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

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	functional outcome at endpoint was assessed by means of the Functioning Assessment Short Test scale (FAST). 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 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.

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Abstract

Background: Improving functioning in patients with bipolar disorder (BD) is a main objective in clinical practice. Of the few psychosocial interventions that have been specifically developed to enhance 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 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 (FAST). 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 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.

Key words: bipolar disorder, cognition, functioning, functional remediation, cognitive 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 (Martínez-Arán *et al.,* 2004)(Bourne et al., 2013). Although these deficits can be present from the onset of the disease, some cognitive deficits may improve in patients who maintain remission after 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 (Iosifescu, 2012)(Sanchez-Moreno, Martinez-Aran, & Vieta,*.,* 2017b)(Depp & Mausbach, 2012). 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 (Mackala, Torres, Kozicky, Michalak, & Yatham, 2014)(Brissos, Dias, & Kapczinski, 2008). 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 with BD, and those have yielded mixed findings. Most of them showed positive results (Torrent *et al.,* 2013)(Zyto, Jabben, Schulte, Regeer, & Kupka, 2016)(Lewandowski *et al.,* 2017), 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 vs. 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, 2011)(Torrent & Vieta, 2015). FR was shown to be effective at improving functioning (Torrent *et al.,* 2013) in a randomized controlled trial with three intervention arms, and its effects were maintained over time (Bonnin et al., 2016). FR was also shown to improve the verbal memory domain in truly neurocognitively impaired patients (Bonnin et al., 2016), and was also effective for patients with subsyndromal symptomatology (Sanchez-Moreno et al., 2017).

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 (Reeder, Smedley, Butt, Bogner, & Wykes, 2006)(Vita *et al.,* 2013)(Kurtz, Seltzer, Fujimoto, Shagan, & Wexler, 2009)(Farreny *et al.* 2016)(Fu *et al.,* 2015)(Scheu *et al.,* 2013)(Twamley, Burton, & Vella, 2011)(Medalia & Richardson, 2005)(Lindenmayer *et al.,* 2017), 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 ≥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 ≤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 manuscript and in the manual for FR (Vieta, Torrent, & Martinez-Aran, 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 hour 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 type of episode (manic, hypomanic or depressive), was collected through revision of medical records.

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 6 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 to 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 Intelligence Quotient (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, with the processing speed index (PS) 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, with the working memory (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 (WCST) (Heaton, 1993), 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 (COWAT) (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 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 literature to influence functioning. To avoid multicollinearity, we required all variables in the model to have variance inflation factor values (VIF) below 5. For these analyses, the last observation carried forward (LOCF) 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 on figure 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 (Figure 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; SD=3.43) compared to the non-completers (mean=12.22; SD=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, SD=8.73), mostly unemployed (76.1%) and the mean years of education was 13.64 (SD=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 regards to affective symptomatology, the HDRS mean score at baseline was 6.24 (SD=3.17) and 5.73 (SD=4.94) at endpoint, and 1.65 (SD=1.78) and 2.46 (SD=3.42) for the YMRS. Concerning neurocognitive performance at 24-month follow-up, we found an improvement in different neurocognitive variables such as processing speed index (p=0.033), working memory index (p=0.022), TMT-A (p=0.011), all CVLT measures ($p \leq 0.001$), 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 (SD=8.12), whereas this score was reduced by more than 5 points at endpoint (mean=28.04; SD=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), processing speed (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, Processing speed 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 (β=-0.255, t=-2.011, p=0.049) and the interference Stroop measure (β=-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: β=-0.474, t= -3.531, P=0.001; verbal memory: β=-0.332, t=-2.222, P=0.032), and none of the comorbidity and medication variables achieved statistical significance (smallest P=0.172).

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 functional remediation. 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 (Medalia & Richardson, 2005)(Lindenmayer *et al.,* 2017)(Kurtz *et al.,* 2009)(Farreny *et al.,* 2016)(Vita *et al.,* 2013)(Fiszdon, Cardenas, Bryson, & Bell, 2005). Our findings would be aligned, in part, with these latter studies; that is, better performance in verbal memory and executive function at baseline were significant predictors of better functioning at two 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 a 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 E, & 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)(Bonnin et al., 2016b). Lastly, we also found significant correlations between higher processing speed and visual memory scores with lower scores on the FAST scale at 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 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., 2017). 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 (Vita *et al.,* 2013)(Lindenmayer *et al.,* 2017)(Rodewald *et al.,* 2014). 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. 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). High cognitive reserve has potentially been seen to protect against neurocognitive and psychosocial impairment in euthymic patients with BD (Grande *et al.,* 2017) (Forcada *et al.,* 2015). Our finding may suggest that patients with more years of formal education may be more used to receiving 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 (Torrent *et al.,* 2013)(Bonnin et al., 2016). 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 psychosocial outcome (Nakagami, Xie, Hoe, & Brekke, 2008). Other potential mediating variables to be considered in further studies would be 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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Conflict of interest

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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."

Benton A, Hamsher K (1976). *Multilingual Aphasia Examination*. University of Iowa: Iowa City.

Bonnín CM, Martínez-Arán A, Torrent C, Pacchiarotti I, Rosa AR, Franco C,… Vieta E (2010). Clinical and neurocognitive predictors of functional outcome in bipolar euthymic patients: A long-term, follow-up study. Elsevier B.V. *Journal of Affective Disorders* **121**, 156–160. doi: 10.1016/j.jad.2009.05.014.

Bonnin CM, Reinares M, Martinez-Aran A, Balanza-Martinez V, Sole B, Torrent C, … Vieta E (2016a). Effects of functional remediation on neurocognitively impaired bipolar patients: enhancement of verbal memory. *Psychological medicine* **46**, 291–301. doi: 10.1017/S0033291715001713.

Bonnin CM, Reinares M, Martínez-Arán A, Balanzá-Martínez V, Sole B, Torrent C, …Vieta E, CIBERSAM Functional Remediation Group (2016b). Effects of functional remediation on neurocognitively impaired bipolar patients: enhancement of verbal memory. *Psychological medicine* **46**, 291–301.

Bonnin CM, Torrent C, Arango C, Amann BL, Sole B, Gonzalez-Pinto A, … Martinez-Aran A (2016c). Functional remediation in bipolar disorder: 1-year follow-up of neurocognitive and functional Outcome. *British Journal of Psychiatry* **208**, 87–93. doi: 10.1192/bjp.bp.114.162123.

Bourne C, Aydemir O, Balanza-Martinez V, Bora E, Brissos S, Cavanagh JTO, … Goodwin GM (2013a). Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: An individual patient data meta-analysis. *Acta Psychiatrica Scandinavica* **128**, 149–162. doi: 10.1111/acps.12133.

Brissos S, Dias VV, Kapczinski F (2008). Cognitive performance and quality of life in bipolar disorder. *Canadian Journal of Psychiatry* **53**, 517–524.

Burdick KE, Russo M, Frangou S, Mahon K, Braga RJ, Shanahan M, Malhotra AK (2014). Empirical evidence for discrete neurocognitive subgroups in bipolar disorder: clinical implications. *Psychological Medicine*, 1–14. doi: 10.1017/S0033291714000439.

Colom F, Vieta E, Martínez-Arán A, Garcia-Garcia M, Reinares M, Torrent C, … Salamero M (2002). Spanish version of a scale for the assessment of mania: Validity and reliability of the Young Mania Rating Scale. *Medicina Clinica,* **119**, 366-71.

