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Evaluating the efficacy of radically open dialectical behavior therapy (RO-DBT) in patients with anorexia nervosa: study protocol for a randomized controlled clinical trial

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Abstract

Background Anorexia nervosa (AN) is a severe and disabling disorder, with relapse rates as high as 50% after the first episode, posing a significant challenge for clinicians. Most therapies excessively focus on nourishment, resulting in temporary weight restoration but with no improvements in general well-being and quality of life. Radically Open Dialectical Behavior Therapy (RO-DBT) is a transdiagnostic treatment designed to address overcontrol, a key aspect in the functioning of patients with AN. To date, no clinical trial (CT) has shown its efficacy in these patients or evaluated its neurobiological mechanism of action.

Methods A randomized CT in weight restored adult AN patients will be conducted, with one group receiving treatment as usual (TAU) and the other TAU plus RO-DBT, with the main outcome being quality of life. Secondary variables will include eating disorders (EDs) symptoms, overcontrol characteristics, autistic traits, and neuroimaging changes.

Discussion The results will address a gap in knowledge regarding AN treatment, with the expectation that patients receiving TAU with RO-DBT will exhibit improved quality of life and experience fewer relapses at the one-year follow-up. This is the first study examining neuroimaging changes in RO-DBT to better understand its underlying mechanisms.

Trial registration The study has been registered in ClinicalTrials.gov in September 22, 2023. It can be found in https://classic.clinicaltrials.gov/ct2/show/NCT06050421. Trial Registration Number: NCT06050421.

Keywords Anorexia nervosa, Radically open dialectical behaviour therapy, Neuroimaging, Overcontrol, Efficacy

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Background

Eating disorders (EDs) are severe psychiatric disorders associated with multiple physical and psychological problems [1]. The prevalence of these disorders is not negligible and continues to rise resulting in a growing health concern [2]. Among the different EDs, anorexia nervosa (AN) is the most severe and difficult to treat [3, 4], with a lifetime prevalence of up to 0.5–0.6% [5]. It frequently has a chronic course and is associated with mortality rates of up to 18% in longitudinal follow-up studies [6]. In addition, numerous studies describe relapse rates over 25%, with some even documenting rates as high as 52% [6]. It has been described that the period with the highest probability of relapse is during the first year following acute treatment [6]. Regarding recovery, AN has long been considered a treatment-resistant disorder, making it a great challenge for clinicians to not only achieve physical weight recovery but also promote psychosocial recovery. A 20-year longitudinal study of AN patients revealed that, despite achieving physical recovery, the majority of patients did not achieve psychosocial recovery [7]. The participants exhibited lower scores on the Global Assessment of Functioning (GAF), with only 50% of patients being married and fewer than half having children. Additionally, half of the cohort obtained employment, while approximately one-third continued to experience significant social isolation [7].

One critical mechanism that may underlie the maintenance of AN is overcontrol, which refers to the tendency to inhibit emotional urges, impulses, and behaviors to achieve long -term goals [8]. AN can be regarded as an overcontrol disorder, characterized by low receptivity and openness, low flexible control, inhibited emotional expressiveness, reduced emotional awareness, and limited social connectedness and intimacy with others [9]. Despite its centrality to AN psychopathology, overcontrol is rarely addressed as a core element in its treatment [10]. Radically Open Dialectical Behavioral Therapy (RO-DBT), developed by Thomas Lynch, is a promising transdiagnostic intervention designed specifically to treat disorders characterized by overcontrol, such as resistant and chronic depression, avoidant and obsessive-compulsive personality disorders, autism spectrum disorders, and AN [11]. RO-DBT emphasizes that emotional well-being involves three key characteristics: openness, flexibility, and social connectedness. In the specific case of AN, it offers a different perspective regarding the etiology and treatment of AN via a biosocial model that accounts for temperamental, familial/environmental, perceptual, and self-control tendencies. Restrictive and ritualized eating is conceptualized as a maladaptive coping style based on overcontrol, which has been intermittently reinforced. To date, some studies have explored the potential of RO-DBT in treating AN. Lycnch et al. [10] applied an adapted 8 -week RO-DBT program to 47 inpatients diagnosed with restrictive AN, showing significant improvements in weight with a large effect size ($d = 1.71$), but no follow-up data were recorded. Using an uncontrolled case series design, Baudinet et al. [12] evaluated the effect of RO-DBT group skills training as an add-on therapy to an intensive day treatment program for adolescents. Two more studies implemented either RO-DBT group skills training added to standard Dialectical Behavioral Therapy (DBT) [8] or an individual RO-DBT program [13] in an outpatient setting for the treatment of AN. These studies provide promising results regarding the acceptability and feasibility of the treatment, but have some limitations, such as small sample sizes, the absence of a control group condition, and short follow-ups. Another factor that may complicate achieving full recovery in patients with AN treatment is its potential overlap with autism spectrum disorder (ASD) traits. High comorbidity between AN and ASD traits has been associated with poorer social adjustment [14], worse eating symptom prognosis [15], and lower quality of life [16]. For instance, Nielsen et al. observed a dose -dependent relationship between the presence of ASD traits and worse psychosocial functioning in an 18 -year follow-up study [17]. Nevertheless, the role of ASD traits is less consistent and remains an area for further investigation.

