This model contained six variables (HDRS baseline total score, number of total episodes at baseline, Stroop interference score, PS index, Rey figure recall, and CVLT short cued recall). Subthreshold depressive symptomatology (HDRS) at baseline was entered in the regression model, based on findings from previous literature. Among those CVLT variables significantly correlated with functioning, only the one with the highest level of statistical significance was introduced in the regression model to avoid multicollinearity. The model was statistically significant ($F_{(6,53)}$: 4.003; $p = 0.002$) as shown in Table 3, and as a whole it explained 31.2% of the variance, with only two independent variables contributing to the model: the CVLT short cued recall ($\beta = -0.255$, $t = -2.011$, $p = 0.049$) and the interference Stroop measure ($\beta = -0.419$, $t = -3.551$, $p = 0.001$). The strongest predictor was the SCWT interference measure.

To investigate the effect of potential confounding effects of medication and comorbidity, we repeated the multiple regression including the latter factors as covariates of no interest. Specifically, we added binary regressors for the presence of comorbidity, lithium, other mood stabilizers, antipsychotics, antidepressants and anxiolytics. The results were nearly identical (SCWT Interference: $\beta = -0.474$, $t = -3.531$, $p = 0.001$; verbal memory: $\beta = -0.332$, $t = -2.222$, $p = 0.032$), and none of the comorbidity and medication variables achieved statistical significance (smallest $p = 0.172$).

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Table 1. Demographic and clinical characteristics of the sample at baseline

	Bipolar patients ($n = 92$)
	Mean (s.d.) or *N* (%)
Sociodemographic	
Age	46.73 (8.73)
Gender (female)	63 (68.5)
Occupation (not working)	70 (76.1)
Marital status (not married)	54 (58.7)
Educational level (years)	13.64 (3.44)
Estimated IQ	106.77 (10.42)
Clinical	
Age at onset	25.84 (8.92)
Diagnosis (BD-I)	63 (68.5)
Illness duration (years)	20.52 (9.99)
Total number of episodes	15.77 (14.81)
Hypomanic episodes	4.99 (6.58)
Manic episodes	2.27 (4.18)
Depressive episodes	7.71 (8.87)
Number of hospital admissions	2.11 (2.68)
Lifetime psychotic symptoms (yes)	48 (52.2)
Lifetime rapid cycling (yes)	16 (17.4)
Family history of affective disorders (yes)	56 (60.9)
Family history of psychiatric disorders (yes)	70 (76.1)
HDRS	6.24 (3.17)
YMRS	1.65 (1.78)
Functioning	
FAST total score	33.57 (8.12)
FAST autonomy	3.48 (2.74)
FAST occupational	12.85 (3.99)
FAST cognitive	8.13 (2.83)
FAST financial	1.20 (1.45)
FAST interpersonal	5.74 (2.73)
FAST leisure time	2.30 (1.66)
Current medications	
Lithium (yes)	55 (59.8)
Other anticonvulsants (yes)	61 (66.3)
Antipsychotic (yes)	76 (82.6)
Antidepressant (yes)	39 (42.4)
Anxiolytic (yes)	35 (38.0)

BD-I, bipolar disorder type I; FAST, Functioning Assessment Short Test; HDRS, Hamilton Depression Rating Scale; IQ, Intelligence quotient; s.d., standard deviation; YMRS, Young Mania Rating Scale.

Table 2. Neurocognitive variables at baseline

	Bipolar patients ($n = 92$)
	Mean (s.d.)
Processing speed	
Processing speed index WAIS-III	99.25 (12.07)
Attention	
CPT-II omissions	72.31 (53.35)
CPT-II commissions	53.10 (11.17)
CPT-II RT	58.63 (14.10)
CPT-II d'	52.77 (10.86)
CPT-II ß	53.65 (14.13)
TMT-A	41.87 (22.20)
Working memory	
Working memory index WAIS-III	93.51 (13.99)
Visual memory	
ROFC	17.26 (8.92)
Verbal memory	
CVLT total words	48.70 (12.36)
CVLT short-free recall	10.10 (3.56)
CVLT short-cued recall	11.21 (3.00)
CVLT delay free recall	10.87 (3.35)
CVLT delay cued recall	11.45 (3.24)
Executive functions	
TMT-B	110.61 (65.96)
WCST categories	4.14 (2.18)
WCST perseverative errors	22.0 (16.90)
SCWT interference	50.82 (7.69)
Phonemic fluency	32.59 (10.70)
Animal naming	18.51 (6.18)

CPT-II, Conners' Continuous Performance Test; CVLT, California Verbal Learning Test; ROCF, Rey-Osterrieth Complex Figure; SCWT, Stroop Color Word Test; TMT, Trail Making Test; WAIS-III, Wechsler Adult Intelligence Test-III; WCST, Wisconsin Card sorting Test.

