Psychological Medicine (2016), **46**, 291–301. © Cambridge University Press 2015
doi:10.1017/S0033291715001713

ORIGINAL ARTICLE

Effects of functional remediation on neurocognitively impaired bipolar patients: enhancement of verbal memory

C. M. Bonnin[1], M. Reinares[1], A. Martínez-Arán[1]*, V. Balanzá-Martínez[2,3], B. Sole[1], C. Torrent[1], R. Tabarés-Seisdedos[2], M. P. García-Portilla[4], A. Ibáñez[5], B. L. Amann[6], C. Arango[7], J. L. Ayuso-Mateos[8], J. M. Crespo[9], A. González-Pinto[10], F. Colom[1], E. Vieta[1] and The CIBERSAM Functional Remediation Group†

[1] *Bipolar Disorders Unit, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain*
[2] *Department of Medicine, University of Valencia, CIBERSAM, Valencia, Spain*
[3] *La Fe University Polytechnic Hospital, Valencia, Spain*
[4] *Department of Psychiatry, University of Oviedo, CIBERSAM, Oviedo, Spain*
[5] *Department of Psychiatry, Ramon y Cajal University Hospital, University of Alcala, IRYCIS, CIBERSAM, Madrid, Spain*
[6] *FIDMAG Hermanas Hospitalarias Research Foundation, CIBERSAM, Barcelona, Spain*
[7] *Child and Adolescent Psychiatry Department, Hospital General Universitario Gregorio Marañón School of Medicine, Universidad Complutense, IiSGM, CIBERSAM, Madrid, Spain*
[8] *Department of Psychiatry, Universidad Autonoma de Madrid, IIS-IP, CIBERSAM, Madrid, Spain*
[9] *Department of Psychiatry, University Hospital of Bellvitge, Bellvitge Biomedical Research Institute (IDIBELL), CIBERSAM, Barcelona, Spain*
[10] *Álava University Hospital, CIBERSAM, University of the Basque Country, Kronikgune, Vitoria, Spain*

Background. Functional remediation is a novel intervention with demonstrated efficacy at improving functional outcome in euthymic bipolar patients. However, in a previous trial no significant changes in neurocognitive measures were detected. The objective of the present analysis was to test the efficacy of this therapy in the enhancement of neuropsychological functions in a subgroup of neurocognitively impaired bipolar patients.

Method. A total of 188 out of 239 DSM-IV euthymic bipolar patients performing below two standard deviations from the mean of normative data in any neurocognitive test were included in this subanalysis. Repeated-measures analyses of variance were conducted to assess the impact of the treatment arms [functional remediation, psychoeducation, or treatment as usual (TAU)] on participants' neurocognitive and functional outcomes in the subgroup of neurocognitively impaired patients.

Results. Patients receiving functional remediation ($n = 56$) showed an improvement on delayed free recall when compared with the TAU ($n = 63$) and psychoeducation ($n = 69$) groups as shown by the group × time interaction at 6-month follow-up [$F_{2,158} = 3.37$, degrees of freedom (df) = 2, $p = 0.037$]. However, Tukey *post-hoc* analyses revealed that functional remediation was only superior when compared with TAU ($p = 0.04$), but not with psychoeducation ($p = 0.10$). Finally, the patients in the functional remediation group also benefited from the treatment in terms of functional outcome ($F_{2,158} = 4.26$, df = 2, $p = 0.016$).

Conclusions. Functional remediation is effective at improving verbal memory and psychosocial functioning in a sample of neurocognitively impaired bipolar patients at 6-month follow-up. Neurocognitive enhancement may be one of the active ingredients of this novel intervention, and, specifically, verbal memory appears to be the most sensitive function that improves with functional remediation.

Received 23 December 2014; Revised 6 August 2015; Accepted 6 August 2015; First published online 21 September 2015

Key words: Bipolar disorder, clinical trials, functional remediation, neuropsychology, verbal memory.

* Address for correspondence: A. Martínez-Arán, Bipolar Disorders Programme, Clinical Institute of Neuroscience, University Clinic Hospital of Barcelona, Villarroel 170 08036-Barcelona, Spain.
(Email: amartiar@clinic.ub.es)

† The CIBERSAM Functional Remediation Group consists of: A. Alegría, S. Al-Halabi, S. Alonso-Lana, C. Anaya, S. Barbeito, J. Bobes, A. Calvo, E. Cerrillo, P. Correa, N. Custal, P. Fernández, M. Fernández, I. Fuentes-Durá, G. Galván, S. Isella, E. Jiménez, R. Landín-Romero, M. Mayoral, J. Manuel Menchón, J. Merchan-Naranjo, J. Ortiz-Gil, I. Pacchiarotti, R. Reyes, A. R. Rosa, M. Rapado-Castro, J. M. Rodao, P. A. Saiz, J. Sánchez-Moreno, M. Salamero, B. Segura, G. Selva-Vera, J. Saiz-Ruiz, V. Soria, M. Subirá, A. Ugarte, J. Valle, E. Valls and P. Vega.

Introduction

The relationship between poorer course of bipolar disorder and greater neurocognitive impairment has been previously reported (Martinez-Aran *et al.* 2007; Lopez-Jaramillo *et al.* 2010), as well as the impact of neurocognitive deficits on psychosocial functioning (Tabares-Seisdedos *et al.* 2008; Bonnin *et al.* 2010; Depp *et al.* 2012; Torrent *et al.* 2012). As a consequence of these findings, the interest in the development of therapeutic strategies that contribute to restoring or mitigating the impact of sustained neurocognitive and functional impairment has grown in the last few years (Fuentes-Dura *et al.* 2012; Vieta, 2014). However, only two publications have addressed this issue so far in well-defined samples of bipolar patients. An open study, using a programme called Cognitive Rehabilitation (Deckersbach *et al.* 2010) and a randomized controlled trial, implementing a programme named Functional Remediation (Torrent *et al.* 2013). Both studies reported the positive impact of the interventions on functional outcomes but the improvement of neurocognition was mild (Deckersbach *et al.* 2010) or non-significant at 6-month follow-up (Torrent *et al.* 2013). Specifically, Deckersbach *et al.* (2010) reported an improvement in residual depressive symptoms, occupational and psychosocial functioning. Moreover, changes in executive functioning accounted, in part, for the improvements in occupational functioning. In a multicentre trial carried out by Torrent *et al.* (2013) no significant effect of treatment group was found on neurocognitive variables, despite significant improvements in psychosocial functioning. The authors hypothesized that this result was most likely due to the study design which did not require a defined cognitive impairment but functional impairment at study entry. Hence, a number of patients showing functional but not cognitive impairment at enrolment may have caused ceiling effects on cognitive measures. Due to an important heterogeneity in the severity of neurocognitive impairment in bipolar disorder (Altshuler *et al.* 2004; Martino *et al.* 2008, 2014), we decided to conduct a subanalysis of the original multicentre randomized controlled trial by Torrent *et al.* (2013), to analyse the response to functional remediation in terms of neurocognitive performance. This subsample consisted of patients who performed below 2 standard deviations from the mean of normative data in any neurocognitive test. The main objective was to ascertain whether neurocognitive enhancement was a potential ingredient of functional remediation, given the high density of neurocognitive tasks involved in the therapy. We hypothesized that the group of neurocognitively impaired patients receiving functional remediation would improve not only their functional outcome but also their neurocognitive functioning, as compared with patients who were randomized to psychoeducation or treatment as usual (TAU).