The new American Psychiatric Association (APA) Guidelines [18] for the treatment of patients with EDs recommend that adults with AN be treated with an eating disorder-focused psychotherapy, which should include normalizing eating and weight control behaviors, restoring weight, and addressing psychological aspects of the disorder. This includes psychotherapies like enhanced Cognitive Behavioral Therapy (CBT) for EDs or the Maudsley Model of Anorexia Nervosa Treatment for Adults (MANTRA), among others. They integrate psychotherapeutic components like in-session weighing, individualized case formulation, motivational phase of treatment, focus on interpersonal issues or emotional expression, monitoring of symptoms, examining associations of symptoms with cognitions, focus on building activities to minimize overconcern with body shape or weight or the use of experimental mindset to change attitudes. Nevertheless, to date, no psychological treatment has comprehensively addressed the overcontrol factor, which may be considered crucial in anorexia nervosa [19]. Besides this, most medical centers specialized in treating EDs focus solely on re-nutrition, which seeks improvements in weight that are difficult to maintain over time, leading to high rates of relapse. In addition, the objectives of re-nutrition do not cover other core psychopathological domains such as psychosocial well-being (including psychosexual, socioeconomic, and social contacts and activities) or improvement of overall quality

of life. This highlights the necessity for novel and more effective approaches/treatments that strive for comprehensive symptom relief.

From a neurobiological perspective, overcontrol capacity has been closely related to a frontoparietal network control, specifically involving the dorsolateral prefrontal cortex (dlPFC) activity [20]. Interestingly, Pauligk et al. explored whether overcontrol in AN, as measured by increased dlPFC activation, is associated with costs in the domain of affective processing. They found that higher activation of the dlPFC during emotion processing predicted increased amygdala reactivity, which, in turn, was associated with heightened self-reported momentary tension in everyday life during the following two weeks [21]. Moreover, they observed a significant association between over-regulation of the reward system during a distancing emotional regulation task and increased body-related rumination, negative affect, and poorer treatment response. Therefore, overcontrolled behavior and negative affect states may reinforce each other, a mechanism that could potentially contribute to the maintenance of AN symptoms and, ultimately, diminish the quality of life of these patients [21]. At the same time, several studies have emphasized the relevance of the insular cortex in the pathophysiology of anorexia nervosa (AN), acting as a central neural hub integrating information from different cortical and subcortical areas. The insula is involved in a variety of functions such as emotional awareness, sensorimotor processing, integration of interoception, information risk prediction, decision-making, and complex social processes such as empathy [22]. Studies using magnetic resonance spectroscopy in AN show some consistent findings: Maier et al. [23] found insular metabolic alterations consisting of lower concentrations of N-acetyl aspartate (NAA) and Glutamate + Glutamine (Glx) in women with AN compared to those recovered. Functional neuroimaging research is demonstrating how psychotherapy can alter brain function by modifying the activity and connectivity of neural circuits related to emotions, fear, and reward [24]. By unravelling the intricate workings of the brain mechanisms involved in RO-DBT for AN, novel targets for intervention will be pinpointed, leading to improved therapeutic outcomes and ultimately transforming the landscape of EDs treatment. However, no previous neuroimaging studies have investigated the specific impact of RO-DBT directly targeting brain-related overcontrolled behavior.

The main objective of this study is to investigate the efficacy of RO-DBT in enhancing the quality of life of individuals who have been previously diagnosed with AN and have undergone a successful weight restoration treatment, achieving a BMI within the normal range. Despite weight restoration, these patients continue to present significant cognitive and affective symptoms of AN, underscoring the need for further therapeutic interventions targeting these residual impairments. Secondary aims: (a) assess the effect of RO-DBT in reducing the number of relapses, (b) study the impact of RO-DBT in decreasing EDs symptoms, (c) analyze the influence of RO-DBT in reducing ASD traits, (d) investigate if ASD traits can modulate changes in quality of life after RO-DBT, (e) determine the impact of RO-DBT in reducing other symptoms that interfere with psychological well-being, (f) estimate the influence of RO-DBT in improving executive function, and (g) gain a deeper understanding of the underlying neurobiological mechanisms of RO-DBT. This represents a novel approach to treating EDs, particularly in the context of AN, where issues related to overcontrol remain insufficiently addressed by other psychotherapies, and specific pharmacotherapy is lacking. Our proposal is innovative and easily applicable to clinical practice, thus boosting the interest of clinicians in AN treatment.

Methods and design

The present study is a randomized controlled clinical trial approved by the Research Ethics Board of the *Hospital de la Santa Creu i Sant Pau (HSCSP).* Two treatment arms will be compared (treatment as usual (TAU) and TAU + RO-DBT) in a sample of patients with AN. The impact of the intervention will be evaluated using clinical variables, clinical scales as well as structural, functional, and metabolic magnetic resonance imaging (MRI).

