Functional remediation for patients with bipolar II disorder: Improvement of functioning and subsyndromal symptoms

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1. Introduction

Bipolar disorder type II (BPII) has been often considered as a mild form of bipolar disorder type I (BPI). However, nowadays it is known that BPII is not a less impairing variant of bipolar disorder. The disease burden in BPII does not differ from that observed in BPI regarding clinical severity, impairment, patterns of comorbidity, suicide attempts, family history and treatment patterns (Merikangas et al., 2007). Moreover, a recent report has demonstrated that BPII patients are as functionally impaired as BPI (Rosa et al., 2010). Similarly, evidence from recent reviews focused on neurocognition suggests that both subtypes of bipolar disorders present with similar neurocognitive deficits, with BPII only showing subtle differences when compared to BPI (Sole et al., 2011;Bora et al., 2011). Furthermore, there exists also a link between neurocognitive deficits and daily functioning in bipolar disorder, similarly to that found in schizophrenia (Depp et al., 2012;Tabares-Seisdedos et al., 2008;Iosifescu, 2012). In fact, a study with a sample of BPII patients reported that impairment in executive functions as well as the presence of subthreshold depressive symptoms were the best predictors of psychosocial outcome (Sole et al., 2012).

Taking all these data into account, it seems necessary to implement therapies focused on enhancing functional outcome in bipolar disorder. In addition to cognitive remediation programs (Deckersbach et al., 2010), recently some psychological interventions, including mindfulness, have been used in order to improve cognition and functioning in bipolar disorder (Stange et al., 2011;Lahera et al., 2013). However, there is still a need for further innovative treatment approaches (Fuentes-Dura et al., 2012;Anaya et al., 2012), especially concerning to BPII population. In this sense, Martinez-Aran and colleagues proposed a new therapeutic intervention named Functional Remediation (FR), designed exclusively for bipolar patients, aimed at improving neurocognition in order to achieve a functional recovery (Martinez-Aran et al., 2011). The efficacy of this new intervention has been recently tested in a randomized controlled trial (RCT), suggesting that the FR program is a promising tool to ameliorate daily functioning in bipolar patients (Torrent et al., 2013). Nevertheless, RCTs devoted to analyze the impact of psychological therapies on BPII patients are scarce (Colom et al., 2009a). In fact, most available therapies targeting BP, derive from studies carried out with BPI or mixed samples of BPI and BPII patients. Therefore, it cannot be concluded whether therapies for BPII patients require adjustments to meet the specific needs showed by this group of patients or not.

Hence, the present subanalysis was aimed to assess the efficacy of the Functional Remediation program specifically in a sample of bipolar II patients concerning global psychosocial functioning, assessed by changes in the means of the Functioning Assessment Short Test (FAST). We hypothesized that bipolar II patients in the Functional Remediation group would experience greater improvement in global psychosocial functioning compared with the other two intervention groups (Psychoeducation and TAU).

2. Experimental procedures

This was a post-hoc, exploratory subanalysis of data obtained from a larger study focused on the efficacy of FR in the psychosocial functioning improvement in euthymic bipolar patients (Torrent et al., 2013). BPI and BPII patients were hereby randomized by means of a computer-generated sequence to either a structured psychoeducative intervention (PSY), or to join a group of patients only following pharmacological treatment as usual (TAU). It was designed as a multicenter, randomized, rater-blind outpatient trial conducted between 2009 and 2011, which was registered with the number NCT 01370668 in www.clinicaltrial.gov. Detailed explanations of the FR intervention and study procedures can be gathered from the original article (Torrent et al., 2013) and the FR manual (in press). The patients were mainly recruited from different specialised bipolar care centers in Spain (Vieta, 2013, 2011).

