Spanish Journal of Psychiatry and Mental Health 17 (2024) 181–189

Available online at www.sciencedirect.com

Spanish Journal of Psychiatry and Mental Health

journal homepage: http://http://www.elsevier.es/sjpmh

Clinical trials and protocols

Functional Remediation for Older Adults with Bipolar Disorder (FROA-BD): Study protocol for a randomized controlled trial

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ARTICLE INFO

Article history:
Received 16 December 2021
Accepted 25 January 2022
Available online 02 February 2022

Keywords:
Older adults with bipolar disorder
Functional remediation
Cognition
Functioning
Interventions

ABSTRACT

Background: Older Adults with Bipolar Disorder (OABD) show cognitive impairments with a negative impact on psychosocial functioning and quality of life. However, to date any intervention for the improvement of functioning has been developed for OABD. The current project aims to demonstrate the efficacy of the Functional Remediation program (FR) specifically adapted to OABD, over 60 years old, for improving functional outcome.
Methods: This is an experimental, randomized-controlled trial. Two groups will be included: the experimental group ($n = 42$) will receive a 4-month intervention consisting of 32 sessions of treatment and the control group which will receive treatment as usual (TAU) ($n = 42$). The intervention will result from the adaptation of the Functional Remediation program for OABD (FROA-BD), that has already proven its efficacy at improving psychosocial functioning in patients with bipolar disorder. Clinical, neuropsychological and functional evaluations will be carried out at baseline, post-intervention and follow-up (one year after baseline evaluation). We hypothesized that patients who have undergone the intervention FROA-BD will improve their psychosocial functioning, cognitive performance, quality of life and well-being. We also hypothesized that all these changes will remain stable after eight month follow-up.
Conclusions: The results will provide evidence of the efficacy in improving psychosocial functioning, cognitive performance and quality of life applying the FROA-BD. This project consists in the first attempt to adapt the FR program to OABD population who needs specific needs and approaches. The novelty of this contribution represents an advance in the framework of psychological treatment in later-life bipolar disorder.

Introduction

Bipolar Disorder (BD) is a chronic and severe mental illness characterized by the emergence of alternating mood episodes which range from extreme depression to manic states. Beyond affective episodes, there is consensus considering that cognitive and functional impairment are also core features in a substantial proportion of patients suffering from this mental condition, being both of them responsible of a negative impact on perceived quality of life (QoL).[1] Despite the association between cognitive performance, clinical and functioning outcomes in patients with BD has been largely explored among adult and middle-aged patients, there is a dearth of research about aging process among older adults with bipolar disorder (OABD) as well as in the design of tailored intervention targeting older individuals. Due to the longer life expectancy and subsequent aging of the world's population, is becoming increasingly common that people presenting with chronic health condition, including BD, survives longer. Currently, it has been estimated roughly the 25% of whole BD population is over 60 years old[2] and it is expected that this percentage will increase up to 50% by 2030.[3] Consequently, there is an urgent need not only to explore specific implication in clinical and neurocognitive course and to investigate symptom development throughout this vital stage elder-life phase, but also to design specific interventions aimed to cope with special needs in this specific population.

In this sense, is strongly advocated that OABD should be considered as a specific population since they present intrinsic clinical,

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https://doi.org/10.1016/j.rpsm.2022.01.004

psychosocial and neurocognitive characteristics, in addition to higher rates of physical comorbidity when compared to younger patients.[4,5] Functional impairment as well as clinical features, cognitive impairment and physical comorbidities are usual among OABD and all contribute to the burden of this disease.[6,7] Results from different studies indicate that the severity of clinical manifestations in OABD differ from those observed among younger patients with BD. In this regard, in a recent work based on the Global Aging & Geriatric Experiments in Bipolar Disorder (GAGE-BD) leaded by Sajatovic and colleagues[2] using a large sample of OABD ($n = 1377$), the authors conclude that higher presence of either manic and depressive symptomatology was associated to poorer functioning, especially in older individuals.

Cognitive performance in this group of patients should be considered as a core variable, since roughly 50% of these patients would present cognitive impairment,[8] mainly, concerning memory, processing speed and executive functions[9] when compared to healthy controls. Likewise, a recent meta-analysis focused on neuropsychological performance of a sample of OABD[10] concluded, that the OABD group showed a significant poorer performance compared to healthy controls across many cognitive domains, especially in verbal learning and memory, and also in processing speed, working memory, psychomotor speed, executive functions, and attention. These results reinforce the idea that cognitive impairment persists in late-life in BD, presenting some particularities compared to those results focused on middle-aged patients with BD.

In addition to that, through a cluster analysis method, a cognitive heterogeneity has been detected in OABD finding three distinctive groups. A 42% of OABD patients had similar cognitive performance than HC while 46% showed mild cognitive impairment and, finally, 12% displayed severe cognitive impairment across many cognitive domains.[11] In fact, it is postulated that the cognitive heterogeneity frequently found in BD could be considered as a predictor of functioning disability, despite further longitudinal studies are needed.[12] Apart from this heterogeneity, other approaches have been proposed from a dimensional approach, rather than categories, to understand the severity of the impairment in severe mental disorders. Thus, clinical staging models have been developed, although their validity in daily clinical practice has not yet been demonstrated.[13]

There are discrepancies among studies concerning the concept of cognitive decline due to aging. On the one hand, some studies did not observed significant differences in cognitive profile when comparing with younger patients.[14–16] However, these studies have some limitations, such as small sample sizes and a restricted follow-up period. On the other hand, results from other studies indicate the presence of a significant cognitive decline among OABD[17] and some studies sustain the idea of a higher risk of developing dementia.[18–20] Overall, all the aforementioned results reinforce the need for the design of specific intervention for OABD, avoiding simple extrapolation of those programs whose design was based on evidence obtained with younger population.[21]

To the best of our knowledge, only one group of researchers, leaded by Schouws et al.,[22] has carried out a pilot study with an intervention specifically aimed to enhance cognitive function as well as social functioning in OABD, which was tested in a small sample ($n = 18$) of patients with BD aged over 50 years. This intervention, called "Braintrain", was based on the Functional Remediation program (FR) by Torrent et al.,[23] and consisted of 12 sessions of cognitive training, also including physical exercise, as well as fostering social encounters with peers. The results presented by the authors do not suggest significant changes after completion the program may be due to the small sample size included in the first pilot study.[22] Other study of Tyler and colleagues,[24] after explored a recovery-focused therapy (RfT) for OABD report that certain adaptations were needed for older ages. A study that applied a cognitive remediation intervention in patients with BD identified the hypo-activity in the prefrontal cortex during a working memory task as the best predictor of the efficacy of the CR treatment in executive function domain.[25]