Method

Participants

Participants in the original trial fulfilled the following inclusion criteria (Torrent *et al.* 2013): (1) diagnosed with bipolar I or II disorder (BD-I or BD-II) according to the Diagnostic and Statistical Manual of Mental Disorders (fourth edition, text revision; American Psychiatric Association, 2000); (2) assessed during euthymia defined as Young Mania Rating Scale (YMRS) score $\leqslant 6$ (Young *et al.* 1978; Colom *et al.* 2002), and Hamilton Depression Rating Scale-17 (HAMD) score $\leqslant 8$ (Hamilton, 1960; Ramos-Brieva & Cordero-Villafáfila, 1986); (3) suffering from at least a moderate level of functional impairment measured by means of the Functioning Assessment Short Test (FAST) scale $\geqslant 18$ (Rosa *et al.* 2007), including a score of four points or more in the cognitive functioning domain of the FAST.

Exclusion criteria were: (1) an intelligence quotient (IQ) < 85 or any medical condition that could affect neuropsychological performance (such as neurological diseases); (2) any co-morbid psychiatric condition, including substance abuse or dependence within the past 3 months; (3) electroconvulsive therapy within the past year; or (4) participation in any structured psychological intervention, such as psychoeducation or cognitive remediation, within the past 2 years.

As mentioned in the original study, all patients provided written informed consent. Ethical approval for the study was granted by the Ethics Committee at every hospital involved in the study.

For the specific purpose of this study, we applied the criteria of Martino *et al.* (2008) to assess neurocognitive impairment in the original sample ($n = 239$), resulting in 188 neurocognitively impaired patients.

Further details of this procedure are explained in the data analysis section.

Interventions

Patients in the original trial (Torrent *et al.* 2013) were assigned in a 1:1:1 ratio to receive 21 weeks of functional remediation, psychoeducation, or TAU. Randomization was stratified by age, sex and education level.

Functional remediation

The functional remediation programme consisted of 21 weekly sessions, each lasting 90 min. This intervention addresses neurocognitive issues such as attention, memory and executive functions, but it focuses even

https://doi.org/10.1017/S0033291715001713 Published online by Cambridge University Press

more on enhancing functioning in daily routine. The content of the intervention is based on ecological tasks to be performed in two settings, in the clinic as well as at home. Patients were trained with exercises for memory, attention, problem solving and reasoning and organization in order to improve their functional outcome. Most of the techniques were based on paper-and-pencil tasks and group activities. For detailed information on the rationale of this intervention, see Martínez-Arán *et al.* (2011), Bonnin *et al.* (2014) and Vieta *et al.* (2014).

Psychoeducation

The psychoeducation also consisted of 21 weekly sessions of 90 min each, aimed at preventing recurrences of bipolar illness by improving four main issues: illness awareness, treatment adherence, early detection of prodromal symptoms of relapse, and lifestyle regularity (Colom *et al.* 2003; Colom & Vieta, 2006).

TAU

In the TAU group, participants received prescribed pharmacological treatment without any adjunctive psychological therapy.

Clinical, neuropsychological and functional assessment

Clinical, neurocognitive and functional variables were collected for all patients both at baseline and at 6 months follow-up (see Torrent *et al.* 2013).

Clinical variables were gathered through a clinical interview and from clinical history records. In addition to this, the HAMD and YMRS were administered to assess affective symptoms.

Neurocognitive performance was evaluated through a comprehensive neuropsychological battery. The same battery was administered at baseline and at 6-month follow-up. It was composed of six domains: (1) estimated IQ, which was evaluated with the Wechsler Adult Intelligence Scale – III (WAIS-III) vocabulary subtest (Wechsler, 1997*a*); (2) the processing speed index, which consists of two subtests of the WAIS-III, the digit–symbol coding and symbol search (Wechsler, 1997*a*); (3) executive function, which was tested by set shifting, verbal fluency, planning, and response inhibition using the Computerized Wisconsin Card Sorting Test (Heaton, 1981), the Stroop Color–Word Interference Test (Golden, 1978), the phonemic (F-A-S) and categorical (animal naming) components of the Controlled Oral Word Association Test (Benton & Hamsher, 1976), the Trail Making Test, part B (Reitan, 1958), and the Rey–Osterrieth Complex Figure (Rey, 1997); (4) visual memory and verbal learning/memory, which were assessed with the Rey–Osterrieth Complex Figure for visual memory and the California Verbal Learning Test (CVLT) (Delis *et al.* 1987) and the Logical Memory Scale (Wechsler Memory Scale-III; WMS-III) (Wechsler, 1997*b*) for learning/memory; (5) the working memory index, which was tested with three subtests of the WAIS-III (Wechsler, 1997*a*): arithmetic, digits forward and backward, and letter–number sequencing; and (6) attention, which was tested with the Trail Making Test, part A (Reitan, 1958), administered together with the Continuous Performance Test-II, version 5 (Conners, 2000), to measure sustained attention.

Finally, psychosocial functioning was assessed by means of the FAST scale (Rosa *et al.* 2007).

Data analysis

Data were analysed using SPSS v.18 for Windows (USA). First, the proportion of patients with neurocognitive impairment was calculated following the criteria established by Martino *et al.* (2008). According to their criteria, a domain was compromised when performance in any test of that domain was below 2 standard deviations or more from the mean of normative data of each test.

In our sample, patients' z scores on each measure were calculated according to data from a healthy control group ($n = 30$) that was comparable in terms of age (mean = 40.6, S.D. = 13.1, $F_{3,262} = 0.08$, $p = 0.77$), estimated IQ (mean = 109.6, S.D. = 8.0, $F_{3,261} = 2.7$, $p = 0.04$) and years of education (mean = 13.7, S.D. = 3.8, $F_{3,260} = 0.51$, $p = 0.47$) with the remaining groups: functional remediation ($n = 77$); psychoeducation ($n = 82$); and TAU ($n = 80$). Even though significant differences were found in the estimated IQ, when a Tukey *post-hoc* test was performed, no significant differences were found between groups. Note that these comparisons were run with the total sample, before excluding the patients without neurocognitive impairment.