Conners C (2000). *Conner's Continuous Performances Test for Win dows (CPT-II).*

Delis D, Kramer J, Kaplan E, Ober B (1987). California Verbal Learning Test (CVLT) Manual. *The*

Psychological Corporation.

Demant KM, Vinberg M, Kessing L V, Miskowiak KW (2015). Effects of Short-Term Cognitive Remediation on Cognitive Dysfunction in Partially or Fully Remitted Individuals with Bipolar Disorder: Results of a Randomised Controlled Trial. *PloS one* **10**, e0127955. doi: 10.1371/journal.pone.0127955. eCollection 2015

Depp C, Mausbach B (2012). Meta-analysis of the association between cognitive abilities and everyday functioning in bipolar disorder. *Bipolar Disord.* **14**, 217–226. doi: 10.1111/j.1399-5618.2012.01011.x.

Farreny A, Aguado J, Corbera S, Ochoa S, Huerta-Ramos E, Usall J (2016). Baseline predictors for success following strategy-based cognitive remediation group training in schizophrenia. *Journal of Nervous and Mental Disease* **204**, 585–589. doi: 10.1097/NMD.0000000000000509.

First MB (1997). Structured clinical interview for DSM-IV axis I disorders. *Biometrics Research Department.*

Fiszdon JM, Cardenas AS, Bryson GJ, Bell MD (2005). Predictors of remediation success on a trained memory task. *Journal of Nervous and Mental Disease* **193**, 602–608.

Forcada I, Mur M, Mora E, Vieta E, Bartrés-Faz D, Portella MJ (2015). The influence of cognitive reserve on psychosocial and neuropsychological functioning in bipolar disorder. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology* **25**, 214–22. doi: 10.1016/j.euroneuro.2014.07.018.

Fu DJ, Turkoz I, Simonson RB, Walling DP, Schooler NR, Lindenmayer JP, … Alphs L (2015). Paliperidone Palmitate once-monthly reduces risk of relapse of psychotic, depressive, and manic symptoms and maintains functioning in a double-blind, randomized study of schizoaffective disorder. *Journal of Clinical Psychiatry* **76**, 253–262. doi: 10.4088/JCP.14m09416.

Golden CJ (1978). Stroop Color and Word Test: A manual for clinical and experimental uses. *Chicago: Stoelting.*

Grande I, Sanchez-Moreno J, Sole B, Jimenez E, Torrent C, Bonnin CM, … Martinez-Aran A (2017). High cognitive reserve in bipolar disorders as a moderator of neurocognitive impairment. *Journal of Affective Disorders* **208**, 621–627. doi: 10.1016/j.jad.2016.10.012.

Hamilton M (1960). A rating scale for depression. *Journal of neurology, neurosurgery, and*

psychiatry **23**, 56-62.

Heaton R (1993). Wisconsin card sorting test: Computer version 4. *Psychological Assessment Resources.*

Ehrminger M, Brunet-Gouet E, Cannavo AS, Aouizerate B, Cussac I, Azorin JM, …Olié E; FondaMental Advanced Centers of Expertise in Bipolar Disorders (FACE-BD) Collaborators, Passerieux C, Roux P (2019). Longitudinal relationships between cognition and functioning over 2 years in euthymic patients with bipolar disorder: a cross-lagged panel model approach with the FACE-BD cohort. *The British Journal of Psychiatry* **13,**1-8. doi: 10.1192/bjp.2019.180.

Iosifescu D V. (2012). The relation between mood, cognition and psychosocial functioning in psychiatric disorders. Elsevier *European Neuropsychopharmacology* **22**, S499–S504.

Jimenez E, Arias B, Castellvi P, Goikolea JM, Rosa AR, Fananas L,… Benabarre A (2012). Impulsivity and functional impairment in bipolar disorder. *Journal of affective disorders* **136**, 491–497. doi: 10.1016/j.jad.2011.10.044.

Kahn RS, Sommer IE, Murray RM, Meyer-Lindenberg A, Weinberger DR, Cannon TD, … Insel TR (2015). Schizophrenia. *Nature reviews. Disease primers* **1**, 15067. doi: 10.1038/nrdp.2015.67.

Kozicky J-M, Torres IJ, Silveira LE, Bond DJ, Lam RW, Yatham LN (2014). Cognitive change in the year after a first manic episode: association between clinical outcome and cognitive performance early in the course of bipolar I disorder. *The Journal of clinical psychiatry* **75**, e587-93. doi: 10.4088/JCP.13m08928.

Kurtz MM, Seltzer JC, Fujimoto M, Shagan DS, Wexler BE (2009). Predictors of change in life skills in schizophrenia after cognitive remediation. *Schizophrenia Research* **107**, 267–274. doi: 10.1016/j.schres.2008.10.014.

Lewandowski KE, Sperry SH, Cohen BM, Norris LA, Fitzmaurice GM, Ongur D, Keshavan MS (2017). Treatment to enhance cognition in bipolar disorder (TREC-BD): Efficacy of a randomized controlled trial of cognitive remediation versus active control. *Journal of Clinical Psychiatry* **78**, e1242-e1249. doi: 10.4088/JCP.17m11476.

Lindenmayer JP, Ozog VA, Khan A, Ljuri I, Fregenti S, McGurk SR (2017). Predictors of response to cognitive remediation in service recipients with severe mental illness. *Psychiatric Rehabilitation Journal* **4**0, 61–69. doi: 10.1037/prj0000252.

Kurtz MM (2012). Cognitive remediation for schizophrenia: Current status, biological correlates and predictors of response. *Expert Review of Neurotherapeutics* **12**, 813–821. doi: 10.1586/ern.12.71.

Mackala SA, Torres IJ, Kozicky J, Michalak EE, Yatham LN (2014). Cognitive performance and quality of life early in the course of bipolar disorder. Elsevier *Journal of Affective Disorders* **168**, 119–124. doi: 10.1016/j.jad.2014.06.045.

Martínez-Arán A, Torrent C, Solé B, Bonnín CM, Rosa AR, Sánchez-Moreno J, Vieta E (2011). Functional Remediation for Bipolar Disorder. *Clinical Practice & Epidemiology in Mental Health* **7**, 112–116. doi: 10.2174/1745017901107010112.

Martínez-Arán A, Vieta E, Reinares M, Colom F, Torrent C, Sánchez-Moreno J…Salamero M (2004). Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. *The American journal of psychiatry* **161**, 262–70.

Martino DJ, Marengo E, Igoa A, Scápola M, Ais ED, Perinot L, Strejilevich SA (2009). Neurocognitive and symptomatic predictors of functional outcome in bipolar disorders: a prospective 1 year follow-up study. *Journal of affective disorders* **116**, 37–42. doi: 10.1016/j.jad.2008.10.023.

Medalia A, Richardson R (2005). What predicts a good response to cognitive remediation interventions? *Schizophrenia Bulletin* **31**, 942–953.

Miskowiak KW, Carvalho AF, Vieta E, Kessing L V (2016a). Cognitive enhancement treatments for bipolar disorder: A systematic review and methodological recommendations. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology* **26**, 1541-61. doi: 10.1016/j.euroneuro.2016.08.011.

Miskowiak KW, Petersen JZ, Ott CV, Knorr U, Kessing LV, Gallagher P, Robinson L (2016b)**.** Predictors of the discrepancy between objective and subjective cognition in bipolar disorder: a novel methodology. *Acta Psychiatrica Scandinavica* **134,** 511-21. doi: 10.1111/acps.12649.