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2.1. Participants

From two hundred thirty-nine euthymic BPI or II patients enrolled in the original trial, 53 (22.2%) fulfilled criteria for BPII disorder and were included in this subanalysis. Current euthymia was defined as a score $\leq 6$ on the Young Mania Rating Scale (YMRS) (Colom et al., 2002; Young et al., 1978) and a score $\leq 8$ on the Hamilton Depression Scale (HAM-D) (Hamilton, 1960; Ramos-Brieva and Cordero, 1986). After the treatment phase of 6 months, 10 BPII patients dropped out from the study due to different reasons (for further details see Fig. 1).

The DSM-IV diagnosis of BPII was confirmed through a clinical interview based on the SCID (First et al., 1997). All patients were aged between 18 and 55 and they had to be euthymic for at least the last three months before randomization. Moreover, all patients presented a "moderate to severe" degree of functional impairment defined as a score $\geq 18$ on the Functioning Assessment Short Test (FAST) (Rosa et al., 2007). Exclusion criteria were: an estimated Intelligence Quotient (IQ) lower than 85, any medical condition that could affect neuropsychological performance, a serious comorbid psychiatric condition, patients who had received electroconvulsive therapy in the previous year and patients who received any structured psychological intervention during the previous two years.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice. The study protocol was approved by an independent ethics committee or an institutional review board at each study center. All patients received extensive information on the study and provided written informed consent prior to be included in the study.

2.2. Treatment

All participants received pharmacological treatment according to the guidelines for the management of bipolar disorder. Moreover, patients in the PSY and FR programs received additional group treatment. The principles of the PSY are extensively explained in the corresponding manual (Colom and Vieta, 2006). A manual for the FR is currently in press, but shortly explained the FR program is focused on the training of neurocognitive strategies in attention, memory and executive functions in order to improve daily functioning. The intervention consists of 21 weekly group sessions over six months. During this period, patients are instructed in a set of strategies and techniques within an ecological framework in order to foster their coping abilities with daily difficulties. More information can be gathered from the publication by Martinez-Aran and colleagues (Martinez-Aran et al., 2011; Torrent et al., 2013).

2.3. Primary outcome measure: functional outcome

The primary outcome measure was the achieved functional improvement after 6 months of treatment which was measured by means of changes in the FAST scores. The FAST is a 24-item scale assessing disability in patients with bipolar disorder and is a valid, reliable and sensitive to change instrument (Rosa et al., 2011). It assesses 6 functional domains, such as autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure. The FAST scores could range from 0 to 72 (higher scores indicate greater disability). It also provides a total global score and 6 subscores for every domain. Since changes detected in FAST scores were the primary outcome criteria of the original study, a single-blind evaluation was required.

2.4. Secondary outcome measures: subclinical symptoms and neurocognitive changes

Secondary outcome measures were changes on the subclinical symptoms, as measured by both the YMRS and the HAM-D, as well as changes in neurocognitive measures from baseline to the end of the intervention. All patients completed a comprehensive neuropsychological battery at pre and post-intervention, based on an extensive review of previous literature. Different tasks were selected to assess 6 cognitive domains (1) Estimated IQ, (2) Processing Speed Index, (3) Working Memory Index, (4) Visual/
Verbal Learning and Memory, (5) Executive Functions, and (6) Attention:

1. the estimated Intelligence Quotient (IQ) was calculated by the Wechsler Adult Intelligence Scale (WAIS-III) vocabulary subtest (Weschler, 1997b),
2. the Processing Speed Index consisted of two subtests from the WAIS-III: the Digit Symbol Coding and the Symbol Search (Weschler, 1997b),
3. the Working Memory Index, tested with three subtests from the WAIS-III: Arithmetic, Digits (forward and backwards) and Letter-Number Sequencing (Weschler, 1997b),
4. visual/verbal Learning and Memory was tested by: on the one hand the Rey Osterrieth Complex Figure (ROCF) (Rey, 1997) for the visual memory and, on the other hand, the California Verbal Learning Test (CVLT) (Delis et al., 1987) and the Logical Memory Scale (WMS-III) for the verbal learning/memory (Weschler, 1997a),
5. executive functions were composed by set shifting, verbal fluency (phonemic and semantic), planning and response inhibition using: the computerized Wisconsin Card sorting Test (WCST) (Heaton, 1981), the Stroop Colour-word Interference Test (SCWT) (Golden, 1978), the FAS and Animal Naming (Controlled Oral Word Association Test) (Benton and Hamsher, 1976), the Trail Making Test-part B (TMT-B) (Reitan, 1958) and the Rey Osterrieth Coppy Figure (ROCF) (Rey, 1997) and
6. attention was tested with the TMT-part A (Reitan, 1958) as well as the Continuous Performance Test-II v.5 to measure sustained attention.