So far, to date implemented psychological interventions for this group of patients present some limitations: firstly, their design has been focused on BD distinctive characteristics but omitting specificities associated to older ages BD population. Secondly, while there are some programs that have been designed for this specific range of age, they are addressed to a wide range of psychiatric conditions without focusing on BD intrinsic features. Another limitation is related to the fact that older-aged participants are usually discharged for participation in clinical trial due to exclusion criteria, especially those participants over 60 years old. Besides, there are some other interventions, non-specific for BD, targeted at older-aged population with severe mental-illness whose main purpose is the improvement of psychosocial functioning which have been demonstrated to exert a positive impact on several psychosocial domain outcomes.[26,27] It follows that to increase the therapeutic benefits in patients belonging to this age group, specific intervention should be designed, adapting them specifically to their needs.[28]

In the last years, the Bipolar and Depressive Disorder Unit has designed and successfully implemented the FR program (FR). This group-format intervention is specifically targeted to patients diagnosed with bipolar disorder which is, nowadays, being adapted to its administration to First-Episode Psychosis (FEP). The original program has demonstrated its efficacy at improving either psychosocial functional outcome,[23] subthreshold affective symptomatology,[29] as well as, verbal memory performance in those patients with a moderate to severe cognitive impairment.[30] Bearing in mind that there is a need to avoid cognitive decline among OABD in order to guarantee an optimal functional outcome and to diminish the burden associate to this mental illness, the next major step involves the adaptation of FR program to be applied to this specific population. In this sense, it should be remarked that a recent systematic review, results suggest that five out of six FR studies carried out reported a clearly benefit in functional outcome, with a moderate size-effect (Cohen's $d = 0.45$), very similar to those obtained with Cognitive Remediation in schizophrenia.[31] Therefore, taking into account that the FR intervention specifically designed for adult patients have demonstrate their efficacy at cognitive and functional outcomes, it seems likely that future design and implementation of specific intervention for OABD would yield similar results.

Aims and hypothesis

This study aims to adapt and evaluate the efficacy of a psychological intervention targeted for OABD (older than 60 years old) for improving functional outcome. This intervention is intended not only to improve psychosocial functioning, but also to reduce clinical symptomatology, which, in turn, may improve autonomy, quality of life and well-being in OABD population. Therefore, our main goals are, (I) to characterize a representative sample of OABD (>60 years old) concerning main demographic, clinical and neurocognitive variables, (II) to test the efficacy of the Functional Remediation for Older Adults with Bipolar Disorder (FROA-BD) versus a Treatment as Usual (TAU) for enhancing functional outcome, and (III) to assess whether the observed improvement remain stable over the eight-month follow-up period (one year after study inclusion). Our secondary outcomes are the (I) improvement of cognitive performance, quality of life and subsyndromal symptoms in the group receiving the intervention compared to TAU group.

As primary outcome, we hypothesize that OABD individuals participating in FROA-BD program will improve their functional outcome as measured by the Functioning Assessment Short Test (FAST)[32] when compared to those individuals receiving TAU. Besides, we expect that this improvement will remain stable at least one year after study inclusion. Secondarily, we hypothesize that OABD patients receiving the FROA-BD intervention would also increase their neurocognitive performance, especially regarding attention, memory and executive functioning domains. In the same vein, we expect that patients participating in the FROA-BD protocol would experience an improvement or their subjective perception of cognitive performance assessed by means of the COBRA; a reduction of affective symptomatology as measured by the Hamilton Depression Rating Scale (HDRS)[33] and the Young Mania Rating Scale (YMRS),[34] as well as an improvement of perceived quality of life and well-being compared to the TAU group.

Methods

Study design

This is a single-center, single-blind, randomized, controlled test-retest clinical study to evaluate the efficacy of the FROA-BD in a representative sample of patients with BD over 60 years old. This study will be carried out in the Bipolar and Depressive Disorders Unit at the Hospital Clinic of Barcelona, which takes part of the Spanish network Center for Biomedical Research in Mental Health (CIBERSAM).[35] It will include two parallel arms (1:1) in order to assess the efficacy of a new psychological intervention as add-on therapy compared with treatment as usual to enhance functional outcome in OABD. This project has been approved by the Ethical Committee of the Hospital Clinic of Barcelona and it will be carried up in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice in compliance with the data protection law in force and anonymization of the collected information.

Participants

The sample will consist of 84 patients with bipolar disorder aged over 60 years that will be recruited at the Bipolar and Depressive Disorder Unit at the Hospital Clinic of Barcelona.

All participants will have to fulfill the following criteria:

1. Inclusion criteria will be: (a) meeting diagnostic criteria according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) for bipolar disorder, either subtype I or II; (b) being aged over 60 years old; (c) being in full or partial remission Young Mania Rating Scale (YMRS) ≤ 10, Hamilton Depression Rating Scale (HDRS) ≤ 14) at the time of the inclusion and assessment; (d) presence of mild to moderate functional impairment as measured by the Functional Assessment Short Test (FAST) ≥ 11; and (e) providing written informed consent to participate.
2. Exclusion criteria will be: (a) presenting an Intelligence Quotient (IQ) lower than 85; (b) having been received any kind of structured psychological intervention in the six previous months; (c) presence of central nervous system (CNS) condition, other than psychiatric, than may influence neurocognitive performance, (such as neurological diseases) or any physical condition that may hamper participation or correct assimilation of the contents of the intervention, (such as severe visual and/or hearing impairment); (d) presenting any other comorbid psychiatric condition except for sleep and/or anxiety disorders, and (e) having received electroconvulsive therapy in the prior six months.

All participants will receive information about the study and relevant questions, if any, will be answered by a member of the research team involved in the study. In order to compensate for time spent on assessment visits and travel, all included patients will receive a financial compensation.