After excluding the patients without neurocognitive impairment, we proceeded with the second part of the analysis. Clinical and sociodemographic variables were analysed using one-way analysis of variance (ANOVA) for continuous variables or the χ^2 test for categorical variables. Finally, repeated-measures ANOVAs were conducted in order to assess the impact of the treatment arms (functional remediation, psychoeducation and TAU) on participants' scores in the different neuropsychological variables and psychosocial functioning at baseline and at follow-up. Repeated-measures analysis only took into account complete cases; hence missing cases due to being lost to follow-up were not analysed. Raw scores were used to compare the three groups since they did not differ in terms of confounding variables.

https://doi.org/10.1017/S0033291715001713 Published online by Cambridge University Press

For the neuropsychological assessment, the following neuropsychological variables were analysed in order to cover the main cognitive domains that have been reported to be affected in bipolar disorder (verbal memory, attention and executive functions) (Bourne *et al.* 2013) and on neurocognitive domains we work on in the functional remediation programme: short free recall, short cued recall, delayed free recall, delayed cued recall, Trail Making Test part A and B, Wisconsin Card Sorting Test perseverative errors, Stroop interference, categorical and phonemic fluencies. Between- and within-effect sizes were calculated for each neurocognitive variable that was examined. For psychosocial functioning, only global scores measured by means of the FAST were analysed conducting another repeated-measure analysis.

The trial is registered under Clinicaltrials.gov identification number: NCT 01370668.

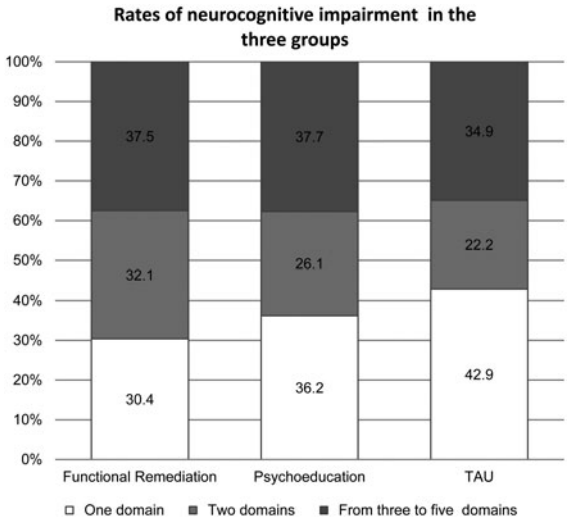

Fig. 1. Rates of neurocognitive impairment. TAU, Treatment as usual.

Results

Rate of neurocognitive impairment

Considering the patients who fulfilled the criteria of Martino *et al.* (2008), we found that from the original sample ($n = 239$) only 20% of patients ($n = 51$) were free of neurocognitive impairment, that is, they did not present any impaired cognitive domain and they were excluded from the present study in order to avoid ceiling effects. The remaining patients ($n = 188$) presented cognitive impairment and they were allocated to the groups as follows: 56 patients in the functional remediation group; 69 patients in the psychoeducation group; and 63 patients in the TAU group. Of note is that there is a broad range of neurocognitive impairment in this sample, highlighting the heterogeneity of neurocognitive impairment that can be observed in bipolar disorder. As shown in Fig. 1, rates of neurocognitive impairment were equally distributed in the three groups ($\chi^2 = 2.45$, $p = 0.65$).

Clinical and sociodemographic variables

As shown in Table 1, all three patient groups were comparable in terms of sociodemographic (age, years of education, and pre-morbid IQ estimation) and clinical variables (number and type of episodes, chronicity, age at onset, HAMD, YMRS and FAST scores).

Attrition rates

During the intervention a total of 27 patients discontinued the study, distributed as follows: 14.3% ($n = 8$), 11.6% ($n = 8$) and 17.5% ($n = 11$) in the functional remediation, psychoeducation and TAU groups, respectively. These rates were not significantly different between groups ($\chi^2 = 0.92$, $p = 0.63$). The main reason for discontinuation was being lost to follow-up. Finally, extra analyses were performed between drop-outs and completers regarding their clinical and sociodemographic characteristics at baseline. No differences were found between both groups in terms of these variables indicating that the drop-out patients were not a source of bias for the present analyses.

Treatment effects on neurocognitive variables and functional outcome

Compared with participants receiving TAU or psychoeducation, those who attended functional remediation improved in delayed free recall on the CVLT at 6-month follow- up, as shown by the significant group x time interaction in the repeated-measures analysis ($F_{2,158} = 3.37$, $p = 0.04$) (see Fig. 2 and Table 2).

Tukey *post-hoc* analyses revealed that functional remediation group was only superior when compared with TAU ($p = 0.04$) but not to psychoeducation ($p = 0.10$). The between-groups effect size was small (Cohen's $d = 0.2$ and 0.3 for functional remediation *v.* TAU and psychoeducation, respectively). However, the within-group effect size, the comparison of pre- and post-treatment, in the functional remediation was moderate (Cohen's $d = 0.64$), in psychoeducation the within-group effect size was small (Cohen's $d = 0.26$) and in the TAU group it was small too (Cohen's $d = 0.39$).

No statistically significant differences were found in the remaining comparisons of neurocognitive variables, although a trend was detected in the group × time interaction towards an improvement in favour of the functional remediation group in verbal learning

https://doi.org/10.1017/S0033291715001713 Published online by Cambridge University Press