Mora E, Portella MJ, Forcada I, Vieta E, Mur M (2013). Persistence of cognitive impairment and its negative impact on psychosocial functioning in lithium-treated, euthymic bipolar patients: a 6-year follow-up study. *Psychological medicine* **43**, 1187–96. doi: 10.1017/S0033291712001948.

Nakagami E, Xie B, Hoe M, Brekke JS (2008). Intrinsic motivation, neurocognition and

psychosocial functioning in schizophrenia: Testing mediator and moderator effects. *Schizophrenia Research* **105**, 95–104. doi: 10.1016/j.schres.2008.06.015.

Newman AL, Meyer TD (2014). Impulsivity: present during euthymia in bipolar disorder? - a systematic review. *International journal of bipolar disorders* **2**, 2. doi: 10.1186/2194-7511-2-2. eCollection 2014.

Penades R, Lopez-Vilchez I, Catalan R, Arias B, Gonzalez-Rodriguez A, Garcia-Rizo C, … Bernardo M (2017). BDNF as a marker of response to cognitive remediation in patients with schizophrenia: A randomized and controlled trial. *Schizophrenia* research **197**, 458-464. doi: 10.1016/j.schres.2017.12.002.

Reeder C, Smedley N, Butt K, Bogner D, Wykes T (2006). Cognitive predictors of social functioning improvements following cognitive remediation for schizophrenia. *Schizophrenia Bulletin* **32**, 123–131.

Reinares M, Papachristou E, Harvey P, Mar Bonnín C, Sánchez-Moreno J, …Frangou S (2013). Towards a clinical staging for bipolar disorder: defining patient subtypes based on functional outcome. *Journal of affective disorders* **144**, 65–71. doi: 10.1016/j.jad.2012.06.005.

Reitan R (1958). Validity of the trail making test as a indication of organic brain damage. *Percept Mot Skills* **8**, 271–276.

Rey A (1997). *Test de copia de una figura compleja. Manual adaptación española.* Ed. T Ediciones. Madrid.

Rodewald K, Holt D V., Rentrop M, Roesch-Ely D, Liebrenz M, Funke J, … Kaiser S (2014). Predictors for Improvement of Problem-Solving during Cognitive Remediation for Patients with Schizophrenia. *Journal of the International Neuropsychological Society* **20**, 455–460. doi: 10.1017/S1355617714000162.

Rosa AR, Sánchez-Moreno J, Martínez-Aran A, Salamero M, Torrent C, Reinares M, …Vieta E (2007). Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. *Clinical Practice and Epidemiology in Mental Health* **3**, 5.

Roux P, Raust A, Cannavo AS, Aubin V, Aouizerate B, Azorin J-M, …Passerieux C (2017). Cognitive profiles in euthymic patients with bipolar disorders: results from the FACE-BD cohort. *Bipolar Disorders* **19**, 146–153. doi: 10.1111/bdi.12485.

Salagre E, Solé B, Tomioka Y, Fernandes BS, Hidalgo-Mazzei D, Garriga M, …Grande I (2017).

Treatment of neurocognitive symptoms in unipolar depression: A systematic review and future perspectives. *Journal of Affective Disorders* **221**, 205–221. doi: 10.1016/j.jad.2017.06.034.

Salagre E, Arango C, Artigas F, Ayuso-Mateos JL, Bernardo M, Castro-Fornieles J, …Vieta E (2019). CIBERSAM: Ten years of collaborative translational research in mental disorders. *Rev Psiquiatr Salud Ment* **12(1):**1-8. doi: 10.1016/j.rpsm.2018.10.001.

Sanchez-Moreno J, Bonnín C, González-Pinto A, Amann BL, Solé B, Balanzá-Martínez V, …Torrent C, CIBERSAM Functional Remediation Group (2017a). Do patients with bipolar disorder and subsyndromal symptoms benefit from functional remediation? A 12-month follow-up study. Elsevier *European Neuropsychopharmacology* **27**, 350–359. doi: 10.1016/j.euroneuro.2017.01.010.

Sanchez-Moreno J, Bonnin CM, González-Pinto A, Amann BL, Solé B, Balanzá-Martinez V, …Vieta E (2018). Factors associated with poor functional outcome in bipolar disorder: sociodemographic, clinical, and neurocognitive variables. *Acta Psychiatrica Scandinavica* **138**, 145–154. doi: 10.1111/acps.12894.

Sanchez-Moreno J, Martinez-Aran A, Vieta E (2017b). Treatment of Functional Impairment in Patients with Bipolar Disorder. *Current Psychiatry Reports* **19**, 1–7. doi: 10.1007/s11920-017-0752-3.

Scheu F, Aghotor J, Pfueller U, Moritz S, Bohn F, Weisbrod M, Roesch-Ely D (2013). Predictors of performance improvements within a cognitive remediation program for schizophrenia. *Psychiatry Research* **209**, 375–380. doi: 10.1016/j.psychres.2013.04.015.

Solé B, Jiménez E, Torrent C, Reinares M, Bonnin CDM, Torres I, … Vieta E (2017). Cognitive impairment in bipolar disorder: Treatment and prevention strategies. *International Journal of Neuropsychopharmacology* **20**, 670–680. doi: 10.1093/ijnp/pyx032.

Stern Y (2006). Cognitive reserve and Alzheimer disease. *Alzheimer disease and associated disorders* **20**, S69-74.

Torrent C, Bonnin C del M, Martínez-Arán A, Valle J, Amann BL, González-Pinto A, …Vieta E (2013). Efficacy of functional remediation in bipolar disorder: a multicenter randomized controlled study. *The American journal of psychiatry* **170**, 852–9. doi: 10.1176/appi.ajp.2012.12070971.

Torrent C and Vieta E (2015). Lifting the burden of bipolar disorder: The role of

psychotherapies. *The Australian and New Zealand journal of psychiatry* **49(8),** 754–755. doi: 10.1177/0004867415587746.

Torres IJ, Kozicky J, Popuri S, Bond DJ, Honer WG, Lam RW, Yatham LN (2014). 12-month longitudinal cognitive functioning in patients recently diagnosed with bipolar disorder. *Bipolar disorders* **16**, 159–71.

Twamley EW, Burton CZ, Vella L (2011). Compensatory cognitive training for psychosis: Who benefits? who stays in treatment? *Schizophrenia Bulletin* **37**, 55–62. doi: 10.1093/schbul/sbr059.

Vieta E (2011). Bipolar units and programmes: are they really needed? *World Psychiatry* **10**, 152–152.

Vieta E, Torrent C, Martinez-Arán A (2014). *Functional Remediation for Bipolar Disorder*. Cambridge University Press.

Vita A, Deste G, De Peri L, Barlati S, Poli R, Cesana BM, Sacchetti E (2013). Predictors of cognitive and functional improvement and normalization after cognitive remediation in patients with schizophrenia. . Elsevier B.V. *Schizophrenia Research* **150**, 51–57. doi: 10.1016/j.schres.2013.08.011.

Wechsler D (1997). *The Wechsler Adult Intelligence Scale- III (WAIS- III).*

Young RC, Biggs JT, Ziegler VE, Meyer DA (1978). A rating scale for mania: Reliability, validity and sensitivity. *British Journal of Psychiatry* **133***,* 429-35.