Procedure

All participants will be examined at baseline prior to inclusion in the study, using an extensive battery of questionnaires and tools aimed to assess main demographic, clinical, functioning, quality of life, well-being, and neurocognitive variables. Once the baseline assessment has been carried out, patients will be randomly allocated into the experimental group, which will receive the FROA-BD programme, or to the control group, which will be treated as usual (TAU). Four months later, when the intervention will be finished, all study participants will be assessed, especially on those areas that are supposed to be targeted by the FROA-BD programme (functional outcome as the main outcome, and neurocognitive performance, clinical symptoms, and quality of life and well-being as secondary outcomes), trying to avoid potential re-assessment learning effect by using alternative versions or tests. Finally, one year after inclusion (8 months after completion of the intervention), a complete assessment, mostly identical to which was used at baseline, will be performed (see Fig. 1). In addition to the aforementioned assessment visits, all participants will also be followed up pharmacologically at the Bipolar and Depressive Disorder Unit of the Hospital Clinic of Barcelona, following the guidelines of good clinical practice. Research members involved in assessment will be blind to condition group (FROA-BD or TAU). Two clinical neuropsychologist (therapist and co-therapist) blind to baseline assessment results will conduct the FROA-BD intervention (Table 1).

Data collection

a) Demographic, clinical variables and comorbidity

A semi-structured clinical interview based on the SCID-5[36] will be administered to gather main demographic and clinical variables. The HDRS and the YMRS will be used to evaluate the presence of depressive and manic symptomatology, respectively. The Cumulative Illness Rating Scale-Geriatrics (CIRS-G) Spanish version[37] will be administered in order to assess the presence of any somatic comorbid condition. Medical records will be also reviewed and considered.

b) Psychosocial functioning, quality of life and well-being

Functional outcome will be assessed by the means of the FAST.[32] This interviewer-administered brief scale, which comprises 24 items, was specifically designed to explore functional difficulties in psychiatric population among six specific functional domains (autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time). Overall scores range from 0 to 72, being higher scores indicators of a worse functional impairment.

Quality of life and well-being will be assessed using the Spanish version of the Short Form-36 Health Survey (SF-36)[38] and the Spanish version of the World Health Organisation-Five Well-Being Index (WHO-5),[1] respectively. The SF-36 is self-administered questionnaire which consists of 36 questions measuring eight separate dimensions related to quality of life (physical functioning, role limitation–physical, role limitation–emotional, vitality, mental health, social functioning, pain, and general health). Higher scores indicate better quality of life. WHO-5 is a self-administered short test consisting of 5 items rated on a 6-point scale assessing how

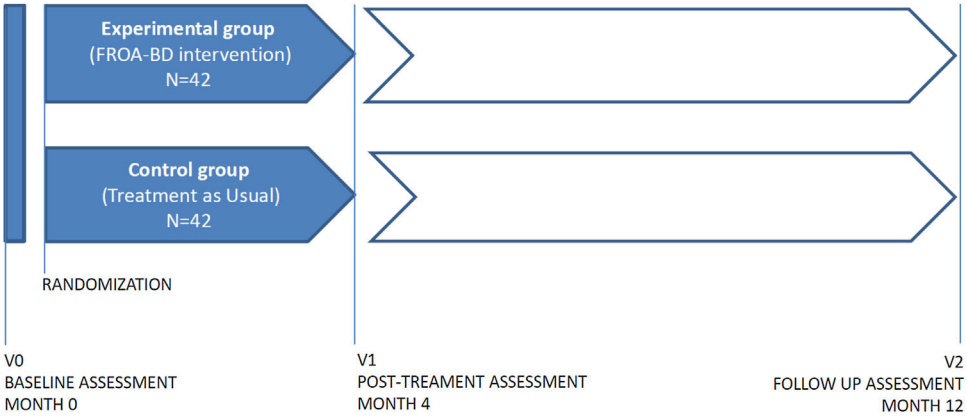

Figure 1. Study design.

Table 1
Outcome measures and assessment time-points.

		Baseline (V0)	Post-treatment (V1-month 4)	Follow-up (V2-month12)
Clinical	HDRS			
	YMRS			
Comorbidity	CIRS-G			
Functioning	FAST			
Well-being and quality of life	SF-36			
	WHO-5			
Cognitive reserve	CRASH			
Cognition	MMSE			
	SCIP-S			
	Vocabulary (WAIS-III)			
	Arithmetic (WAIS-III)			
	Symbol Search (WAIS-III)			
	Digit-Symbol coding (WAIS-III)			
	Digits (WAIS-III)			
	Letter-Number Sequencing (WAIS-III)			
	WSCT			
	SCWT			
	ROCF			
	CPT-II			
	TMT-A			
	TMT-B			
	CVLT			
	F-A-S (COWAT)			
	Animal Naming (COWAT)			
	Boston Naming Test			
	Juice Line Orientation-form H			
	COBRA			

CIRS-G: Cumulative Illness Rating Scale-Geriatrics; COBRA: Cognitive Complaints in Bipolar Disorder Rating Assessment; COWAT: Controlled Oral Word Association Test; CPT: Continuous Performance Test; CRASH: Cognitive Reserve Assessment Scale in Health; CVLT: California Verbal Learning test; FAST: Functional Assessment Short Test; HDRS: Hamilton Depression Rating Scale; MMSE: Mini-Mental State Examination; ROCF: Rey Osterrieth Copy figure; SCIP: Screen for Cognitive Impairment in Psychiatry; SCWT: Stroop Color Word Test; SF-36: Short Form-36 Health Survey; TMT-A: Trail Making Test part A; TMT-B: Trail Making Test part B; YMRS: Young Mania Rating Scale; WAIS-III: Wechsler Adults Intelligence Scale 3rd edition; WCST: Wisconsin Card Sorting Test; WHO-5: World Health Organisation-Five Well-Being Index.

the individual has been feeling over the last two weeks. Raw score ranges from 0 to 25. The higher scores the better perceived subjective well-being. In order to obtain the feedback from the patients, we also will consider the patient's satisfaction with the intervention through a self-applied instrument measured in likert scale (from 0 to 10) where the maximum score corresponds to completely satisfied.

c) Cognitive reserve

The Cognitive Reserve Assessment Scale in Health (CRASH)[39] is an interviewer-administered, quick and easy-to-apply tool which was designed to evaluate cognitive reserve in psychiatric patients, especially in those suffering from severe mental conditions. This 23-item scale assess the three domains: education, occupation and intellectual and leisure activities, which are the main domains involved in cognitive reserve. This scale provides an overall score as well as a score for each assessed domain. The maximum score is 90. Higher scores indicate higher cognitive reserve.

d) Neuropsychological assessment

In this study, we will to assess cognitive performance both from the subjective and objective perspective. For gathering data

regarding subjective cognitive complaints, we will use the Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA).[40] This self-administered instrument consist of 16 items which are rated on a 4-point scale ((0) never; (1) sometimes; (2) frequently; (3) always). COBRA total score results is calculated by totaling all item scores and higher scores indicate a worse subjective cognitive performance.