Table 1. *Clinical and sociodemographic characteristics*

	Functional remediation ($n = 56$)	Psychoeducation ($n = 69$)	TAU ($n = 63$)	Statistics	
				F or χ^2	p
Age, years	40.7 (9.2)	39.3 (9.2)	39.9 (9.3)	$F_{2,183} = 0.36$	0.70
Estimated IQ	102.8 (12.1)	101.7 (10.9)	104.8 (14.1)	$F_{2,184} = 1.06$	0.35
Years of education	12.3 (4.2)	12.8 (3.5)	12.8 (3.6)	$F_{2,182} = 0.40$	0.05
Age at onset, years	26.3 (8.1)	26.5 (8.9)	24.2 (7.7)	$F_{2,183} = 1.41$	0.24
Number of previous hospitalizations	3.0 (3.5)	2.6 (2.5)	2.6 (2.2)	$F_{2,182} = 0.48$	0.61
Number of previous manias	2.1 (4.3)	2.1 (4.0)	2.0 (3.6)	$F_{2,182} = 0.15$	0.86
Number of previous depressions	4.9 (6.5)	4.3 (5.6)	5.7 (6.4)	$F_{2,182} = 0.89$	0.41
Years of illness	14.3 (8.9)	12.7 (9.1)	15.7 (8.9)	$F_{2,120} = 1.80$	0.16
HAMD scores	3.9 (2.6)	4.4 (2.6)	4.3 (2.5)	$F_{2,184} = 0.70$	0.49
YMRS scores	1.3 (1.7)	1.7 (1.9)	1.3 (1.7)	$F_{2,184} = 1.07$	0.34
FAST scores	31.5 (10.0)	31.1 (10.8)	29.5 (9.4)	$F_{2,185} = 0.63$	0.53
Gender: female, *n* (%)	33 (58.9)	42 (60.9)	37 (58.7)	$\chi^2 = 0.07$	0.96
Bipolar subtype: type I, *n* (%)	44 (78.6)	49 (73.1)	47 (77.0)	$\chi^2 = 0.54$	0.76
Lifetime psychotic symptoms, *n* (%)	33 (58.9)	43 (64.2)	44 (71.0)	$\chi^2 = 1.89$	0.38
Family history of affective disorders, *n* (%)	31 (56.4)	42 (61.8)	38 (61.3)	$\chi^2 = 0.43$	0.80
Axis II co-morbidity, *n* (%)	2 (3.6)	4 (6.1)	2 (3.4)	$\chi^2 = 0.64$	0.72
Medication, *n* (%)					
Stabilizer + antipsychotic	15 (26.8)	18 (26.1)	23 (36.5)	$\chi^2 = 2.05$	0.36
Stabilizer + antipsychotic + benzodiazepine	8 (14.3)	15 (21.7)	11 (17.5)	$\chi^2 = 1.18$	0.55
Stabilizer + atypical + antidepressant	8 (14.3)	7 (10.1)	5 (7.9)	$\chi^2 = 1.28$	0.52
Monotherapy: either atypical or mood stabilizer	9 (16.1)	4 (5.8)	9 (14.3)	$\chi^2 = 3.77$	0.15
Combination of two stabilizers	3 (5.4)	5 (7.2)	2 (3.2)	$\chi^2 = 1.08$	0.58
Stabilizer + antidepressant + benzodiazepine	7 (12.5)	8 (11.6)	6 (9.5)	$\chi^2 = 0.28$	0.86
Other combinations	3 (5.4)	11 (15.9)	4 (6.3)	$\chi^2 = 5.13$	0.07

Data are given as mean (standard deviation) unless otherwise indicated.

TAU, Treatment as usual; IQ, intelligence quotient; HAMD, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale; FAST, Functioning Assessment Short Test.

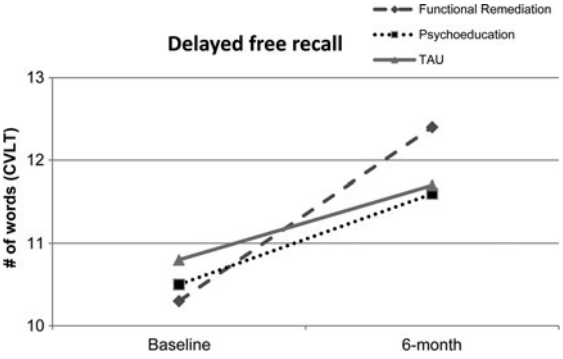

Fig. 2. Changes in delayed free recall at 6-month follow-up. TAU, Treatment as usual; CVLT, California Verbal Learning Test.

($F_{2,158} = 2.8$, $p = 0.064$) (Table 2), showing a medium within-group effect size (Cohen's $d = 0.6$). The between-groups effect size at follow-up was small for functional remediation when compared with both the TAU (Cohen's $d = 0.3$) and psychoeducation (Cohen's $d = 0.4$) groups.

The group receiving functional remediation also improved significantly their functional outcome when compared with psychoeducation and TAU as shown by the group x time interaction ($F_{2,158} = 4.26$, $p = 0.016$). These results do not differ from the original study (Torrent *et al.* 2013). See Fig. 3 for further details.

Changes in the FAST scale and changes in the CVLT free delayed recall were not significantly correlated ($r = 0.10$, $p = 0.22$). However, at the end of the study there was a significant association between higher FAST total score and lower free delayed score in the CVLT ($r = -0.25$, $p = 0.002$). Finally, changes in CVLT free delayed recall did not correlate with changes in HAMD total score ($r = 0.17$, $p = 0.29$) or with YMRS total score ($r = 0.14$, $p = 0.39$).

Discussion

The main result of this study was that participants selected for being neurocognitively impaired improved after the administration of functional remediation. Specifically, they presented better performance in

https://doi.org/10.1017/S0033291715001713 Published online by Cambridge University Press

Table 2. *Neuropsychological outcomes at baseline and at 6-month follow-up*

	Functional remediation		Psychoeducation		TAU		Statistics	
	Baseline ($n = 56$)	6-month follow-up ($n = 48$)	Baseline ($n = 69$)	6-month follow-up ($n = 61$)	Baseline ($n = 63$)	6-month follow-up ($n = 52$)	F	p
Verbal learning (lists 1–5)	46.8 (13.4)	54.4 (11.8)	48.8 (9.4)	49.3 (11.2)	48.4 (12.1)	50.8 (12.4)	$F_{2,158} = 2.8$	0.06
Short free recall	9.9 (3.2)	11.5 (3.5)	9.9 (2.9)	11 (2.9)	10.2 (3.4)	11.6 (3.4)	$F_{2,158} = 0.28$	0.75
Short cued recall	11.4 (2.8)	13.0 (2.4)	11.3 (2.3)	12.1 (2.5)	11.3 (2.9)	12.8 (3.1)	$F_{2,158} = 2.05$	0.13
Delayed free recall	10.3 (3.4)	12.4 (3.1)	10.5 (2.7)	11.6 (2.8)	10.8 (3.4)	11.7 (3.3)	$F_{2,158} = 3.37$	0.04
Delayed cued recall	11.4 (3.19)	13.1 (2.6)	11.1 (2.9)	12.3 (2.7)	11.3 (3.2)	12.6 (3.1)	$F_{2,158} = 0.51$	0.59
Trail Making Test – part A	47.9 (23.4)	43.5 (42.1)	48.7 (28.4)	43.4 (22.9)	44.2 (26.3)	41.4 (18.8)	$F_{2,156} = 0.16$	0.85
Trail Making Test – part B	113.2 (61.2)	111.6 (52.8)	131.4 (86.3)	118.6 (80.0)	120.6 (75.6)	103.7 (52.5)	$F_{2,152} = 0.75$	0.47
WCST perseverative errors	22.9 (16.6)	16.3 (12.1)	23.6 (22.6)	21.3 (18.0)	24.3 (17.5)	23.5 (21.1)	$F_{2,158} = 1.05$	0.33
SCWT interference	−0.9 (69.4)	6.7 (13.0)	−1.7 (8.3)	6.31 (10.7)	−0.9 (8.7)	6.1 (11.4)	$F_{2,158} = 0.06$	0.94
F-A-S[a]	33.7 (13.5)	34.6 (14.2)	32.1 (11.1)	32.3 (10.1)	31 (12.8)	33.4 (7.0)	$F_{2,158} = 0.65$	0.52
Animal naming[a]	18.8 (6.0)	18.6 (5.7)	17.8 (6.1)	17.7 (5.1)	18.3 (5.1)	18.6 (5.6)	$F_{2,152} = 0.17$	0.83

Data are given as mean (standard deviation).
TAU, Treatment as usual; WCST, Wisconsin Card Sorting Test; SCWT, Stroop Color and Word Test.
[a] Phonemic (F-A-S) and categorical (animal naming) components of the Controlled Oral Word Association Test.