Zyto S, Jabben N, Schulte PFJ, Regeer BJ, Kupka RW (2016). A pilot study of a combined group and individual functional remediation program for patients with bipolar i disorder. . Elsevier *Journal of Affective Disorders* **194**, 9–15. doi: 10.1016/j.jad.2016.01.029.

Figure 1. Patients' flow chart

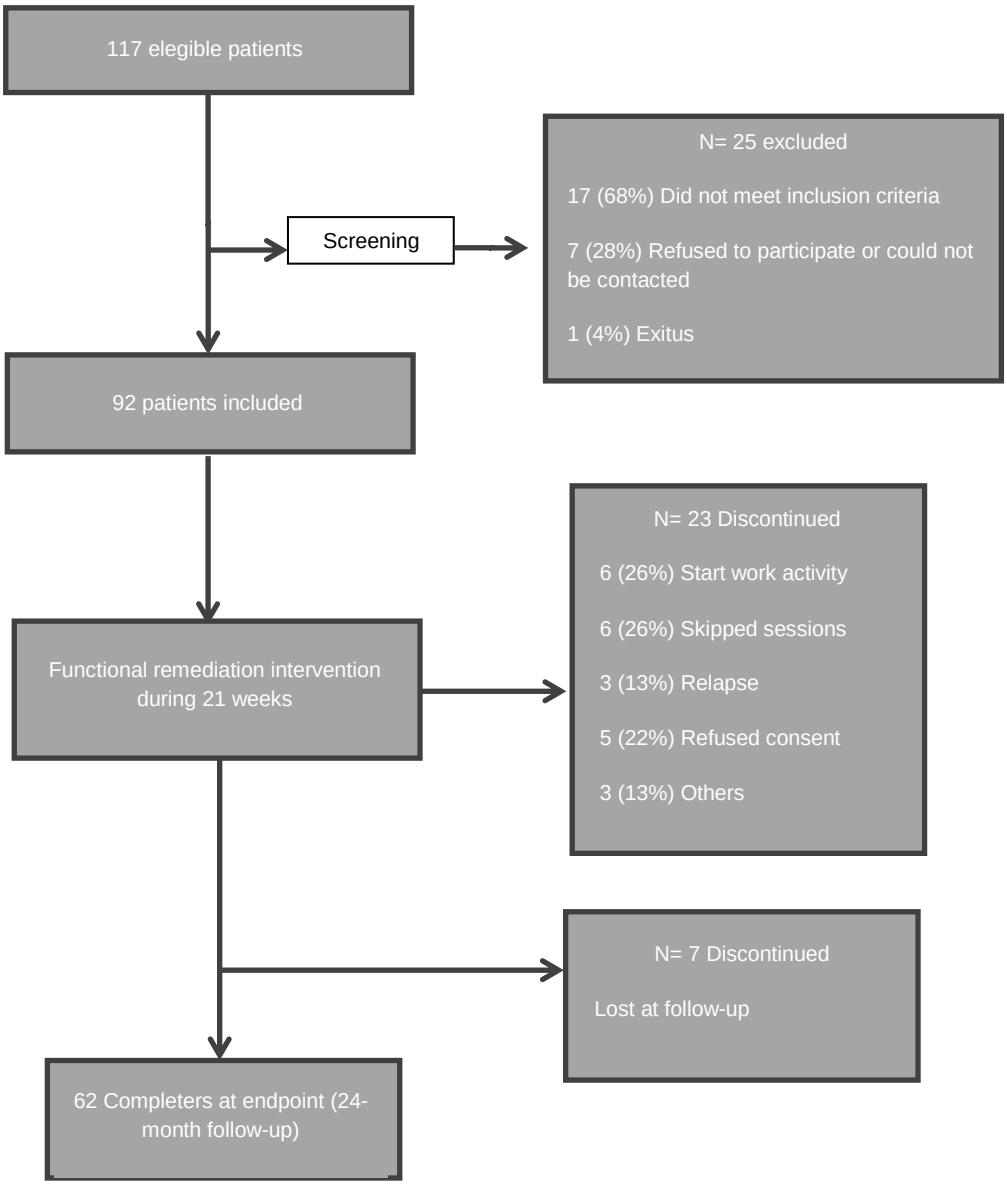

Table 1. Demographic and clinical characteristics of the sample at baseline.

	Bipolar patients (n=92)
	Mean (SD) 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 Scale, IQ: Intelligence quotient, SD: Standard deviation, YMRS: Young Mania Rating Scale, ,

Table 2. Neurocognitive variables at baseline.

	Bipolar patients (n=92)
	Mean (SD)
Cognition	
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, ROFC: Osterrieth Rey Figure, SCWT: Stroop Colour Word Test, TMT: Trail Making Test, WAIS-III: Wechsler Adult Intelligence Test-III, WCST: Wisconsin Card sorting Test.

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
Number total 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**		

Footnotes: FAST: Functional Assessment Short Test; HDRS: Hamilton Depression Rating Scale; SCWT: Stroop Colour Word Test

Title: 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 a main objective in clinical practice. Of the few psychosocial interventions that have been specifically developed to enhance 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 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 (FAST). 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 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.

Key words: bipolar disorder, cognition, functioning, functional remediation, cognitive 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 (Martínez-Arán *et al.,* 2004)(Bourne et al., 2013). Although these deficits can be present from the onset of the disease, some cognitive deficits may improve in patients who maintain remission after 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 (Iosifescu, 2012)(Sanchez-Moreno, Martinez-Aran, & Vieta, ~~*et al.,*~~ 2017b)(Depp & Mausbach, 2012). 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 (Mackala, Torres, Kozicky, Michalak, & Yatham ~~et al.~~, 2014)(Brissos, Dias, & Kapczinski ~~et al.~~, 2008). 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 ~~et al.~~, 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 with BD, and those have yielded mixed findings. Most of them showed positive results (Torrent *et al.,* 2013)(Zyto, Jabben, Schulte, Regeer, & Kupka ~~et al.~~, 2016)(Lewandowski *et al.,* 2017), 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 ~~et al.~~, 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 vs. 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, 2011)(Torrent & Vieta, 2015). FR was shown to be effective at improving functioning (Torrent *et al.,* 2013) in a randomized controlled trial with three intervention arms, and its effects were maintained over time (Bonnin et al., 2016). FR was also shown to improve the verbal memory domain in truly neurocognitively impaired patients (Bonnin et al., 2016), and was also effective for patients with subsyndromal symptomatology (Sanchez-Moreno et al., 2017).

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 (Reeder, Smedley, Butt, Bogner, & Wykes ~~et al.~~, 2006)(Vita *et al.,* 2013)(Kurtz, Seltzer, Fujimoto, Shagan, & Wexler ~~et al.~~, 2009)(Farreny *et al.* 2016)(Fu *et al.,* 2015)(Scheu *et al.,* 2013)(Twamley, Burton, & Vella ~~et al.~~, 2011)(Medalia & Richardson, 2005)(Lindenmayer *et al.,* 2017), 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 ≥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 ~~et al.~~, 1978), both ≤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 manuscript and in the manual for FR (Vieta, Torrent, & Martinez-Aran, ~~*et al.,*~~ 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 hour 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 type of episode (manic, hypomanic or depressive), was collected through revision of medical records.