For the objective assessment of neurocognitive function two different batteries of tests have been selected depending of time-point assessment:

(I) Extended battery

Overall cognition will be assessed by means of the Mini Mental Status Examination (MMSE)[41] and the Spanish version of the Screen for Cognitive Impairment in Psychiatry (SCIP-S).[42] Both of these brief scales were specifically designed for detecting cognitive deficits, being the latter specific for psychiatric population. The SCIP-S has three alternative forms as three different time-points of the study in order to avoid learning effect bias.

The **estimated Intelligence quotient** (IQ) will be calculated based on the results in the Vocabulary subtest from the Wechsler Adult Intelligence Scale (WAIS-III).[43]

The **Executive functions** will be measured through the computerized Wisconsin Card Sorting Test (WSCT),[44] the Stroop Color-Word Test (SCWT)[45]; the Phonemic (F-A-S) component of the Controlled Oral Word Association Test (COWAT)[46] the copy of the Rey Osterrieth Complex Figure (ROCF)[47] and the Trail Making Test-Part B (TMT-B).[48]

Attention will be assessed by using the computerized version of the Continuous Performance Test (CPT-II)[49] and the Trail Making Test-Part A (TMT-A).[48]

The **Working memory index (WM)** will be calculated based on the performance in three subtest from the WAIS-III: Arithmetic, Digits, and Letter-Number sequencing.[43]

The assessment of the **Processing speed** index will comprise two subtests of the WAIS-III: the Symbol Search and the Digit-symbol Coding subtests from the WAIS-III.[43]

Verbal Learning and Memory performance will be evaluated through the California Verbal Learning Test (CVLT).[50]

To examine **visual memory** The Rey Osterrieth Complex Figure-immediate recall (ROCF)[47] will be administered.

Language domain will be examined by means of the Boston Naming Test (BNT)[51] and the Categorical (Animal Naming) component of the COWAT.[46]

Visuoespatial domain will be assessed by the Juice Line Orientation (JLO).[52]

This battery will be administered at baseline visit (V0) and 12-month follow-up visit after inclusion (V2), with the exception of vocabulary subtest which only will be applied at baseline visit since it is a measure of estimated IQ.

(II) Brief cognitive battery

In order to avoid potential learning effects, we selected a brief cognitive battery consisting of the SCIP-S form 2, the SCWT, the TMT part A and B, the CPT-II, and the semantic and phonemic components of the COWAT. This brief battery of test will be administered at post-intervention visit (V1), four months after inclusion.

Intervention

In the FROA-BD trial, patients will be allocated in a 1:1 ratio to receive 16 weeks of FROA-BD intervention, or treatment as usual, stratified by age, sex and educational level. Randomization will be accomplished with the use of a computer-generated sequence.

The FROA-BD is an adaptation of the Functional Remediation Program.[23] The original FR program, which has been implemented in our institution, consists of 21 sessions in a 90 min weekly format. The content of the sessions includes psychoeducation about cognitive deficits, their impact on daily life with the objective of providing strategies to cope with cognitive deficits. Last sessions are focused at improving communication skills, autonomy and giving coping strategies to deal with stress. However, based on the intrinsic characteristics of OABD population and our expertise in the field, we consider that both duration and contents of sessions are unsuited to this specific population. Therefore, we propose an adaptation that involves modifications concerning duration, specific contents and frequency of the sessions. In the same line as in its original version, we will maintain its ecological nature, using an attractive and adapted material which could be applicable in daily life. The present intervention (FROA-BD), aimed to improve functioning in daily life, also addresses, in line with original FR program, neurocognitive issues such as attention, memory, and executive functions, but also new additional domains, such as language and visuospatial skills, since those have been reported to be affected in advances ages and in OABD population. All the intervention is based on ecological tasks that could be easily transported from clinical setting to home and activities of daily living. Patients will be also trained in some skills and techniques targeting most affected cognitive domains in this group of age in order to enhance their functional outcome. Most of the techniques will be based on paper-and-pencil tasks. Activities could be carried out individually or involving the whole group. Audiovisual material and mobile apps will be also used.

As a general rule, the sessions will begin with an explanation by the therapists of the theoretical basis, followed by individual and group practice of what has been explained throughout the session. At the end of each session, participants will be invited to do some "homework" aimed to reinforce the strategies worked on during the session. These tasks will be optional and will be adjusted to the individual profile of the patient if needed.

This intervention will consist of 32 face-to-face group sessions (30 for patients and 2 for relatives) lasting 90 min that will be performed twice a week. Table 2 describes the content of the sessions. The content will focus on the following domains: Cognitive impairment and bipolar disorder (2 sessions), healthy lifestyle habits (2 sessions), attention (4 sessions), visual and verbal memory (6 sessions), executive functions and its components (6 sessions), language (2 sessions), visuospatial skills and orientation (1 session), analogical and digital strategies for everyday life (2 sessions), emotional management and social skills (2 sessions), autonomy (2 sessions) that will be conducted by the social worker of our unit, and a final session to sum up the contents of the program, obtain feedback and to evaluate patients' satisfaction. In addition to these 30 patient-oriented sessions, two sessions will be carried out with one or two relatives per patient. The aim of these latter sessions would be to introduce the FROA-BD intervention to the family as well as to give some advice on how they can help their relatives to enhance practice and reinforce them. Sessions with relatives will be run out without patients being present.

Outcome measures

The primary outcome measure will be changes in functioning assessed by means of the FAST from baseline to endpoint, post-intervention. Other secondary outcomes will be changes in (a) cognitive performance assessed by the neuropsychological tests included in the aforementioned cognitive batteries, (b) indexes of quality of life and well-being assessed by SF-36 and WHO-5, (c) clinical symptomatology using the HDRS and the YMRS, and (d) subjective cognitive complaints by means of the COBRA. Objective

Table 2
Summary of the FROA-BD intervention.