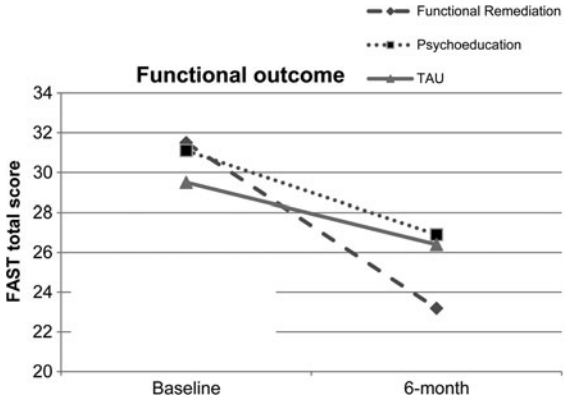

Fig. 3. Improvement of functional outcome. TAU, Treatment as usual; FAST, Functioning Assessment Short Test.

verbal memory measures such as the delayed free recall measured by the CVLT only when compared with TAU, with a moderate effect size (Cohen's $d = 0.6$). Although not significant, a trend in improving verbal learning was in the same direction. In addition to this, patients in the functional remediation group also improved their psychosocial functioning, which was the primary outcome of the original trial. Overall, it seems that functional remediation, when applied to neurocognitively impaired patients, enhances not only functional outcome but also verbal memory, and, more specifically, learning and delayed free recall.

There may be different reasons to explain why functional remediation improves verbal memory particularly. First, this intervention involves training exercises related to memory and learning skills, such as association, categorization and mental imagery. This module represents almost one-third of the whole intervention and it is the most extensive part when compared with the remaining neurocognitive training sessions. Furthermore, of all the neuropsychological functions involved, verbal memory is perhaps the most sensitive function related to the enhancement of psychosocial functioning, especially when measured with the CVLT, since there is an international agreement (International Society for Bipolar Disorders-Battery for Assessment of Neurocognition; ISBD-BANC) on this test as the most suitable one to assess verbal learning and memory in bipolar disorder (Yatham *et al.* 2010). These results introduce a clinically relevant topic in the field of the rehabilitation of psychiatric patients

https://doi.org/10.1017/S0033291715001713 Published online by Cambridge University Press

which is whether the level of neurocognitive impairment may influence the response to psychological interventions or not. According to our results, neurocognitively impaired bipolar patients not only improved in psychosocial functioning, but also in delayed free recall. The fact that most of these patients were chronic with a long duration of illness and multiple episodes suggests that functional remediation may be effective in later stages of the illness. This is at odds with the results of Deckersbach *et al.* (2010), who found that patients with neurocognitive impairment benefit less from their cognitive rehabilitation. However, patients in that trial were mildly symptomatic, which can influence neuropsychological and functional outcome (Bonnin *et al.* 2012). Regarding the present results, it is worth mentioning that the changes in delayed free recall were not correlated with changes in functional outcome. This was an unexpected result, since it has been consistently found that verbal memory impairment is related to worse functional outcome (Martínez-Arán *et al.* 2007; Martino *et al.* 2009; Bonnin *et al.* 2010). Even though these are preliminary results, we have different hypotheses that may explain this lack of relationship between the two variables: first, it might be attributed to the loss of statistical power due to small sample size in the functional remediation group. Second, these results may suggest that, at least, in patients with neurocognitive impairment, the improvement of verbal memory (delayed free recall) and the improvement of functional outcome are independent from each other; despite the neurocognitive changes being subtle, patients have acquired a broad range of strategies to cope with difficulties in daily life. Controversially, in a recent study of functional remediation, a correlation between neurocognitive changes and functional outcome was found at 12-month follow-up (Bonnín *et al.* in press). In light of this, it may be hypothesized that the 6-month follow-up is not long enough to detect significant correlations and that the consolidation of learned skills requires time. It may depend mainly on training and sustained practice of such strategies that become evident at 12-month follow-up. Finally, changes in verbal memory were not related either to changes in mood symptomatology, measured by means of the HAMD and the YMRS scores changes.

The high rate of impaired bipolar patients fulfilling criteria for neurocognitive impairment may sound bad news for the field; however, this result is most probably due to different artifacts of this subanalysis. First, it may be related to the inclusion criteria in the original study by Torrent *et al.* (2013), which required a high level of functional impairment and as a consequence of this, more severe patients were selected. Second, it may also be related to the cut-off we have used to establish neurocogntive impairment (Martino *et al.* 2008). There is a great variability in the literature using different cut-offs to establish neurocognitive impairment (van der Werf-Eldering *et al.* 2010; Hellvin *et al.* 2012; Martino *et al.* 2014; Volkert *et al.* 2015). The application of one or other criteria will inevitably lead not only to different results but also to different rates of neurocognitive impairment (Altshuler *et al.* 2004; Reichenberg *et al.* 2009; Burdick *et al.* 2014). One of the limitations of the criteria used for the present study is that the criteria of Martino *et al.* (2008), together with other previous studies (Hellvin *et al.* 2012; Volkert *et al.* 2015), might be among the less restrictive ones in the literature, especially with respect to other works that evaluate neurocognitive impairment in healthy controls where the occurrence of a single impaired test score on a neuropsychological battery is not uncommon (Binder *et al.* 2009; Iverson *et al.* 2011). However, using the criteria of Martino *et al.* (2008) in the present study ensured that the 20% of patients excluded to perform this analysis were the ones with the most preserved neurocognitive performance of the sample and allowed us to include all the heterogeneity in the neurocognitive impairment that can be observed in bipolar disorder (Martino *et al.* 2014). Because of this, the present results should be interpreted with caution and they also highlight the need to achieve a consensus about the cut-off to establish neurocognitive impairment in bipolar disorder.