Other clinical and sociodemographic variables collected were age, gender, level of education, occupational status, body mass index (BMI), number and type of episodes, chronicity (illness duration), age at first hospitalization, age at onset, number of hospitalizations, number of suicide attempts, history of psychosis, family psychiatric history, comorbidities and several course specifiers, such as rapid cycling, atypical symptoms, melancholia, and psychotic depression.

All patients were clinically, neuropsychologically and functionally assessed at baseline and at the end of the intervention.

2.5. Data analysis

Data were analyzed using the Statistical Package of Social Sciences (SPSS, IL, Chicago, 18th version). First, descriptive analysis of clinical and sociodemographic characteristics at baseline were carried out. Continuous variables were analyzed using one-way ANOVA. Chi Square Tests were applied for the categorical variables. Secondly, repeated-measures ANOVA were conducted to assess the impact of the three different arms of treatment (FR, PSY and TAU) on participants scores in functional outcome (assessed by means of the FAST) across two time periods (pre and post-intervention). Analyses of each domain of the FAST scale were also performed.

For the secondary analysis, repeated-measures ANOVA were also conducted to test changes in neurocognition and clinical variables.

3. Results

Although diagnostic subtype was not matter of stratification at the randomization phase, allocation was balanced in the three groups: FR (n=17; 32.1%); PSY (n=19; 35.8%) and TAU (n=19; 32.1%). At baseline, there were no statistically significant differences between groups in neither demographic characteristics nor clinical variables (data summarized in Table 1). The average age was around 40 years and BPII participants had suffered a mean of 5 depressive episodes and 3 hypomanic episodes from illness onset. FAST scores at baseline were around 30 points in the three

<table>
<thead>
<tr>
<th>Demographic and clinical variables</th>
<th>Functional remediation Baseline (n=17)</th>
<th>Psychoeducation Baseline (n=19)</th>
<th>TAU Baseline (n=17)</th>
<th>Statistical analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>42.59 (8.5)</td>
<td>40.21 (8.27)</td>
<td>40.35 (7.46)</td>
<td>F = 0.41, p = 0.67</td>
</tr>
<tr>
<td>Educational level (years)</td>
<td>12 (2.93)</td>
<td>13.11 (3.10)</td>
<td>13.94 (3.33)</td>
<td>F = 1.60, p = 0.21</td>
</tr>
<tr>
<td>BMI (Kg/m2)</td>
<td>26.52 (5.98)</td>
<td>26.00 (5.27)</td>
<td>26.44 (5.51)</td>
<td>F = 0.04, p = 0.95</td>
</tr>
<tr>
<td>Estimated premorbid IQ</td>
<td>105.59 (13)</td>
<td>105.74 (10.63)</td>
<td>106.76 (15.2)</td>
<td>F = 0.04, p = 0.95</td>
</tr>
<tr>
<td>Age at onset</td>
<td>26.53 (8.31)</td>
<td>25.37 (9.66)</td>
<td>25.24 (9.03)</td>
<td>F = 0.16, p = 0.21</td>
</tr>
<tr>
<td>Chronicity</td>
<td>16.06 (9.8)</td>
<td>14.84 (9.31)</td>
<td>15.12 (9.63)</td>
<td>F = 0.07, p = 0.92</td>
</tr>
<tr>
<td>Hypomanic episodes</td>
<td>3.18 (3.62)</td>
<td>3.79 (8.05)</td>
<td>3.63 (5.79)</td>
<td>F = 0.04, p = 0.95</td>
</tr>
<tr>
<td>Depressive episodes</td>
<td>5.47 (4.34)</td>
<td>4.89 (5.14)</td>
<td>6.44 (6.14)</td>
<td>F = 0.38, p = 0.68</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>3.00 (4.48)</td>
<td>2.79 (2.78)</td>
<td>2.24 (2.07)</td>
<td>F = 0.25, p = 0.77</td>
</tr>
<tr>
<td>FAST Total Score</td>
<td>28.94 (10.79)</td>
<td>31.16 (10.71)</td>
<td>29.00 (7.47)</td>
<td>F = 0.30, p = 0.74</td>
</tr>
<tr>
<td>HAM-D</td>
<td>5.59 (2.06)</td>
<td>4.84 (2.73)</td>
<td>4.71 (2.20)</td>
<td>F = 0.69, p = 0.50</td>
</tr>
<tr>
<td>YMRS</td>
<td>2.24 (1.95)</td>
<td>1.68 (2.13)</td>
<td>2.18 (1.97)</td>
<td>F = 0.40, p = 0.66</td>
</tr>
</tbody>
</table>