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 6 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 to 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 Intelligence Quotient (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, with the processing speed index (PS) 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, with the working memory (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, ~~et al.,~~ 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 (WCST) (Heaton, 1993), 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 (COWAT) (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 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 literature to influence functioning. To avoid multicollinearity, we required all variables in the model to have variance inflation factor values (VIF) below 5. For these analyses, the last observation carried forward (LOCF) 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 on figure 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 (Figure 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; SD=3.43) compared to the non-completers (mean=12.22; SD=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, SD=8.73), mostly unemployed (76.1%) and the mean years of education was 13.64 (SD=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 regards to affective symptomatology, the HDRS mean score at baseline was 6.24 (SD=3.17) and 5.73 (SD=4.94) at endpoint, and 1.65 (SD=1.78) and 2.46 (SD=3.42) for the YMRS. Concerning neurocognitive performance at 24-month follow-up, we found an improvement in different neurocognitive variables such as processing speed index (p=0.033), working memory index (p=0.022), TMT-A (p=0.011), all CVLT measures (p≤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 (SD=8.12), whereas this score was reduced by more than 5 points at endpoint (mean=28.04; SD=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), processing speed (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, Processing speed 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 (β=-0.255, t=-2.011, p=0.049) and the interference Stroop measure (β=-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: β=-0.474, t= -3.531, P=0.001; verbal memory: β=-0.332, t=-2.222, P=0.032), and none of the comorbidity and medication variables achieved statistical significance (smallest P=0.172).

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 functional remediation. 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 (Medalia & Richardson, 2005)(Lindenmayer *et al.,* 2017)(Kurtz *et al.,* 2009)(Farreny *et al.,* 2016)(Vita *et al.,* 2013)(Fiszdon, Cardenas, Bryson, & Bell ~~et al.~~, 2005). Our findings would be aligned, in part, with these latter studies; that is, better performance in verbal memory and executive function at baseline were significant predictors of better functioning at two 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 a 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 E, & Mur ~~*et al.*~~, 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)(Bonnin et al., 2016b). Lastly, we also found significant correlations between higher processing speed and visual memory scores with lower scores on the FAST scale at 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 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., 2017). 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 (Vita *et al.,* 2013)(Lindenmayer *et al.,* 2017)(Rodewald *et al.,* 2014). 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. 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). High cognitive reserve has potentially been seen to protect against neurocognitive and psychosocial impairment in euthymic patients with BD (Grande *et al.,* 2017) (Forcada *et al.,* 2015). Our finding may suggest that patients with more years of formal education may be more used to receiving 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 (Torrent *et al.,* 2013)(Bonnin et al., 2016). 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 psychosocial outcome (Nakagami, Xie, Hoe, & Brekke ~~et al.~~, 2008). Other potential mediating variables to be considered in further studies would be 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.). ~~Participants in the study were on a variety of different combinations of pharmacological treatment which meant that pharmacotherapy was not controlled for. Nevertheless, the sample would be representative of the patients seen in~~

~~clinical practice.~~ 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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Conflict of interest

Dr. Vieta has received grants and served as consultant, advisor or CME speaker for the following entities: AB-Biotics, Abbott, Allergan, Angelini, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Farmindustria, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, SAGE, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, the Brain and Behaviour Foundation, the Generalitat de Catalunya (PERIS), the Spanish Ministry of Science and Innovation (CIBERSAM), EU Horizon 2020, and the Stanley Medical Research Institute.

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The other authors declare no conflict of interest related to this manuscript.

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."

Benton A, Hamsher K (1976). *Multilingual Aphasia Examination*. University of Iowa: Iowa City.

Bonnín CM, Martínez-Arán A, Torrent C, Pacchiarotti I, Rosa AR, Franco C,… Vieta E (2010). Clinical and neurocognitive predictors of functional outcome in bipolar euthymic patients: A long-term, follow-up study. Elsevier B.V. *Journal of Affective Disorders* **121**, 156–160. doi: 10.1016/j.jad.2009.05.014.

Bonnin CM, Reinares M, Martinez-Aran A, Balanza-Martinez V, Sole B, Torrent C, … Vieta E (2016a). Effects of functional remediation on neurocognitively impaired bipolar patients: enhancement of verbal memory. *Psychological medicine* **46**, 291–301. doi: 10.1017/S0033291715001713.

Bonnin CM, Reinares M, Martínez-Arán A, Balanzá-Martínez V, Sole B, Torrent C, …Vieta E, CIBERSAM Functional Remediation Group (2016b). Effects of functional remediation on neurocognitively impaired bipolar patients: enhancement of verbal memory. *Psychological medicine* **46**, 291–301.

Bonnin CM, Torrent C, Arango C, Amann BL, Sole B, Gonzalez-Pinto A, … Martinez-Aran A (2016c). Functional remediation in bipolar disorder: 1-year follow-up of neurocognitive and functional Outcome. *British Journal of Psychiatry* **208**, 87–93. doi: 10.1192/bjp.bp.114.162123.

Bourne C, Aydemir O, Balanza-Martinez V, Bora E, Brissos S, Cavanagh JTO, … Goodwin GM (2013a). Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: An individual patient data meta-analysis. *Acta Psychiatrica Scandinavica* **128**, 149–162. doi: 10.1111/acps.12133.

Brissos S, Dias VV, Kapczinski F (2008). Cognitive performance and quality of life in bipolar disorder. *Canadian Journal of Psychiatry* **53**, 517–524.

Burdick KE, Russo M, Frangou S, Mahon K, Braga RJ, Shanahan M, Malhotra AK (2014). Empirical evidence for discrete neurocognitive subgroups in bipolar disorder: clinical implications. *Psychological Medicine*, 1–14. doi: 10.1017/S0033291714000439.

Colom F, Vieta E, Martínez-Arán A, Garcia-Garcia M, Reinares M, Torrent C, … Salamero M (2002). Spanish version of a scale for the assessment of mania: Validity and reliability of the Young Mania Rating Scale. *Medicina Clinica,* **119**, 366-71.

Conners C (2000). *Conner's Continuous Performances Test for Win dows (CPT-II).*

Delis D, Kramer J, Kaplan E, Ober B (1987). California Verbal Learning Test (CVLT) Manual. *The*

Psychological Corporation.

Demant KM, Vinberg M, Kessing L V, Miskowiak KW (2015). Effects of Short-Term Cognitive Remediation on Cognitive Dysfunction in Partially or Fully Remitted Individuals with Bipolar Disorder: Results of a Randomised Controlled Trial. *PloS one* **10**, e0127955. doi: 10.1371/journal.pone.0127955. eCollection 2015

Depp C, Mausbach B (2012). Meta-analysis of the association between cognitive abilities and everyday functioning in bipolar disorder. *Bipolar Disord.* **14**, 217–226. doi: 10.1111/j.1399-5618.2012.01011.x.

Farreny A, Aguado J, Corbera S, Ochoa S, Huerta-Ramos E, Usall J (2016). Baseline predictors for success following strategy-based cognitive remediation group training in schizophrenia. *Journal of Nervous and Mental Disease* **204**, 585–589. doi: 10.1097/NMD.0000000000000509.

First MB (1997). Structured clinical interview for DSM-IV axis I disorders. *Biometrics Research Department.*

Fiszdon JM, Cardenas AS, Bryson GJ, Bell MD (2005). Predictors of remediation success on a trained memory task. *Journal of Nervous and Mental Disease* **193**, 602–608.

Forcada I, Mur M, Mora E, Vieta E, Bartrés-Faz D, Portella MJ (2015). The influence of cognitive reserve on psychosocial and neuropsychological functioning in bipolar disorder. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology* **25**, 214–22. doi: 10.1016/j.euroneuro.2014.07.018.