Discussion

As far as we know, this is the first attempt to investigate the potential role of a range of demographic, clinical and neurocognitive variables in predicting functional outcome following the FR intervention in fully or partially remitted patients with BD and functional impairment, using a longitudinal design. Our results indicate that only a few cognitive characteristics at baseline, such as verbal memory and inhibitory control, may be important factors in predicting long-term functioning after receiving FR. Some previous studies in patients with schizophrenia indicated that poorer neuropsychological performance at baseline was related to better treatment outcomes, with patients having more room to improve (Scheu et al., 2013; Twamley et al., 2011), whereas a number of studies found that a better cognitive profile at baseline predicted a positive response to cognitive remediation (Farreny et al., 2016; Fiszdon, Cardenas, Bryson, & Bell, 2005; Kurtz et al., 2009; Lindenmayer et al., 2017; Medalia & Richardson, 2005; Vita et al., 2013). Our findings would be aligned, in part, with these latter studies; that is, better performance in verbal memory and executive function at baseline were

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Table 3. Regression analysis to predict FAST outcome at 2 years, after receiving the Functional Remediation program

Predictor variable	β	t	p	R^2	Model signification
				0.312	$F_{(6,53)}$: 4.003 $p = 0.002$
Total number of episodes	−0.123	−1.030	0.307		
HDRS	0.162	1.369	0.177		
Processing speed	0.060	0.418	0.677		
Verbal memory	−0.255	−2.011	**0.049**		
Visual memory	−0.119	−0.879	0.384		
SCWT Interference	−0.419	−3.551	**0.001**		

FAST, Functional Assessment Short Test; HDRS, Hamilton Depression Rating Scale; SCWT, Stroop Color Word Test.
Bold text in the table indicates significant value

significant predictors of better functioning at 2 years. Executive functions, along with verbal memory, are the cognitive functions that have probably been most consistently found to be associated with psychosocial functioning. Inhibitory control is the ability to inhibit inappropriate responses in favor of more suitable ones. This task is also linked to selective attention, how individuals react selectively to information in their environment and focus on what matters, suppressing the attention given to irrelevant stimuli. This is a measure of executive function associated with the ventrolateral prefrontal cortex, and several studies have provided evidence of impairment in this function in BD (Bourne et al., 2013). Dysfunctional inhibitory control, in turn, has also been related to impulsivity; individuals with difficulties in inhibiting automatic mechanisms and reducing the interference exerted by irrelevant stimuli would be more impulsive (Newman & Meyer, 2014). Our results seem to suggest that those patients with higher resistance to interference may have better functioning after receiving training with different neurocognitive strategies. Patients would be more able to focus attention actively on important elements and ignore distractions or to keep to a task and complete it despite distractions. This may allow patients to apply new strategies learned during the intervention and inhibit older automatic actions or unwanted thoughts. Along these lines, some strategies taught in FR such as reflective listening and problem-solving imply inhibitory control, and are useful strategies for improving communication and interpersonal relationships. In accordance with our results, Reinares and colleagues also identified inhibitory control as one of the cognitive predictors of functional outcome (Reinares et al., 2013). Similarly, higher impulsivity measured by self-reported impulsiveness scales has been associated with increases in global functional impairment (Jimenez et al., 2012).

As mentioned above, the other cognitive function that may predict patient functioning following FR is verbal memory. This cognitive domain has been reported as a good predictor of global functional outcome in earlier follow-up studies with BD (Bonnín et al., 2010; Martino et al., 2009; Mora, Portella, Forcada, Vieta, & Mur, 2013). Likewise, immediate verbal memory was also found to be a predictor of cognitive remediation response in studies with patients with schizophrenia (Fiszdon et al., 2005; Vita et al., 2013). One interpretation of the current findings would be that patients with higher verbal memory capacity may retain better what they have learnt, and are thus more able to implement this in their daily life in order to have better functional outcomes. Moreover, bearing in mind that the verbal memory assessment was done with the CVLT test, our results may also suggest the contribution made by frontal executive components, since semantic organization strategies are needed to encode information. Interestingly, an improvement in verbal memory was previously detected in truly neurocognitively impaired patients upon finishing a FR program and also as an effect of FR at 1-year follow-up in a RCT (Bonnin et al., 2016a, 2016b). Lastly, we also found significant correlations between higher PS and visual memory scores with lower scores on the FAST scale at the endpoint, although these two functions do not seem to predict functional outcome after receiving FR.