| N (%)                             | N (%)                                  | N (%)                        | χ²                  | p      |
|-----------------------------------|----------------------------------------|-------------------------------|---------------------|
| Gender, female                    | 10 (58.8)                              | 10 (52.6)                    | 11 (64.7)           | 0.54   |
| Lifetime psychotic symptoms (Yes) | 6 (35.3)                               | 10 (52.6)                    | 9 (52.9)            | 1.41   |
| Psychotic depression (Yes)        | 2 (11.8)                               | 4 (21.1)                     | 4 (40)              | 2.72   |
| Axis II comorbidity               | 2 (11.8)                               | 3 (16.7)                     | 1 (6.3)             | 0.88   |
| Family history of affective disorders | 11 (68.8)                          | 14 (73.7)                    | 10 (58.8)           | 0.92   |

BMI: body mass index, YMRS: Young Mania Rating Scale, HAM-D: Hamilton Depression Scale, FAST: Functioning Assessment Short Test.
groups. Regarding residual symptoms, there were no significant differences in the baseline mean total scores on the HAM-D and YMRS between groups.

A total of 10 patients (58.8%) completed the FR intervention; 14 patients (73.7%) completed the PSY program and 15 patients the TAU group (88.2%). These differences were not statistically significant (Chi square ($\chi^2$)=3.78; $p=0.151$). Fig. 1 represents patients disposition for the present post-hoc analyses. The most common reasons for discontinuation were loss of follow-up/withdrawal ($n=7$; 3 in FR, 2 in PSY and 2 in TAU) and relapses ($n=3$; 2 in FR and 1 in PSY). Other reasons were finding a job ($n=2$ in FR) and missing too many sessions ($n=2$ in PSY).

### 3.1. Primary outcome: functional improvement (FAST)

Data were available from 75.4% of BPll patients (12/17 FR; 13/19 PSY; 15/17 TAU; all BPll patients did not complete the endpoint assessment). Longitudinal-repeated measures analyses regarding the treatment effect of the primary outcome showed significant differences between groups (Pillai’s Trace=0.164; $F=3.619$; $p=0.037$), suggestive for an interaction between program pertinence and time (pre-post) (see Fig. 2). Nevertheless, when changes between pre-intervention and post-intervention in the various domains of the FAST were analyzed, no statistically significant differences were found between groups (Autonomy: $F=0.694$, df=2; $p=0.505$; Occupational: $F=1.690$, df=2; $p=0.198$; Cognitive: $F=1.463$, df=2; $p=0.244$; Financial: $F=0.156$, df=2; $p=0.856$; Interpersonal: $F=0.539$, df=2; $p=0.588$; Leisure: $F=2.347$, df=2; $p=0.109$). Neither any differences were found on any specific domain of the FAST in favor of the FR. Hence, only differences in FAST overall score were found. This improvement in functioning was a mean change of six points from baseline (28.94) to endpoint (23.00). There was no improvement in the FAST for PSY (baseline=31.16, endpoint=32.08) and TAU groups (baseline=29.00, endpoint=30.00).