Fu DJ, Turkoz I, Simonson RB, Walling DP, Schooler NR, Lindenmayer JP, … Alphs L (2015). Paliperidone Palmitate once-monthly reduces risk of relapse of psychotic, depressive, and manic symptoms and maintains functioning in a double-blind, randomized study of schizoaffective disorder. *Journal of Clinical Psychiatry* **76**, 253–262. doi: 10.4088/JCP.14m09416.

Golden CJ (1978). Stroop Color and Word Test: A manual for clinical and experimental uses. *Chicago: Stoelting.*

Grande I, Sanchez-Moreno J, Sole B, Jimenez E, Torrent C, Bonnin CM, … Martinez-Aran A (2017). High cognitive reserve in bipolar disorders as a moderator of neurocognitive impairment. *Journal of Affective Disorders* **208**, 621–627. doi: 10.1016/j.jad.2016.10.012.

Hamilton M (1960). A rating scale for depression. *Journal of neurology, neurosurgery, and*

psychiatry **23**, 56-62.

Heaton R (1993). Wisconsin card sorting test: Computer version 4. *Psychological Assessment Resources.*

Ehrminger M, Brunet-Gouet E, Cannavo AS, Aouizerate B, Cussac I, Azorin JM, …Olié E; FondaMental Advanced Centers of Expertise in Bipolar Disorders (FACE-BD) Collaborators, Passerieux C, Roux P (2019). Longitudinal relationships between cognition and functioning over 2 years in euthymic patients with bipolar disorder: a cross-lagged panel model approach with the FACE-BD cohort. *The British Journal of Psychiatry* **13,**1-8. doi: 10.1192/bjp.2019.180.

Iosifescu D V. (2012). The relation between mood, cognition and psychosocial functioning in psychiatric disorders. Elsevier *European Neuropsychopharmacology* **22**, S499–S504.

Jimenez E, Arias B, Castellvi P, Goikolea JM, Rosa AR, Fananas L,… Benabarre A (2012). Impulsivity and functional impairment in bipolar disorder. *Journal of affective disorders* **136**, 491–497. doi: 10.1016/j.jad.2011.10.044.

Kahn RS, Sommer IE, Murray RM, Meyer-Lindenberg A, Weinberger DR, Cannon TD, … Insel TR (2015). Schizophrenia. *Nature reviews. Disease primers* **1**, 15067. doi: 10.1038/nrdp.2015.67.

Kozicky J-M, Torres IJ, Silveira LE, Bond DJ, Lam RW, Yatham LN (2014). Cognitive change in the year after a first manic episode: association between clinical outcome and cognitive performance early in the course of bipolar I disorder. *The Journal of clinical psychiatry* **75**, e587-93. doi: 10.4088/JCP.13m08928.

Kurtz MM, Seltzer JC, Fujimoto M, Shagan DS, Wexler BE (2009). Predictors of change in life skills in schizophrenia after cognitive remediation. *Schizophrenia Research* **107**, 267–274. doi: 10.1016/j.schres.2008.10.014.

Lewandowski KE, Sperry SH, Cohen BM, Norris LA, Fitzmaurice GM, Ongur D, Keshavan MS (2017). Treatment to enhance cognition in bipolar disorder (TREC-BD): Efficacy of a randomized controlled trial of cognitive remediation versus active control. *Journal of Clinical Psychiatry* **78**, e1242-e1249. doi: 10.4088/JCP.17m11476.

Lindenmayer JP, Ozog VA, Khan A, Ljuri I, Fregenti S, McGurk SR (2017). Predictors of response to cognitive remediation in service recipients with severe mental illness. *Psychiatric Rehabilitation Journal* **4**0, 61–69. doi: 10.1037/prj0000252.

Kurtz MM (2012). Cognitive remediation for schizophrenia: Current status, biological correlates and predictors of response. *Expert Review of Neurotherapeutics* **12**, 813–821. doi: 10.1586/ern.12.71.

Mackala SA, Torres IJ, Kozicky J, Michalak EE, Yatham LN (2014). Cognitive performance and quality of life early in the course of bipolar disorder. Elsevier *Journal of Affective Disorders* **168**, 119–124. doi: 10.1016/j.jad.2014.06.045.

Martínez-Arán A, Torrent C, Solé B, Bonnín CM, Rosa AR, Sánchez-Moreno J, Vieta E (2011). Functional Remediation for Bipolar Disorder. *Clinical Practice & Epidemiology in Mental Health* **7**, 112–116. doi: 10.2174/1745017901107010112.

Martínez-Arán A, Vieta E, Reinares M, Colom F, Torrent C, Sánchez-Moreno J…Salamero M (2004). Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. *The American journal of psychiatry* **161**, 262–70.

Martino DJ, Marengo E, Igoa A, Scápola M, Ais ED, Perinot L, Strejilevich SA (2009). Neurocognitive and symptomatic predictors of functional outcome in bipolar disorders: a prospective 1 year follow-up study. *Journal of affective disorders* **116**, 37–42. doi: 10.1016/j.jad.2008.10.023.

Medalia A, Richardson R (2005). What predicts a good response to cognitive remediation interventions? *Schizophrenia Bulletin* **31**, 942–953.

Miskowiak KW, Carvalho AF, Vieta E, Kessing L V (2016a). Cognitive enhancement treatments for bipolar disorder: A systematic review and methodological recommendations. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology* **26**, 1541-61. doi: 10.1016/j.euroneuro.2016.08.011.

Miskowiak KW, Petersen JZ, Ott CV, Knorr U, Kessing LV, Gallagher P, Robinson L (2016b)**.** Predictors of the discrepancy between objective and subjective cognition in bipolar disorder: a novel methodology. *Acta Psychiatrica Scandinavica* **134,** 511-21. doi: 10.1111/acps.12649.

Mora E, Portella MJ, Forcada I, Vieta E, Mur M (2013). Persistence of cognitive impairment and its negative impact on psychosocial functioning in lithium-treated, euthymic bipolar patients: a 6-year follow-up study. *Psychological medicine* **43**, 1187–96. doi: 10.1017/S0033291712001948.

Nakagami E, Xie B, Hoe M, Brekke JS (2008). Intrinsic motivation, neurocognition and

psychosocial functioning in schizophrenia: Testing mediator and moderator effects. *Schizophrenia Research* **105**, 95–104. doi: 10.1016/j.schres.2008.06.015.

Newman AL, Meyer TD (2014). Impulsivity: present during euthymia in bipolar disorder? - a systematic review. *International journal of bipolar disorders* **2**, 2. doi: 10.1186/2194-7511-2-2. eCollection 2014.

Penades R, Lopez-Vilchez I, Catalan R, Arias B, Gonzalez-Rodriguez A, Garcia-Rizo C, … Bernardo M (2017). BDNF as a marker of response to cognitive remediation in patients with schizophrenia: A randomized and controlled trial. *Schizophrenia* research **197**, 458-464. doi: 10.1016/j.schres.2017.12.002.

Reeder C, Smedley N, Butt K, Bogner D, Wykes T (2006). Cognitive predictors of social functioning improvements following cognitive remediation for schizophrenia. *Schizophrenia Bulletin* **32**, 123–131.