Similarly, the fact that 80% of the patients from the Torrent *et al.* (2013) study qualified for this subanalysis [compared with 62% in the Martino *et al.* (2014) study, using the same criteria] may be attributable to different reasons. First, and as mentioned before, one of the inclusion criteria in the original study was to have a FAST score $\geqslant$18, which means that patients were markedly impaired in their psychosocial functioning at baseline. In addition, patients had to have a score of at least 4 points in the cognitive domain of this scale; this indicated that patients presented neurocognitive complaints detected by the clinician, since this scale is not self-administered. Clinicians hereby took into account not only patients' subjective complaints but also the information by relatives and clinical history. Second, patients in the present study were recruited from different specialized reference centres in Spain which usually treat difficult-to-treat and severe cases, hence this potential source of bias cannot be ruled out. Finally, another reason for the discrepancy of our results compared with those of Martino *et al.* (2014) may be the different percentage of BD-I and BD-II patients in each sample. While in the study of Martino *et al.* (2014), BD-I and BD-II were equally distributed (48% BD-I and 52% BD-II), in our sample, the vast majority of patients were diagnosed

https://doi.org/10.1017/S0033291715001713 Published online by Cambridge University Press

with BD-I (up to 76%), who usually show more severe neurocognitive deficits than BD-II patients (Sole *et al.* 2011). All these differences taken together may help to explain the discrepancy of impaired patients in both studies, even following the same method as described by Martino *et al.* (2014).

Methodological caveats of our study must be taken into account when translating results to clinical practice. First, the 6-month follow-up period is short and the results cannot be generalizable for long-term outcome. For the same reason, evident conclusions cannot be deduced whether the improvement remains stable or varies over time. Second, as this was an exploratory subanalysis, we have not conducted any statistic procedure to control for multiple comparisons when analysing neurocognition; instead we selected a number of variables based on previous literature and on neurocognitive domains we work on in the functional remediation programme. Despite all, caution is needed, since only one out of 11 comparisons (delayed recall) among the neurocognitive variables was found to be statistically significant, and a trend was detected for another variable (verbal learning).

Finally, as stated before, the majority of subjects included in this trial were chronic patients with multiple admissions and with marked functional impairment which might interfere with a generalization of less severe cases with bipolar disorder.

Despite the previous limitations, this study shows that functional remediation at 6-month follow-up is effective not only at improving psychosocial functioning, but also at enhancing delayed free recall in the CVLT in a sample of patients with neurocognitive impairment. It supports the notion that neurocognitive enhancement is an active ingredient of functional remediation, at least in this subsample of patients, and that verbal memory seems to be more amenable to treatment than other neurocognitive domains. If the present results are confirmed by further studies, these findings may have important consequences in treating chronic bipolar patients, bringing hope to the subset of patients with neurocognitive and functional decline, and for whom there is the utmost unmet need (Reinares *et al.* 2014).

Acknowledgements

This study was supported by an ETES grant from the Spanish Ministry of Economy and Competitiveness: PI080180, PI08/90825, PI08/90327, PI08/90675, PI08/90224, PI08/90654, PI08/90189, PI08/90916, PI08/90416, PI08/90094, PI11/00637, PI12/00912, integrated in the Plan Nacional de I + D + I and cofinanced by el Fondo Europeo de Desarrollo Regional (FEDER), the CIBERSAM and the Comissionat per a Universitats i Recerca del DIUE de la Generalitat de Catalunya to the Bipolar Disorders Group (2014 SGR 398).

M.R. was supported by Beatriu de Pinós, Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement, de la Generalitat de Catalunya i del programa COFUND de les Accions Marie Curie del 7è Programa marc de recerca i desenvolupament tecnològic de la Unió Europea.

M.R.-C. was supported by a Sara Borrell Health Research Fellowship from the Institute of Health Carlos III, Spanish Ministry of Economy and Competitiveness, an Alicia Koplowitz Research Grant and an Alicia Koplowitz Grant for Short-Term Placements from the Alicia Koplowitz Foundation (Madrid, Spain).

F. C. would like to thank the support and funding of the Spanish Ministry of Health, Instituto de Salud Carlos III, CIBERSAM. F.C. is also funded by the Spanish Ministry of Economy and Competitiveness, Instituto Carlos III, through a 'Miguel Servet' contract (CP08/00140) and the Fondo de Investigación Sanitaria (FIS) (PI 12/00910).

A.M.-A.'s project is supported in part by a 2013 NARSAD, Independent Investigator Grant from the Brain & Behavior Research Foundation.

B.L.A. would like to thank the support and funding of the Spanish Ministry of Health, Instituto de Salud Carlos III, for a 'Miguel Servet' contract (CP06/00359) which has been extended in 2013 as a stabilization contract (CES 12/024).

Declaration of Interest

E.V. has served as consultant, advisor or speaker for the following companies: Alexza, Almirall, AstraZeneca, Bial, Bristol-Myers Squibb, Elan, Eli Lilly, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, Janssen-Cilag, Jazz, Johnson & Johnson, Lundbeck, Merck and Co. Inc., Novartis, Organon, Otsuka, Pfizer Inc., Roche, Sanofi-Aventis, Servier, Schering-Plough, Shire, Sunovion, Takeda, United Biosource Corporation and Wyeth.

A.M.-A. has served as speaker or advisor for the following companies: Bristol-Myers Squibb, Otsuka, Lundbeck and Pfizer.

C.A. has been a consultant to or has received honoraria or grants from Abott, AMGEN, AstraZeneca, Bristol-Meyers Squibb, Caja Navarra, CIBERSAM, Fundación Alicia Koplowitz, Instituto de Salud Carlos III, Janssen Cilag, Lundbeck, Merck, Ministerio de Ciencia e Innovación, Ministerio de Sanidad, Ministerio de Economía y Competitividad, Mutua Madrileña, Otsuka, Pfizer, Roche, Servier, Shire, Takeda and Schernig Plough.

V.B.-M. has received grants and served as consultant, advisor or continuing medical education (CME)

speaker during the last 3 years for the following entities: Almirall, Angelini, AstraZeneca, Bristol-Myers-Squibb, Janssen; Juste, Lundbeck, Otsuka, and Fundación Alicia Koplowitz.

M.P.G.-P. has served as consultant and/or speaker for Janssen-Cilag, Lilly, Lundbeck, Otsuka, Pfizer, Servier, Roche, and Rovi, and has received grants from the Ministry of Economy and Competitiveness (Instituto de Salud Carlos III, FIS), European Comission (FP7) and CIBERSAM.

F.C. has served as advisor or speaker for the following companies (lifetime): Adamed, Astra Zeneca, Bristol-Myers, Eli Lilly, Glaxo-Smith-Kline, Lundbeck, MSD Merck, Otsuka, Pfizer Inc., Rovi, Sanofi-Aventis, Sanovel, Shire and Tecnifar. He has received copyright fees from: Cambridge University Press, Igaku-Shoin Ltd, Solal Ed., Ars Médica, Giovani Fioriti Ed., Medipage, La Esfera de Los Libros, Morales i Torres Ed., Panamericana, Mayo Ed. & Columna.