### 3.2. Secondary outcomes: clinical and neurocognitive changes pre and post-intervention

With regard to subclinical symptomatology, we found an interaction between time (pre-post intervention) and group pertinence (Pillai’s Trace=0.157; $F=3.635$; $p=0.036$). Specifically, patients in the FR group showed a significant reduction in subclinical depressive symptoms only when compared to the PSY group ($p=0.041$) (see Fig. 3). With regard to subclinical manic symptoms, no changes were detected across groups (Pillai’s Trace=0.033; $F=0.675$; $p=0.515$).

Finally, repeated measures of neuropsychological variables revealed no significant effect for treatment group (Pillai’s Trace=1.487; $F=1.373$; $p=0.238$). However, a substantial main effect for time (baseline to post-treatment) was observed when analyzing neurocognitive performance. In fact, some tests were found to change over time: the Trail Making Test-A ($F=4.60$ df=1; $p=0.041$), visual memory assessed with ROCF ($F=5.34$, df=1; $p=0.029$) and all recall measures of the CVLT related with the recall: short-delay free recall ($F=8.76$, df=1; $p=0.006$), short-delay cued recall ($F=11.05$, df=1; $p=0.003$), long-delay free recall ($F=12.61$, df=1; $p=0.001$) and long-delay cued recall ($F=5.03$, df=1; $p=0.034$).

### 4. Discussion

This manuscript provides preliminary evidence that FR may be an effective tool in improving overall functional outcome and reducing subclinical depressive symptoms in a sample of BPll patients. These results are in line with the recent RCT that showed the efficacy of FR in improving functioning in a larger sample of bipolar I and II patients. However, in the original study the authors did not find a decrease in

![Fig. 2 Overall FAST pre and post intervention scores. Legend. FAST: Functioning Assessment Short Test.](image-url)
subclinical depressive symptomatology (Torrent et al., 2013).

This subanalysis shows further differences in comparison with the original study. Despite the original study found a strong superiority of FR when compared to TAU, our results did not reveal a clear superiority of FR when compared to PSY and TAU. Furthermore, we did not find significant changes pre-post intervention in any specific domain of the FAST, while in the original article patients assigned to FR program showed significant enhancement in the interpersonnal relationships and the occupational domains of the FAST. Bearing in mind that obtained results come from a sub-analysis of the original sample, and that the original study was designed and powered to show differences between FR and TAU with a sample calculation of more than 200 patients, the marginal significance found in this subgroup of BPII patients is likely to be due to lack of power (type II error). Hence, the improvement in the overall functional outcome was quite similar in both studies. In the present subanalysis BPII patients improved a mean of 6 points in the FAST scale while patients in Torrent’s report improved a mean of 8 points.

Surprisingly, the reduction in subsyndromal depressive symptoms was unexpected since FR was not designed to target subclinical symptomatology. However, patients in the FR group improved a mean of two points in the HAM-D scale. This reduction was not only statistically significant but it may also be of clinical relevance since patients were required to be stable with strict euthymia criteria (HAM-D < 8; YMRS < -6) for at least three months at the study entry. In line with our results, Deckersbach et al. (2010) found a reduction in the depressive symptomatology when testing the efficacy of a neurocognitive intervention to improve functioning in a sample of mildly depressed bipolar patients. Moreover, the latter intervention shows two important differences to FR: first, their intervention was designed to treat both cognitive impairment and residual depressive symptoms, whereas the FR program only targets neurocognitive deficits in order to enhance daily functioning; and second, they tested the efficacy in an open trial design, while the efficacy of the FR program has been tested in a RCT.