Reinares M, Papachristou E, Harvey P, Mar Bonnín C, Sánchez-Moreno J, …Frangou S (2013). Towards a clinical staging for bipolar disorder: defining patient subtypes based on functional outcome. *Journal of affective disorders* **144**, 65–71. doi: 10.1016/j.jad.2012.06.005.

Reitan R (1958). Validity of the trail making test as a indication of organic brain damage. *Percept Mot Skills* **8**, 271–276.

Rey A (1997). *Test de copia de una figura compleja. Manual adaptación española.* Ed. T Ediciones. Madrid.

Rodewald K, Holt D V., Rentrop M, Roesch-Ely D, Liebrenz M, Funke J, … Kaiser S (2014). Predictors for Improvement of Problem-Solving during Cognitive Remediation for Patients with Schizophrenia. *Journal of the International Neuropsychological Society* **20**, 455–460. doi: 10.1017/S1355617714000162.

Rosa AR, Sánchez-Moreno J, Martínez-Aran A, Salamero M, Torrent C, Reinares M, …Vieta E (2007). Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. *Clinical Practice and Epidemiology in Mental Health* **3**, 5.

Roux P, Raust A, Cannavo AS, Aubin V, Aouizerate B, Azorin J-M, …Passerieux C (2017). Cognitive profiles in euthymic patients with bipolar disorders: results from the FACE-BD cohort. *Bipolar Disorders* **19**, 146–153. doi: 10.1111/bdi.12485.

Salagre E, Solé B, Tomioka Y, Fernandes BS, Hidalgo-Mazzei D, Garriga M, …Grande I (2017).

Treatment of neurocognitive symptoms in unipolar depression: A systematic review and future perspectives. *Journal of Affective Disorders* **221**, 205–221. doi: 10.1016/j.jad.2017.06.034.

Salagre E, Arango C, Artigas F, Ayuso-Mateos JL, Bernardo M, Castro-Fornieles J, …Vieta E (2019). CIBERSAM: Ten years of collaborative translational research in mental disorders. *Rev Psiquiatr Salud Ment* **12(1):**1-8. doi: 10.1016/j.rpsm.2018.10.001.

Sanchez-Moreno J, Bonnín C, González-Pinto A, Amann BL, Solé B, Balanzá-Martínez V, …Torrent C, CIBERSAM Functional Remediation Group (2017a). Do patients with bipolar disorder and subsyndromal symptoms benefit from functional remediation? A 12-month follow-up study. Elsevier *European Neuropsychopharmacology* **27**, 350–359. doi: 10.1016/j.euroneuro.2017.01.010.

Sanchez-Moreno J, Bonnin CM, González-Pinto A, Amann BL, Solé B, Balanzá-Martinez V, …Vieta E (2018). Factors associated with poor functional outcome in bipolar disorder: sociodemographic, clinical, and neurocognitive variables. *Acta Psychiatrica Scandinavica* **138**, 145–154. doi: 10.1111/acps.12894.

Sanchez-Moreno J, Martinez-Aran A, Vieta E (2017b). Treatment of Functional Impairment in Patients with Bipolar Disorder. *Current Psychiatry Reports* **19**, 1–7. doi: 10.1007/s11920-017-0752-3.

Scheu F, Aghotor J, Pfueller U, Moritz S, Bohn F, Weisbrod M, Roesch-Ely D (2013). Predictors of performance improvements within a cognitive remediation program for schizophrenia. *Psychiatry Research* **209**, 375–380. doi: 10.1016/j.psychres.2013.04.015.

Solé B, Jiménez E, Torrent C, Reinares M, Bonnin CDM, Torres I, … Vieta E (2017). Cognitive impairment in bipolar disorder: Treatment and prevention strategies. *International Journal of Neuropsychopharmacology* **20**, 670–680. doi: 10.1093/ijnp/pyx032.

Stern Y (2006). Cognitive reserve and Alzheimer disease. *Alzheimer disease and associated disorders* **20**, S69-74.

Torrent C, Bonnin C del M, Martínez-Arán A, Valle J, Amann BL, González-Pinto A, …Vieta E (2013). Efficacy of functional remediation in bipolar disorder: a multicenter randomized controlled study. *The American journal of psychiatry* **170**, 852–9. doi: 10.1176/appi.ajp.2012.12070971.

Torrent C and Vieta E (2015). Lifting the burden of bipolar disorder: The role of

psychotherapies. *The Australian and New Zealand journal of psychiatry* **49(8),** 754–755. doi: 10.1177/0004867415587746.

Torres IJ, Kozicky J, Popuri S, Bond DJ, Honer WG, Lam RW, Yatham LN (2014). 12-month longitudinal cognitive functioning in patients recently diagnosed with bipolar disorder. *Bipolar disorders* **16**, 159–71.

Twamley EW, Burton CZ, Vella L (2011). Compensatory cognitive training for psychosis: Who benefits? who stays in treatment? *Schizophrenia Bulletin* **37**, 55–62. doi: 10.1093/schbul/sbr059.

Vieta E (2011). Bipolar units and programmes: are they really needed? *World Psychiatry* **10**, 152–152.

Vieta E, Torrent C, Martinez-Arán A (2014). *Functional Remediation for Bipolar Disorder*. Cambridge University Press.

Vita A, Deste G, De Peri L, Barlati S, Poli R, Cesana BM, Sacchetti E (2013). Predictors of cognitive and functional improvement and normalization after cognitive remediation in patients with schizophrenia. . Elsevier B.V. *Schizophrenia Research* **150**, 51–57. doi: 10.1016/j.schres.2013.08.011.

Wechsler D (1997). *The Wechsler Adult Intelligence Scale- III (WAIS- III).*

Young RC, Biggs JT, Ziegler VE, Meyer DA (1978). A rating scale for mania: Reliability, validity and sensitivity. *British Journal of Psychiatry* **133***,* 429-35.

Zyto S, Jabben N, Schulte PFJ, Regeer BJ, Kupka RW (2016). A pilot study of a combined group and individual functional remediation program for patients with bipolar i disorder. . Elsevier *Journal of Affective Disorders* **194**, 9–15. doi: 10.1016/j.jad.2016.01.029.

May 18th 2020
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Dear Editor-in-Chief
Prof. Robin M Murray

Thank you for considering our manuscript PSM-D-19-01588 entitled "LONG-TERM OUTCOME PREDICTORS AFTER FUNCTIONAL REMEDIATION IN PATIENTS WITH BIPOLAR DISORDER" for further revision in Psychological Medicine. We are grateful to the reviewers for their effort and comments and we appreciate that many of the changes that they suggested have contributed to improve our manuscript. We have adjusted the text according to their suggestions as appropriate. The changes appear detailed below in response to each of the reviewers' comments.
Please find our responses in bold facetypes. We hope that the current version of the paper will be suitable for publication in your journal.

REVIEWER 1:

Excellent article, very well elaborated, well-written, clear and relevant. The subject is presented in a succinct but sufficient way. The article definitely contributes to the knowledge in the field.

Thanks for all your positive comments.

-One critic would be that in the limits or in the choice of the analysis method, it could have been interesting to comment on the fact that the functional outcome measure, the FAST, also includes a measure of neurocognitive variables, which creates an overlap with cognitive functions. They do not appear to be completely independent.