A. I. has served as speaker or advisor for the following companies: Adamed, Bristol-Myers Squibb, Ferrer, Janssen-Cilag, Lundbeck, Pfizer, Servier and Otsuka.

B.L.A. has served as a speaker for Bristol-Myers Squibb, Otsuka and Janssen-Cilag.

J.M.C. has served as advisor or speaker for the following entities: Almirall, AstraZeneca, Bristol-Myers Squibb, Janssen-Cilag, Ferrer, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Sanofi-Aventis, Servier, the Spanish Ministry of Science and Innovation (CIBERSAM), the Ministry of Science (Carlos III Institute) and Wyeth.

A.G.-P. has received grants and served as consultant, advisor or CME speaker for the following entities: AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Janssen-Cilag, Lundbeck, Merck, Otsuka, Pfizer, Sanofi-Aventis, Servier, the Spanish Ministry of Science and Innovation (CIBERSAM), the Ministry of Science (Carlos III Institute), the Basque Government, the Stanley Medical Research Institute and Wyeth.

The remaining authors have no conflicts of interest.

References

Altshuler LL, Ventura J, van Gorp WG, Green MF, Theberge DC, Mintz J (2004). Neurocognitive function in clinically stable men with bipolar I disorder or schizophrenia and normal control subjects. *Biological Psychiatry* **56**, 560–569.

American Psychiatric Association (2000). Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR). APA: Arlington, VA.

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

Binder LM, Iverson GL, Brooks BL (2009). To err is human: 'abnormal' neuropsychological scores and variability are common in healthy adults. *Archives of Clinical Neuropsychology* **24**, 31–46.

Bonnin CM, Martinez-Aran A, Torrent C, Pacchiarotti I, Rosa AR, Franco C, Murru A, Sanchez-Moreno J, Vieta E (2010). Clinical and neurocognitive predictors of functional outcome in bipolar euthymic patients: a long-term, follow-up study. *Journal of Affective Disorders* **121**, 156–160.

Bonnin CM, Sanchez-Moreno J, Martinez-Aran A, Sole B, Reinares M, Rosa AR, Goikolea JM, Benabarre A, Ayuso-Mateos JL, Ferrer M, Vieta E, Torrent C (2012). Subthreshold symptoms in bipolar disorder: impact on neurocognition, quality of life and disability. *Journal of Affective Disorders* **136**, 650–659.

Bonnín CM, Torrent C, Arango C, Amann BL, Solé B, González-Pinto A, Crespo JM, Tabarés-Seisdedos R, Reinares M, Ayuso-Mateos JL, García Portilla MP, Ibáñez A, Salamero M, Vieta E, Martínez-Arán A, the CIBERSAM Functional Remediation Group (in press). Functional remediation in bipolar disorder: 1-year follow-up of neurocognitive and functional outcome. *British Journal of Psychiatry* **207**, doi:10.1192/bjp.bp.114.162123.

Bonnin CM, Torrent C, Vieta E, Martínez-Arán A (2014). Restoring functioning in bipolar disorder: functional remediation. *Harvard Review of Psychiatry* **22**, 326–330.

Bourne C, Aydemir O, Balanza-Martinez V, Bora E, Brissos S, Cavanagh JT, Clark L, Cubukcuoglu Z, Dias VV, Dittmann S, Ferrier IN, Fleck DE, Frangou S, Gallagher P, Jones L, Kieseppa T, Martinez-Aran A, Melle I, Moore PB, Mur M, Pfennig A, Raust A, Senturk V, Simonsen C, Smith DJ, Bio DS, Soeiro-de-Souza MG, Stoddart SD, Sundet K, Szoke A, Thompson JM, Torrent C, Zalla T, Craddock N, Andreassen OA, Leboyer M, Vieta E, Bauer M, Worhunsky PD, Tzagarakis C, Rogers RD, Geddes JR, Goodwin GM (2013). Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. *Acta Psychiatrica Scandinavica* **128**, 149–162.

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* **44**, 3083–3096.

Colom F, Vieta E (2006). *Psychoeducation Manual for Bipolar Disorder*. Cambridge University Press: Cambridge, UK.

Colom F, Vieta E, Martinez-Aran A, Garcia-Garcia M, Reinares M, Torrent C, Goikolea JM, Banus S, Salamero M (2002). Spanish version of a scale for the assessment of mania: validity and reliability of the Young Mania Rating Scale. *Medicina Clinica* (*Barcelona*) **119**, 366–371.

Colom F, Vieta E, Martinez-Aran A, Reinares M, Goikolea JM, Benabarre A, Torrent C, Comes M, Corbella B, Parramon G, Corominas J (2003). A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. *Archives of General Psychiatry* **60**, 402–407.

Conners CK (2000). *Conner's Continuous Performance Test II (CPT-II V.5)*. Multi-Health Systems: North Tonawanda, NY.

Deckersbach T, Nierenberg AA, Kessler R, Lund HG, Ametrano RM, Sachs G, Rauch SL, Dougherty D (2010). RESEARCH: cognitive rehabilitation for bipolar disorder: an open trial for employed patients with residual

depressive symptoms. *CNS. Neurosciences and Therapeutics* **16**, 298–307.

Delis DC, Kramer JH, Kaplan E, Ober B (1987). *California Verbal Learning Test*. Psychological Corporation: New York.

Depp CA, Mausbach BT, Harmell AL, Savla GN, Bowie CR, Harvey PD, Patterson TL (2012). Meta-analysis of the association between cognitive abilities and everyday functioning in bipolar disorder. *Bipolar Disorders* **14**, 217–226.

Fuentes-Dura I, Balanza-Martinez V, Ruiz-Ruiz JC, Martinez-Aran A, Giron M, Sole B, Sanchez-Moreno J, Gomez-Beneyto M, Vieta E, Tabares-Seisdedos R (2012). Neurocognitive training in patients with bipolar disorders: current status and perspectives. *Psychotherapy and Psychosomatics* **81**, 250–252.

Golden CJ (1978). *Stroop Color and Word Test*. Stoelting: Chicago, IL.

Hamilton M (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry* **23**, 56–62.

Heaton RK (1981). *Wisconsin Card Sorting Test Manual*. Psychological Assessment Resources: Odessa, FL.

Hellvin T, Sundet K, Simonsen C, Aminoff SR, Lagerberg TV, Andreassen OA, Melle I (2012). Neurocognitive functioning in patients recently diagnosed with bipolar disorder. *Bipolar Disorders* **14**, 227–238.