It is worth mentioning that despite literature is teeming with studies suggesting a link between neurocognitive impairment, subdepressive symptomatology and psychosocial functioning, the directionality of this association remains to be elucidated. Several studies have shown that subdepressive symptoms exert a negative impact on cognitive functioning as well as on psychosocial functioning (Martino et al., 2009; Gitlin et al., 2011; Burdick et al., 2010; Rosa et al., 2010; Bonnin et al., 2010). Bonnin et al. (2012), among other authors (Weinstock and Miller, 2010), suggested that the relationship between functional outcome and subdepressive symptomatology is circular and influence each other.

Persistent residual depressive symptoms are very common in BPII disorder (Benazzi, 2001); hence, these type of patients could benefit even more with specifically tailored therapy programs emphasizing techniques to reduce residual depressive symptoms (Colom et al., 2009b). Our results suggest that, in the case of BPII, the FR program seems to be an effective intervention to treat subclinical depressive symptomatology and, more directly or indirectly, to improve the general functioning in this subgroup of patients. Future studies focused on elucidating which kind of depressive symptoms would be more functionally disabling are needed in order to proceed to treat them and to increase functional outcome. For instance, Gitlin et al. (2011) found that fatigability was the main depressive symptom that predicted slower functional recovery. Deckersbach et al. (2010) included a module focused on mood monitoring and treatment of residual depressive symptoms with standard techniques, such as activity management and problem solving, among others. Some of these techniques (programming and organizing activities, problem solving technique, self-monitoring, etc.) were implemented in our FR program but mainly for the treatment of the executive dysfunction; indirectly the intervention may also help to explain an increasing feeling of self-efficacy in BPII patients if they are able to engage in activities in a more organized way. These sessions aimed to treat executive functions may have accounted for some improvement in residual depressive symptoms, however, other sessions related to strategies to improve memory as well as to improve communication, autonomy and stress management could also explain the improvement of subsyndromal symptoms.

With regard to neurocognitive performance, our results comport with the original study as we did not find any significant effect of treatment group on neurocognitive variables. Patients who received the FR program showed changes in some neurocognitive measures related to attention and visual and verbal memory, however, these differences were not statistically significant when compared with the other two groups. These changes across time in the three groups may be related to factors such as type II error or to learning effects, among others.

This study shows some limitations such as the small sample size of BPII patients in each arm and the fact that this is an exploratory post-hoc analysis. Moreover, the present data analysis is only focused on the immediate effects of the intervention and it is not known if these changes will remain in the long-term. Other limitations are related to the methodology of the original study, such as inclusion criteria regarding functional impairment which may limit the generalization of the results, and the lack of parallel neuropsychological tests at follow-up to control for practice effects. Finally, the effects of psychopharmacological treatments were not taken into account (Dias et al., 2012).

Although these data come from a post-hoc exploratory subanalysis, our focus of interest was to analyze the efficacy of FR in patients with BPII disorder. Our results suggest that FR might enhance functional outcome of BPII patients and it might be even an effective way of reducing subclinical depressive symptomatology in this group of patients. Therapies and studies specifically designed and focused on BPII samples are needed since this subtype may not only be different in terms of clinical outcome and pharmaceutical treatment but also in terms of treatment response.

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Contributors

All the authors have been sufficiently involved in the submitted study and have approved the final paper.

Conflict of interest

Dr. Amann has served as a speaker for Bristol-Myers Squibb/Otsuka. Dr. González-Pinto has received grants from or has served as consultant, adviser, or CME speaker for Almirall, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Sanofi-Aventis, Schering-Plough, and the Spanish Ministry of Science and Innovation (CIBERSAM).

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