Sessions	Content
Sessions 1 and 2	**Cognitive impairment and bipolar disorder** Explanation and definition of cognitive functions and how they affect in bipolar disorder Factors that are influencing cognitive performance How cognitive impairment affects daily life Dementia, risk factors and warning signs of cognitive impairment Psychoeducation of BD and specifically in OABD
Sessions 3 and 4	**Healthy lifestyle habits** Importance of maintaining a healthy and balanced diet. Promotion of physical exercise Sleep disturbances and sleep hygiene Substance misuse Late-life medical comorbidities Late-life pharmacological management Leisure activities Practical and ecological tasks focused on this content
Sessions 5, 6, 7 and 8	**Attention** Explanation of attention and its different types (sustained, selective, divided, focused, etc) How it is affected in daily live Learning and practicing attention techniques Exercises for improvement attention ability Strategies and useful tools for daily improvement
Sessions 9, 10, 11, 12, 13 and 14	**Memory** Description of the functioning of memory and its components (encoding, learning, short and long term memory, verbal and visual memory) Exercises for improving encoding, learning and memory abilities Useful resources and strategies to promote its functioning in daily life
Sessions 15, 16, 17, 18, 19 and 20	**Executive functions and its components** Explanation of executive functions and their different components: planning, time management, inhibition, problem solving, cognitive flexibility, verbal fluency. Strategies to promote their functioning Explanation and application of problem solving technique Tasks and exercise for their improvement and maintenance
Sessions 21 and 22	**Language** How language is affected with age. Normal and abnormal signs (anomie, tip of tongue effect, etc.) Task for training verbal fluency, comprehension, naming, description, narrative language, etc
Session 23	**Visuospatial ability and orientation** Description of visuospatial ability and space orientation Orientation in unfamiliar and familiar places Orientation to time Strategies for improving these skills
Sessions 24 and 25	**Strategies for everyday life** Provide resources that can be easily used on a daily life. Combining physical/analogical resources (agendas, notes, organizers, etc.) and electronic resources (apps, mobile, etc.) Introduction to the use of apps and other IT resources
Sessions 26 and 27	**Emotional management and social skills** Social and emotional cognition training Metacognition Cognitive distortions, attribution biases, etc. Detection and understanding of emotions How to improve social communication Social skills, communication, assertiveness, etc.
Sessions 28 and 29	**Autonomy** Explanation of social and community resources for these ages provided by government agencies Dependency and disability laws In people with medical comorbidities, vision problems, hearing, mobility, among others, provide information of some resources (wheelchairs, importance of enabling housing, etc)
Sessions 30 and 31	**Sessions for the relatives/caregivers** Explanation of cognition and how it is affected in BD. Specificities of advanced ages. Importance of the role of the family and caregiver Caregiver burden Resources and strategies for the disease management
Session 32	**Resume. Q&A about the contents of the intervention** Session dedicated to summarize all the content previously learned and give the opportunity to resolve doubts Promote that the strategies learned in the intervention can be applied on a daily basis

and subjective stability in the aforementioned outcome will be also analyzed.

Statistical analyses

The data will be analyzed using the IBM SPSS statistical package (version 23). First, a descriptive analysis of the sample will be carried out to detect potential differences between both groups (experimental group and TAU). Continuous variables will be expressed as means, standard deviations and ranges. For the description of categorical variables, frequencies and/or percentages will be used. For the comparison of categorical and continuous variables between groups, Chi-square, Student's *t*-test or analysis of variance tests will be used, as appropriate, for each type of variable to be analyzed. Secondly, for the longitudinal analysis, a repeated measures ANOVA analysis will be carried out to evaluate the differences between those patients who have received the FROA-BD intervention (experimental group) and those who have not received it (TAU control group). The level of significance will be set at $p < 0.05$. For the main statistical analysis, mixed models for repeated measures will be used to minimize the effect of dropout rates at 12 months follow-up. For each primary and secondary outcomes, results for each group, and the estimated effect size and its precision (95% confidence interval) will be reported.

Based on the previous study of the efficacy of functional rehabilitation in patients with bipolar disorder type I and type II[29,53] where a minimum decrease in the FAST scale of 6 points ($d = 6$) was found, it is estimated that to find a difference of at least 5 points, considering an alpha significance level of 5% and a statistical power (1-beta) of 80%, a total sample of 72 patients (36 per branch) is required, which adjusted by 15% of estimated dropouts results in a total sample of 84 (42 per branch) (calculated with GRANMO software).

Discussion

Population ageing has been increasing in the last decades and the number of older patients with bipolar disorder is expected to significantly increase throughout next years. However, there is a scarcity of specifically targeted interventions in this group of patients. As far as we know, this is the first study intended to adapt and evaluate the efficacy of a psychological intervention specifically tailored for elder patients with BD for improving functional outcome. The purpose of the FROA-BD goes beyond enhancing functioning and also aims to increase autonomy, cognitive performance, subsyndromal symptoms as well as quality of life of this group of patients. In addition, this study would also try to shed light about potential liability factors that may be associated with a poorer daily life adjustment among this population. Specific psychological interventions used in this group of patients are so far virtually non-existent and most of available treatments applied to OABD are simply exportations of therapeutic resources that have been proved to be effective in younger samples or were designed for other psychiatric diagnosis, such as schizophrenia or major depression, or a wider spectrum of them.

These are the cases of both the FR Program[23] and the integrative psychotherapy for BD.[54] The FR Program has been proved to enhance not only functional outcome in adult patients with BD, but also ameliorates subsyndromal symptomatology in patients with BDII.[29] However, despite the improvement of psychosocial functioning in patients who received FR or psychoeducation interventions, no effects were found on peripheral brain derived neurotrophic factor in one-year follow up study.[55] Positive results improving subsyndromal depressive symptoms have also been reported regarding the integrative psychotherapy.[54] This multicomponent therapy combines different evidence-based treatments, such as psychoeducation for patient and caregivers, mindfulness and cognitive and functional remediation.