Thank for this clarification. We have added in the Methods section (Measures subsection; page 6) a brief comment about this (see below), as the reviewer suggested. Even so, we should keep in mind that neurocognitive variables are objective measures and the cognitive

FAST domain is based on patient's self-reported cognitive complaints and the clinician's subjective appraisal during a structured interview, since it is an interviewer-administered tool. Therefore, although it intends to be as objective as possible, it is not based on patient's objective performance as the performance in neuropsychological tests. Moreover, there is compiling evidence for a discrepancy between objective and subjective cognitive measures, with studies showing controversial results. Most of them have indicated a partial association or lack of correspondence between patients' reports complaints using subjective screening tools specifically designed for it and the objective performance in neuropsychological tests (e.g. Burdick et al., 2005; Martinez-Aran et al., 2005; van der Werf-Eldering et al. 2011; Svendensen et al., 2012; Jensen et al., 2015Miskowiak et al., 2016).

-*"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 several studies there is only partial correspondence between objective and subjective cognitive measures (Miskowiak et al., 2016)."*

REVIEWER 2:

Dear authors,

Thank you for letting me review this interesting article. I have a few suggestions to make to improve your manuscript.

-First, the literature review lacks some recent studies dealing with the topic (for instance, Ehrminger 2019 used longitudinal SEM models to study the relationships between cognition and functioning). You should then consider updating your review with those more recent papers.

Thanks for this suggestion. Indeed, the article is very interesting and related with the topic of our study. Therefore, we have updated our manuscript including a reference to this study in the introduction section (page 3, first paragraph), as follows: *"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)".*

-Then, did you measure cognitive variables at the 24 month-follow-up or did you only measure functioning at this time-point? If you did, it would be interesting to see how cognitive performances evolved during the 2 years of follow-up.

We also measured cognitive variables at the 24-month follow-up. We did not include this information on the previous version of the manuscript since our variable of interest, the main outcome, was functional outcome. Nonetheless, following the reviewer's suggestion, we have now included a brief summary about changes in cognitive variables, as follows: (in page 8, Results section): ***"Concerning neurocognitive performance at 24-month follow-up, we found an improvement in different neurocognitive variables such as processing speed index (p=0.033), working memory index (p=0.022), TMT-A (p=0.011), all CVLT measures (p≤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)".***

-Also, it is not clear whether the depression score you included in your regression model is the score at baseline or at follow-up. As depressive symptoms can fluctuate pretty much, is it really relevant to include depression at baseline as a regressor of the outcome 2 years later? I think it's more relevant to include current depressive symptoms as a covariate in the model, i.e. depression at follow-up (concurrent to the final outcome measure), as depression was previously found to be a cross-sectional determinant of functioning.

Thanks to the reviewer to bring up this point. We fully agree that current subclinical depressive symptoms could also be introduced in the regression model as a covariate since it is well known that is a relevant predictive factor of psychosocial functioning. This could have been a valid alternative. Even so, according to the objective of our study, we included the subclinical depressive symptoms at baseline in order to see if it could be a potential predictor together with other clinical and neurocognitive variables. In the same way, in previous literature, other studies also included this variable at baseline, showing that subclinical depressive symptomatology is a significant predictor of long-term functional outcome (Bonnin et al., 2010; Martino et al., 2009). To avoid confusion, we have clarified in the manuscript that depressive symptomatology included in the regression model was the score at baseline (on page 9, Regression model subsection).

-Finally, it would also have been interesting to see how those increases in FAST translate into real-world measures of functioning (employment, marital statuts, ...), as the FAST score is only in part objective, and largely depends on the clinician's perception of what the patient reports. For instance, to the best of my knowledge, the cognitive component of the FAST is only mildly

correlated with the actual cognitive performance of the subject, as the FAST Cognition score only reflects what the clinician perceives of a patient's self-reported cognitive complaint. Thus, it would be interesting to measure the objective functional outcomes at 24 months and integrate them in your analyses to see how FR improves them and to investigate the determinants of the putative changes. If you cannot do so, please ensure you mention it in the limitations, because the FAST is not a totally objective means of measuring functional outcome.

We agree with the reviewer that it would have been interesting to measure and show these objective functional outcomes at 24 months and integrate them in our analyses. Unfortunately we don't have all these measures of functioning to show how changes in the FAST scale translate into real-world functioning. Therefore, we have mentioned this issue in the limitations section (page 12) (see below). Nevertheless, we would like to underscore that the FAST occupational domain takes into account, at least in part, the employment status. Scores in items throughout the occupational domains varies according to employment status.

"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.)."

-These are minor suggestions, and I don't think these will be a major issue for you to take into account. Other than that, most biases and limitations are acknowledged and the work is interesting.

We really appreciate your comments and suggestions that, for sure, will contribute to improve our manuscript.

REVIEWER 3:

This article focused on an interesting topic about which pre-intervention variables affect BD patients' response to functional rehabilitation. I have some concerns for statistical analysis of the study.

Major:

1. It seems that the "62 Completers" were fitted in a regression model. The authors should conduct a power analysis to determine the appropriate sample size of this analysis since so many predictors with certain levels were included in the model.

Following the reviewer suggestion, we have conducted a power analysis.

With the "pwr.f2.test" function for R (Champeley, 2020), we estimated that a multiple regression with 6 regressors and 60 individuals has 97.6% statistical power to detect an effect size Cohen's f^2 = 0.453 (corresponding to explaining R^2 = 31.2% of variance).

[REF]: Stephane Champely (2020). pwr: Basic Functions for Power Analysis. R package version 1.3-0. https://CRAN.R-project.org/package=pwr

2. Considering that there was only one single small sample in the current research and there were other related variables (for example, medication and somatic comorbidities) that were not well controlled, a validation data set would be necessary. If there is no available independent validation sample, one suggestion is that another regression model with the FAST change score as the outcome variable and change scores of other related variables as the predictor could be one resolution for this concern.

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: β=-0.474, t= -3.531, P=0.001; verbal memory: β=-0.332, t=-2.222, P=0.032), and none of the comorbidity and medication variables achieved statistical significance (smallest P=0.172). We have added this same information in the Results section (page 9).

Minor

1. What the control-group participants were doing when the intervention-group participants undertook FR should be briefly introduced. If the current study included only the patients who received FR intervention in the previous RCT study, it should be clearly stated in the article.

The efficacy of Functional Remediation was published some years ago in a multicenter (10 sites) randomized controlled trial with 2 comparator groups: a group which only received pharmacological treatment as usual and another one with psychoeducation (Torrent et al., 2013). After that, FR was implemented in our united care with no other comparator arms. The sample size for this study was recruited in our center, as stated in the methods section *("…recruited from the Bipolar and Depressive Disorders Unit at the Hospital Clinic of Barcelona between September 2009 and February 2018…"),* therefore, the sample is not the same as in the previous RCT. Moreover, it was stated in the manuscript, in the limitation section, that the study lacked of a control group. However, we have clearly stated this issue

again in the intervention subsection within the methods section (page 5) as follows: "*After the baseline assessment, all participants received the FR program for 6 months, with no control group".*

2. "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 authors should explain why the one with the highest significant CVLT, instead of CVLT total score, was included in the regression model. What about other CVLT subtests?

Given the potential limitations derived from the sample size, we were only able to introduce a limited number of variables in the regression model (only six). Then, as CVLT includes several variables highly correlated between them, we considered more appropriate introducing only the variable more correlated with functioning to avoid multicollinearity between the independent variables. Additionally, when we run the partial correlations, the CVLT total score and CVLT short free recall were not correlated with the FAST total score. That is the reason why we did not introduce the CVLT total score in the regression model