Iverson GL, Brooks BL, Langenecker SA, Young AH (2011). Identifying a cognitive impairment subgroup in adults with mood disorders. *Journal of Affective Disorders* **132**, 360–367.

Lopez-Jaramillo C, Lopera-Vasquez J, Gallo A, Ospina-Duque J, Bell V, Torrent C, Martinez-Aran A, Vieta E (2010). Effects of recurrence on the cognitive performance of patients with bipolar I disorder: implications for relapse prevention and treatment adherence. *Bipolar Disorders* **12**, 557–567.

Martínez-Arán A, Torrent C, Solé B, Bonnín CM, Rosa AR, Sánchez-Moreno J, Vieta E (2011). Functional remediation for bipolar disorder. *Clinical Practice and Epidemiology in Mental Health* **7**, 112–116.

Martinez-Aran A, Vieta E, Torrent C, Sanchez-Moreno J, Goikolea JM, Salamero M, Malhi GS, Gonzalez-Pinto A, Daban C, Alvarez-Grandi S, Fountoulakis K, Kaprinis G, Tabares-Seisdedos R, Ayuso-Mateos JL (2007). Functional outcome in bipolar disorder: the role of clinical and cognitive factors. *Bipolar Disorders* **9**, 103–113.

Martino DJ, Marengo E, Igoa A, Scapola 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.

Martino DJ, Strejilevich SA, Marengo E, Ibáñez A, Scápola M, Igoa A (2014). Toward the identification of neurocognitive subtypes in euthymic patients with bipolar disorder. *Journal of Affective Disorders* **167**, 118–124.

Martino DJ, Strejilevich SA, Scapola M, Igoa A, Marengo E, Ais ED, Perinot L (2008). Heterogeneity in cognitive functioning among patients with bipolar disorder. *Journal of Affective Disorders* **109**, 149–156.

Ramos-Brieva JA, Cordero-Villafáfila A (1986). Validation of the Castillian version of the Hamilton Rating Scale for Depression [article in Spanish]. *Actas luso-españolas de Neurología, Psiquiatría y Ciencias Afines* **14**, 324–334.

Reichenberg A, Harvey PD, Bowie CR, Mojtabai R, Rabinowitz J, Heaton RK, Bromet E (2009). Neuropsychological function and dysfunction in schizophrenia and psychotic affective disorders. *Schizophrenia Bulletin* **35**, 1022–1029.

Reinares M, Sanchez-Moreno J, Fountoulakis KN (2014). Psychosocial interventions in bipolar disorder: what, for whom, and when. *Journal of Affective Disorders* **156**, 46–55.

Reitan RM (1958). Validity of the Trailmaking Test as a indication of organic brain damage. *Perceptual and Motor Skills* **8**, 271–276.

Rey A (1997). *Test de copia de la figura compleja (The Rey–Osterrieth Complex Figure)*. TEA ediciones: Madrid.

Rosa AR, Sanchez-Moreno J, Martinez-Aran A, Salamero M, Torrent C, Reinares M, Comes M, Colom F, Van RW, Ayuso-Mateos JL, Kapczinski F, Vieta E (2007). Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. *Clinical Practice and Epidemology in Mental Health* **3**, 5.

Sole B, Martinez-Aran A, Torrent C, Bonnin CM, Reinares M, Popovic D, Sanchez-Moreno J, Vieta E (2011). Are bipolar II patients cognitively impaired? A systematic review. *Psychological Medicine* **41**, 1791–1803.

Tabares-Seisdedos R, Balanza-Martinez V, Sanchez-Moreno J, Martinez-Aran A, Salazar-Fraile J, Selva-Vera G, Rubio C, Mata I, Gomez-Beneyto M, Vieta E (2008). Neurocognitive and clinical predictors of functional outcome in patients with schizophrenia and bipolar I disorder at one-year follow-up. *Journal of Affective Disorders* **109**, 286–299.

Torrent C, Bonnin CM, Martinez-Aran A, Valle J, Amann BL, Gonzalez-Pinto A, Crespo JM, Ibanez A, Garcia-Portilla MP, Tabares-Seisdedos R, Arango C, Colom F, Sole B, Pacchiarotti I, Rosa AR, Ayuso-Mateos JL, Anaya C, Fernandez P, Landin-Romero R, Alonso-Lana S, Ortiz-Gil J, Segura B, Barbeito S, Vega P, Fernandez M, Ugarte A, Subira M, Cerrillo E, Custal N, Menchon JM, Saiz-Ruiz J, Rodao JM, Isella S, Alegria A, Al-Halabi S, Bobes J, Galvan G, Saiz PA, Balanza-Martinez V, Selva G, Fuentes-Dura I, Correa P., Mayoral M., Chiclana G., Merchan-Naranjo J., Rapado-Castro M, Salamero M, Vieta E (2013). Efficacy of functional remediation in bipolar disorder: a multicenter randomized controlled study. *American Journal of Psychiatry* **170**, 852–859.

Torrent C, Martinez-Aran A, del Mar BC, Reinares M, Daban C, Sole B, Rosa AR, Tabares-Seisdedos R, Popovic D, Salamero M, Vieta E (2012). Long-term outcome of cognitive impairment in bipolar disorder. *Journal of Clinical Psychiatry* **73**, e899–e905.

van der Werf-Eldering MJ, Burger H, Holthausen EA, Aleman A, Nolen WA (2010). Cognitive functioning in patients with bipolar disorder: association withdepressive symptoms and alcohol use. *PLoS ONE* **28**, 5.

Vieta E (2014). The bipolar maze: a roadmap through translational psychopathology. *Acta Psychiatrica Scandinavica* **129**, 323–327.

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

Volkert J, Kopf J, Kazmaier J, Glaser F, Zierhut KC, Schiele MA, Kittel-Schneider S, Reif A (2015). Evidence for cognitive subgroups in bipolar disorder and the influence of subclinical depression and sleep disturbances. *European Neuropsychopharmacology* **25**, 192–202.

Wechsler D (1997*a*). *The Wechsler Adult Intelligence Scale – III (WAIS-III)*. Psychological Corporation, San Antonio, TX.

Wechsler D (1997*b*). *Wechsler Memory Scale*, 3rd edn. Psychological Corporation, San Antonio, TX.

Yatham LN, Torres IJ, Malhi GS, Frangou S, Glahn DC, Bearden CE, Burdick KE, Martinez-Aran A, Dittmann S, Goldberg JF, Ozerdem A, Aydemir O, Chengappa KN (2010). The International Society for Bipolar Disorders-Battery for Assessment of Neurocognition (ISBD-BANC). *Bipolar Disorders* **12**, 351–363.

Young RC, Biggs JT, Ziegler VE, Meyer DA (1978). A rating scale for mania: reliability, validity and sensitivity. *British Journal of Psychiatry* **133**, 429–435.