Concerning younger ages, multiple preventive interventions strategies have been also developed. For instance, in populations which are at high risk for developing bipolar disorder or schizophrenia due to genetic conditions,[56] and also for patients experiencing their first psychotic episode. However, since these interventions are more characteristic of earlier stages of the disease, these are mainly focused on enhancing modifiable strategies to promote an increase in cognitive reserve. However, staging models should be considered in interventional trials,[57] since probably patients in earlier stages may need shorter interventions, whereas more chronic patients with multiple episodes, in later stages, might need longer or at least more intensive treatments to improve their functioning.

A cognitive remediation program has been applied in BD patients showing that the improvement in cognitive abilities had positive effects on functioning,[58] contributing to the improvement of daily-live activities. It is well recognized the straight link between cognitive performance and psychosocial functioning in BD spectrum. Indeed, the cognitive performance is considered as a good long-term predictor of functional outcome. Previous studies have demonstrated the significant impact of cognitive impairment in the functioning in activities of daily living, especially those of memory, attention and executive functions.[59–61] Therefore, based in the widely reported link between and the efficacy of the original FR program[23] in decreasing functional impairment among patients with BD, even in the follow-up period,[62] we consider that training and reinforcement of different cognitive abilities among older patient would enhance not only functional outcome but also quality of life and clinical improvement. Furthermore, we are aimed to design and adapt the FR program format to older age characteristics, all from the perspective of an ecological approach, providing strategies that could be easily applied in daily- life activities and, thus, facilitating the transference to everyday situations. We expect a direct impact on the improvement of daily functioning, on well-being and on quality of life. Apart from the benefits that could be obtained on functioning, the longitudinal follow-up will provide an opportunity to further identify risk factors that may increase the cognitive impairment. Secondly, it lets a strategy to get a close monitoring of these patients who, due to the age and BD disease, are at increased risk of developing a progressive cognitive decline, thus, it is also a potential tool to make a preventive strategy in terms of cognitive decline.

Concerning the age for the inclusion criteria, note that, in contrast to the last ISBD task force consensus[63] in which the age to consider OABD was established at 50, we will include patients at 60 or older. This is due to the fact that the original FR program on which we have inspired as well as other intervention programs commonly carried out, used to establish the cut-off point below the age of 60; therefore, we tried to cover that age range that has been traditionally excluded in clinical trials.

Differently from the original FR program, the present adaptation differs in terms of length and frequency (21 sessions/weekly during 6 months *vs* 32 sessions, twice a week for 4 months). On the one hand, this will allow the creation of a more in-depth and tailored content of the sessions to be more easily assimilated by this specific group of elder participants. Due to the aging process itself, this group will have different needs when it comes to assimilating and consolidating information. Therefore, the content as well as number of sessions dedicated to each cognitive domain will be adapted and structured according to this group of age characteristics. On the other hand, the intensive format of the FROA-BD, with shorter length of the treatment and increased number of sessions per week for a reduced number of participants, would enhance recruitment

and make easier to be implemented in all kind of clinical sites. It also would enhance the monitoring and follow-up of possible changes in clinical symptomatology and, thus, early detection of potential relapses among participants. Despite the frequency of sessions per week is high, we expect high attendance rates since patients in this range of age are more free from work commitments and have more free time, facilitating compliance to the therapy. Finally, due to the higher rates of disability observed in this group of patients, we believe that this intervention may be a cost-effective tool to enhance autonomy and to reduce consumption of public health and social resources by this population.

This study is not exempt from limitations. One of the possible limitations is the potential loss of subjects during the intervention or the follow-up period. It is also possible that drop-outs from therapy may occur due to the frequent presence of different medical comorbidities among this group of patients. However, since the majority of patients will be followed in our program, we expect the number of withdrawals to be lower than expected (around 15%). On the other hand, the inclusion of patients in clinical remission (and not with strict criteria of euthymia) could have a confounding effect on the results, but at the same time it would allow us to broaden the population to be treated and may be more representative of daily clinical practice real-world population. Nevertheless, when the analysis of the results will be carried out, the impact of these confounding variables will be taken into account, following the recommendations of the ISBD Cognition Task Force. All important adverse events or unintended effects in each group will be reported. Finally, although it would be interesting to explore the stability of the results after the intervention over a longer period of time, we have chosen to adjust the study design to the time frame requested by the characteristics of the funding call (3 years per project).

Authors' contributions

LM, EJ, AMA and EV conceived the study with substantial contributions from the other authors. LM and EJ wrote the first draft with critical and intellectual contributions from AMA, BS, CT, CMB and EV. All authors substantially participated in and approved the final draft for submission to the journal.

Funding

This study is funded by the Ministerio de Ciencia e Innovación, Instituto de Salud Carlos III through FIS-Proyectos de Investigación en salud (PI20/00060).

Conflict of interest

All the authors declare no conflict of interest related to this manuscript.

Acknowledgments

The authors of this study would like to thank the support of the Spanish Ministry of Science and Innovation (PI20/0060) integrated into the Plan Nacional de I+D+I and co-financed by the ISCIII-Subdirección General de Evaluación and the Fondo Europeo de Desarrollo Regional (FEDER); the Instituto de Salud Carlos III; the CIBER of Mental Health (CIBERSAM); the Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017 SGR 1365) and the CERCA Programme.