Although a few baseline clinical characteristics were associated with functioning at 2 years, none of them survived in the regression model, and thus are not predictors of patient functioning following the FR program. Hence, it seems that improved functioning at long term after being enrolled in FR may not be related to illness factors such as chronicity (illness duration) or the number of episodes, suggesting that individuals with different clinical profiles can benefit from FR treatment (Twamley et al., 2011). In this regard, subclinical depressive symptoms have consistently been found to impact on overall functioning in previous studies (Bonnín et al., 2010; Martino et al., 2009). However, contrary to our expectations, we did not find that this symptomatology helped to predict functioning after receiving a FR intervention. In agreement with our findings, a previous study demonstrated that patients with subsyndromal symptoms also improved their functional outcome after finishing the FR intervention, regardless of mood symptoms (Sanchez-Moreno et al., 2017a, 2017b). Therefore, such symptoms should not interfere with benefits from FR. On the other hand, contrary to our expectations, we did not find differences in functional outcome at endpoint between patients who remained stable and those who suffered an affective episode. In contrast, in the area of schizophrenia, some baseline demographic and clinical characteristics, such as age, illness duration or pharmacological treatment have been found to influence the improvement in cognitive remediation (Lindenmayer et al., 2017; Rodewald et al., 2014; Vita et al., 2013). However, further studies will be needed to confirm similar findings in BD.

Beyond this, we also found that patients who completed the intervention had more years of education than the dropout group. The total number of years of education completed, or educational level is considered to be one of the proxies for measuring cognitive reserve, along with IQ and occupational attainment (Stern, 2006). The high cognitive reserve has potentially been seen to protect against neurocognitive and psychosocial impairment in euthymic patients with BD (Forcada et al., 2015; Grande et al., 2017). Our finding may suggest that patients with more years of formal education may be more used to receiving

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training, and therefore may find it easier to engage with the sessions and the cognitive stimulation techniques, and to attend more regularly.

This study has several caveats and limitations to be noted, meaning our results should be interpreted with caution. First, the lack of a control group means we cannot ensure that outcomes were exclusively due to the effect of the intervention. Even so, it is important to note that the efficacy of FR was proven in a large RCT trial with positive results in functioning (Bonnin et al., 2016a, 2016b; Torrent et al., 2013). Secondly, the sample size can limit the number of potential predictors that could be explored in the regression model analysis. In that regard, the proportion of variance explained by predictive variables also suggests that other variables not measured may be associated with functioning. For instance, we did not assess intrinsic motivation, an important component that has repeatedly been suggested to have an influence on treatment response in the area of schizophrenia (Medalia & Richardson, 2005). In fact, intrinsic motivation has been proposed to mediate the impact of neurocognition on the psychosocial outcome (Nakagami, Xie, Hoe, & Brekke, 2008). Other potential mediating variables to be considered in further studies would be an insight into cognitive difficulties, with measures of subjective complaints, and the role of social cognition variables. Moreover, additional overlooked variables may also have influenced functioning through the long follow-up (2 years). Another caveat is that functional assessment could have been paired with other objective measures reflecting the functional outcome of patients in the real world (e.g. employment status, marital status, etc.). Lastly, our findings cannot be generalized since the sample was characterized by individuals with marked functional difficulties at baseline.

Despite the aforementioned limitations, this is the first study to date to examine factors associated with response to FR in a long-term follow-up with a sample composed exclusively of patients with BD. This is an exploratory analysis of predictors of FR long-term outcome; therefore, findings should be regarded as preliminary. Understanding the variables that may help to predict which patients benefit from a specific intervention is useful for clinicians to be able to match patients to appropriate interventions and to tailor treatments according to each patient's profile, as well as avoiding a misuse of resources, such as time and costs. In our study, the findings suggest that a better performance in verbal memory and executive functions at baseline may mean positive effects in psychosocial functioning in the long-term and, therefore, add to the existing data regarding the link between cognition and psychosocial functioning in BD. Nevertheless, further research is needed to enhance our understanding of the sources of differences in response to FR in BD, in order to provide the most effective treatments or to individualize interventions. In this vein, in the area of other psychiatric illnesses such as schizophrenia, it has been demonstrated that cognitive remediation produces greater effects when it is offered as part of a more general and integrative rehabilitation program (Kurtz, 2012). At this point, it would be necessary to define whether FR would need to be accompanied by other interventions to maintain or enhance its effect, such as computerized cognitive modules to facilitate practice between sessions, as well as the issue of booster sessions, and the frequency and intensity needed to guarantee the consolidation of the knowledge acquired.

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Ethical standards. 'The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.'

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