References

1. Bonnín CM, Yatham LN, Michalak EE, Martínez-Arán A, Dhanoa T, Torres I, et al. Psychometric properties of the well-being index (WHO-5) spanish version in a sample of euthymic patients with bipolar disorder. *J Affect Disord*. 2018;228:153–159.
2. Sajatovic M, Dols A, Rej S, Almeida OP, Beunders AJM, Blumberg HP, et al. Bipolar symptoms, somatic burden, and functioning in older-age bipolar disorder: analyses from the Global Aging & Geriatric Experiments in Bipolar Disorder Database project. *Bipolar Disord*. 2021:1–12.
3. Jeste DV, Alexopoulos GS, Bartels SJ, Cummings JL, Gallo JJ, Gottlieb GL, et al. Consensus statement on the upcoming crisis in geriatric mental. Research agenda for the next 2 decades. *Arch Gen Psychiatry*. 1999;56:848–853.
4. Kessing LV. Diagnostic subtypes of bipolar disorder in older versus younger adults. *Bipolar Disord*. 2006;8:56–64.
5. Nivoli AMA, Murru A, Pacchiarotti I, Valenti M, Rosa AR, Hidalgo D, et al. Bipolar disorder in the elderly: a cohort study comparing older and younger patients. *Acta Psychiatr Scand*. 2014;130:364–373.
6. Gildengers A, Tatsuoka C, Bialko C, Cassidy KA, Dines P, Emanuel J, et al. Correlates of disability in depressed older adults with bipolar disorder. *Cut Edge Psychiatry Pract*. 2013;2013:332–338.
7. Lala SV, Sajatovic M. Medical and psychiatric comorbidities among elderly individuals with bipolar disorder: a literature review. *J Geriatr Psychiatry Neurol*. 2012;25:20–25.
8. Gildengers AG, Butters MA, Seligman K, McShea M, Miller MD, Mulsant BH, et al. Cognitive functioning in late-life bipolar disorder. *Am J Psychiatry*. 2004;161:736–738.
9. Samamé C, Martino DJ, Strejilevich SA. A quantitative review of neurocognition in euthymic late-life bipolar disorder. *Bipolar Disord*. 2013;15:633–644.
10. Montejo L, Torrent C, Jiménez E, Blumberg HP, Martínez-Arán A, Burdick KE, et al. Cognition in older adults with bipolar disorder: an ISBD task force systematic review and meta-analysis based on a comprehensive neuropsychological assessment. *Bipolar Disord*. 2021.
11. Montejo L, Jiménez E, Solé B, Murru A, Arbelo N, Benabarre A, et al. Identifying neurocognitive heterogeneity in Older Adults with Bipolar Disorder: a cluster analysis. *J Affect Disord*. 2022;298:522–531.
12. Burdick KE, Millett CE. Cognitive heterogeneity is a key predictor of differential functional outcome in patients with bipolar disorder. *Eur Neuropsychopharmacol*. 2021;53:4–6.
13. de la Fuente-Tomas L, Sánchez-Autet M, García-Álvarez L, González-Blanco L, Velasco Á, Sáiz Martínez PA, et al. Clinical staging in severe mental disorders; bipolar disorder, depression and schizophrenia. *Rev Psiquiatr Salud Ment*. 2019;12:106–115.
14. Delaloye C, Moy G, De Bilbao F, Weber K, Baudois S, Haller S, et al. Longitudinal analysis of cognitive performances and structural brain changes in late-life bipolar disorder. *Int J Geriatr Psychiatry*. 2011;26:1309–1318.
15. Schouws S, Comijs H, Dols A, Beekman ATF, Stek ML. Five-year follow-up of cognitive impairment in older adults with bipolar disorder. *Bipolar Disord*. 2016;18:148–154.
16. Strejilevich SA, Martino DJ. Cognitive function in adulthood and elderly euthymic bipolar patients: a comparison to test models of cognitive evolution. *J Affect Disord*. 2013;150:1188–1191.
17. Gildengers AG, Mulsant BH, Begley A, Mazumdar S, Hyams AV, Reynolds CF, et al. The longitudinal course of cognition in older adults with bipolar disorder. *Bipolar Disord*. 2009;11:744–752.
18. Wu KY, Chang CM, Liang HY, Wu CS, Chia-Hsuan Wu E, Chen CH, et al. Increased risk of developing dementia in patients with bipolar disorder: a nested matched case-control study. *Bipolar Disord*. 2013;15:787–794.
19. Velosa J, Delgado A, Finger E, Berk M, Kapczinski F, de Azevedo Cardoso T. Risk of dementia in bipolar disorder and the interplay of lithium: a systematic review and meta-analyses. *Acta Psychiatr Scand*. 2020.
20. Diniz BS, Teixeira AL, Cao F, Gildengers A, Soares JC, Butters MA, et al. History of bipolar disorder and the risk of dementia: a systematic review and meta-analysis. *Am J Geriatr Psychiatry*. 2017;25:357–362.
21. Dols A, Beekman A. Older age bipolar disorder. *Clin Geriatr Med*. 2020;36:281–296.
22. Schouws SNTM, Orhan M, Korten N, Zyto S, Beekman ATF, Kupka RW, et al. Evaluating feasibility and satisfaction of a group intervention for mild cognitive impairment in older age bipolar disorder: «Brain train». *Bipolar Disord*. 2021.
23. Torrent C, Del Mar Bonnin C, Martínez-Arán A, Valle J, Amann BL, González-Pinto A, et al. Efficacy of functional remediation in bipolar disorder: a multicenter randomized controlled study. *Am J Psychiatry*. 2013;170:852–859.
24. Tyler E, Lobban F, Long R, Jones SH. Developing a recovery-focused therapy for older people with bipolar disorder: a qualitative focus group study. *BMJ Open*. 2021;11:1–10.
25. Miskowiak KW, Møller AB, Ott CV. Neuronal and cognitive predictors of improved executive function following action-based cognitive remediation in patients with bipolar disorder. *Eur Neuropsychopharmacol*. 2021;47:1–10.
26. Mueser KT, Pratt SI, Bartels SJ, Swain K, Forester B, Cather C, et al. Randomized trial of social rehabilitation and integrated health care for older people with severe mental illness. *J Consult Clin Psychol*. 2010;78:561–573.
27. Patterson TL, Mausbach BT, McKibbin C, Goldman S, Bucardo J, Jeste DV. Functional Adaptation Skills Training (FAST): a randomized trial ofz a psychosocial intervention for middle-aged and older patients with chronic psychotic disorders. *Schizophr Res*. 2006;86:291–299.

28. Corbera S, Wexler BE, Poltorak A, Thime WR, Kurtz MM. Cognitive remediation for adults with schizophrenia: does age matter? *Psychiatry Res*. 2017;247:21–27.
29. Solé B, Bonnin CM, Mayoral M, Amann BL, Torres I, González-Pinto A, et al. Functional remediation for patients with bipolar II disorder: improvement of functioning and subsyndromal symptoms. *Eur Neuropsychopharmacol*. 2015;25:257–264.
30. Bonnin CM, Reinares M, Martínez-Arán A, Balanzá-Martínez V, Sole B, Torrent C, et al. Effects of functional remediation on neurocognitively impaired bipolar patients: enhancement of verbal memory. *Psychol Med*. 2016;46:291–301.
31. Tsapekos D, Seccomandi B, Mantingh T, Cella M, Wykes T, Young AH. Cognitive enhancement interventions for people with bipolar disorder: a systematic review of methodological quality, treatment approaches, and outcomes. *Bipolar Disord*. 2019.
32. Rosa AR, Sánchez-Moreno J, Martínez-Aran A, Salamero M, Torrent C, Reinares M, et al. Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. *Clin Pract Epidemiol Ment Health*. 2007;3:5.
33. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56.
34. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;133:429–435.
35. Salagre E, Arango C, Artigas F, Ayuso-Mateos JL, Bernardo M, Castro-Fornieles J, et al. CIBERSAM: ten years of collaborative translational research in mental disorders. *Rev Psiquiatr Salud Ment*. 2019;12:1–8.
36. First MB. *SCID-5-CV: structured clinical interview for DSM-5 disorders, clinician version*. vol. 95; 2016.
37. Rosas-Carrasco O, González-Flores E, Brito-Carrera AM, Vázquez-Valdez OE, Peschard-Sáenz E, Gutiérrez-Robledo LM, et al. Evaluación de la comorbilidad en el adulto mayor. *Rev Med Inst Mex Seguro Soc*. 2011;49:153–162.
38. Alonso J, Prieto L, Antó JM. The Spanish version of the SF-36 Health Survey (the SF-36 health questionnaire): an instrument for measuring clinical results. *Med Clin (Barc)*. 1995;104:771–776.
39. Amoretti S, Cabrera B, Torrent C, Bonnín CDM, Mezquida G, Garriga M, et al. Cognitive Reserve Assessment Scale in Health (CRASH): its validity and reliability. *J Clin Med*. 2019;8:586.
40. Rosa AR, Mercadé C, Sánchez-Moreno J, Solé B, Mar Bonnin C, Del, et al. Validity and reliability of a rating scale on subjective cognitive deficits in bipolar disorder (COBRA). *J Affect Disord*. 2013;150:29–36.
41. Folstein MF, Folstein SE, McHugh PR. «Mini-mental state». *J Psychiatr Res*. 1975;12:189–198.
42. Pino O, Guilera G, Rojo JE, Gómez-Benito J, Bernardo M, Crespo-Facorro B, et al. Spanish version of the Screen for Cognitive Impairment in Psychiatry (SCIP-S): psychometric properties of a brief scale for cognitive evaluation in schizophrenia. *Schizophr Res*. 2008;99:139–148.
43. Wechsler D. *Wechsler memory scale*. 3rd ed. San Antonio, TX: Psychological Corporation; 1997.
44. Heaton RK. *Wisconsin card sorting test manual*. Odessa, FL: Psychological Asessment Resources; 1981.
45. Golden C. *The stroop color and word test: a manual for clinical and experimental uses*. Chicago, IL: Stoelting; 1978.
46. Benton A, Hamsher K. *Multilingual aphasia examination*. Iowa City: University of Iowa; 1978.
47. Rey A. *Test de Copia de Una Figura Compleja. Manual Adaptación Española. Ediciones. Madrid*; 1997.
48. Reitan R. Validity of the trail making test as a indication of organic brain damage. *Percept Mot Ski*. 1958;8:271–276.
49. Conners CK, Staff M. *Conners' continuous performance test II: computer program for windows technical guide and software manual*. North Tonwanda, NY: Mutli-Health Systems; 2000.
50. Delis DC, Freeland J, Kramer JH, Kaplan E. Integrating clinical assessment with cognitive neuroscience: construct validation of the California Verbal Learning Test. *J Consult Clin Psychol*. 1988;56:123–130.
51. Kaplan E, Goodglass H, Weintraub S. *The Boston naming test*. Philadelphia: Lea & Febige; 1983.
52. Benton AL, Varney NR, Hamsher KD. Visuospatial judgment: a clinical test. *Arch Neurol*. 1978;35:364–367.
53. Torrent C, Bonnin C del M, Martínez-Arán A, Valle J, Amann BL, González-Pinto A, et al. Efficacy of functional remediation in bipolar disorder: a multicenter randomized controlled study. Am J Psychiatry. s.f.;170:852–9.
54. Valls È, Bonnín CM, Torres I, Brat M, Prime-Tous M, Morilla I, et al. Efficacy of an integrative approach for bipolar disorder: preliminary results from a randomized controlled trial. *Psychol Med*. 2021.
55. Bonnin C, del M, Valls E, Rosa AR, Reinares M, Jimenez E, et al. Functional remediation improves bipolar disorder functioning with no effects on brain-derived neurotrophic factor levels. *Eur Neuropsychopharmacol*. 2019;29:701–710.
56. de la Serna E, Montejo L, Solé B, Castro-Fornieles J, Camprodon-Boadas P, Sugranyes G, et al. Effectiveness of enhancing cognitive reserve in children, adolescents and young adults at genetic risk for psychosis: study protocol for a randomized controlled trial. *Rev Psiquiatr y Salud Ment*. 2021.
57. Guidi J, Rafanelli C, Fava GA. The clinical role of well-being therapy. *Nord J Psychiatry*. 2018;72:447–453.
58. Tsapekos D, Strawbridge R, Cella M, Young AH, Wykes T. Does cognitive improvement translate into functional changes? Exploring the transfer mechanisms of cognitive remediation therapy for euthymic people with bipolar disorder. *Psychol Med*. 2021.
59. Solé B, Bonnín CM, Radua J, Montejo L, Hogg B, Jimenez E, et al. Long-term outcome predictors after functional remediation in patients with bipolar disorder. *Psychol Med*. 2020.
60. Martino DJ, Marengo E, Igoa A, Scápola M, Ais ED, Perinot L, et al. Neurocognitive and symptomatic predictors of functional outcome in bipolar disorders: a prospective 1 year follow-up study. *J Affect Disord*. 2009;116:37–42.
61. Tsapekos D, Strawbridge R, Cella M, Wykes T, Young AH. Predictors of psychosocial functioning in euthymic patients with bipolar disorder: a model selection approach. *J Psychiatr Res*. 2021;143:60–67.
62. Bonnin CM, Torrent C, Arango C, Amann BL, Solé B, González-Pinto A, et al. Functional remediation in bipolar disorder: 1-year follow-up of neurocognitive and functional outcome. *Br J Psychiatry*. 2016;208:87–93.
63. Sajatovic M, Strejilevich SA, Gildengers AG, Dols A, Al Jurdi RK, Forester BP, et al. A report on older-age bipolar disorder from the International Society for Bipolar Disorders Task Force. *Bipolar Disord*. 2015;17:689–704.