Participants

The EQUATOR network served as the basis for determining the required sample size in this study. With an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, each treatment arm should consist of 30 subjects for a statistically significant detection of a difference greater than or equal to 7 units in the quality of life scale employed. Based on previous literature, the common standard deviation is assumed to be 8 [25]. Anticipating a drop-out rate of 35% based on our previous experience with extended group therapies in our EDs unit, and considering that the intervention is designed for groups of 8 individuals, we have decided to include 32 subjects per arm. The sample of patients will be recruited at the EDs Unit of the *HSCSP*, which is the main unit within the public health system treating EDs patients in the city of Barcelona.

Inclusion criteria and exclusion criteria considered for the study are summarized in Table 1.

Study design

Figure 1; Table 2 present a comprehensive study schedule. Eligible patients will be assessed (V1) to ensure they fulfill all inclusion and exclusion criteria. Afterward, they

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
- Diagnosis of AN - Normal BMI (> 19 kg/m^2) - Female - Aged 18 to 65 years old - Overcontrol personality style (assessed by ASC- WP)	- Diagnosis of other severe mental illness (i.e., schizophrenia or other psychosis, bipolar disorder, major depressive disorder, substance use disorder) - Positive result in McLean Screening Instrument for BPD and diagnosis of BPD - Intellectual disability - Being under standardized psychotherapy - Being illiterate or not able to understand the Spanish language - Contraindications to MRI scanning

* AN: anorexia nervosa. BMI: body mass index. ASC-WP: assessing styles of coping - word-pair. BPD: borderline personality disorder. MRI: magnetic resonance imaging

will be invited to participate in the study. Detailed oral and written extensive information about the study will be provided to all eligible patients. If they wish to participate, informed consent (IC) will be signed by all participants (V1), and further appointments will be scheduled for the baseline assessment. After signing the IC, patients will be randomized into one of the two treatment arms using a computerized random number generation program, carried out by an independent statistician from the Department of Epidemiology (HSCSP). To ensure a balanced sample size across groups, a block randomization method will be used with a block size of 16 (8 patients per arm in four consecutive blocks). A junior researcher conducting data collection through all the study will remain blinded to the participants' treatment allocation. Following randomization, a senior clinical researcher will inform each participant about their assigned treatment arm and provide the necessary instructions to initiate the intervention. A systematic and protocolled collection of sociodemographic and clinical variables of every participant will be held through a data collection notebook at two different times so as to avoid lengthen the exploration (V2.1 and V2.2). This will be carried out by the junior researcher who will be trained for the purposes of the study. Patients will undergo the first neuroimaging acquisition (V3) before starting the intervention. Clinical and neuroimaging assessments will be carried out in a maximum time period of one week per patient. The intervention will be conducted by two senior experienced psychologists who have completed training in RO-DBT. Supervision sessions will be taking place periodically in order to ensure therapy adherence. Compliance will be assessed by collecting attendance at treatment sessions and study visits. Changes in pharmacological treatment will be allowed when indicated under medical criteria and will be collected and considered as a possible confounding variable. Adverse effects derived from the psychotherapeutic intervention are not expected. However, in the case of any adverse event during participation in the study, these will be collected and further considered. During the intervention, both groups will have monthly appointments with the junior researcher in order to monitor body mass index (BMI), Eating Attitudes Test (EAT) scale, or prescribed medication changes (V4.1 to V4.6). The first post-intervention evaluation, including the data collection notebook (V5.1 and V5.2) and the second neuroimaging acquisition (V6), will occur within one week after the first month following the completion of RO-DBT therapy. A follow-up evaluation will take place 12 months after the completion of the intervention (V8.1 and 8.2) when patients will be again assessed by clinical scales included in the data collection notebook. As before, monthly appointments will be scheduled during the follow-up period with the junior researcher to maintain the monitoring of BMI, EAT scale, and prescribed medication changes (V7.1 to V7.12).

Intervention

Selected patients will be randomized to one of two treatment arms. Each patient randomization code will be maintained and identified in a separate document from the clinical data collection notebook. Both treatment arms have the same duration (30 weeks).

1. TAU: The TAU condition will follow the standard treatment of the EDs Unit of the HSCSP for AN. This treatment consists of visits with a psychiatrist with a frequency decided according to the clinical situation and, in some cases, nursing follow-up and/or relapse prevention group that takes place twice per month.
2. TAU + RO-DBT: In this treatment arm, a RO-DBT group skills training therapy will be added to TAU. *Treatment and therapists*: RO-DBT group skills training consists of a 30-week intervention program in which a set of skills specifically designed to treat overcontrol are taught on an ongoing basis. The duration of each session is 2 h. Table 3 provides an overall summary of each skill training session content. Detailed information about the treatment can be found elsewhere [11, 26]. Three clinical psychologists and one psychiatrist will conduct the treatment, all of whom have undergone extensive training in RO-DBT. A maximum of two therapists will be in charge of each session, and the same two therapists will go throughout each group intervention. The team will be monitored by an approved RO-DBT supervisor who will evaluate adherence to the treatment.

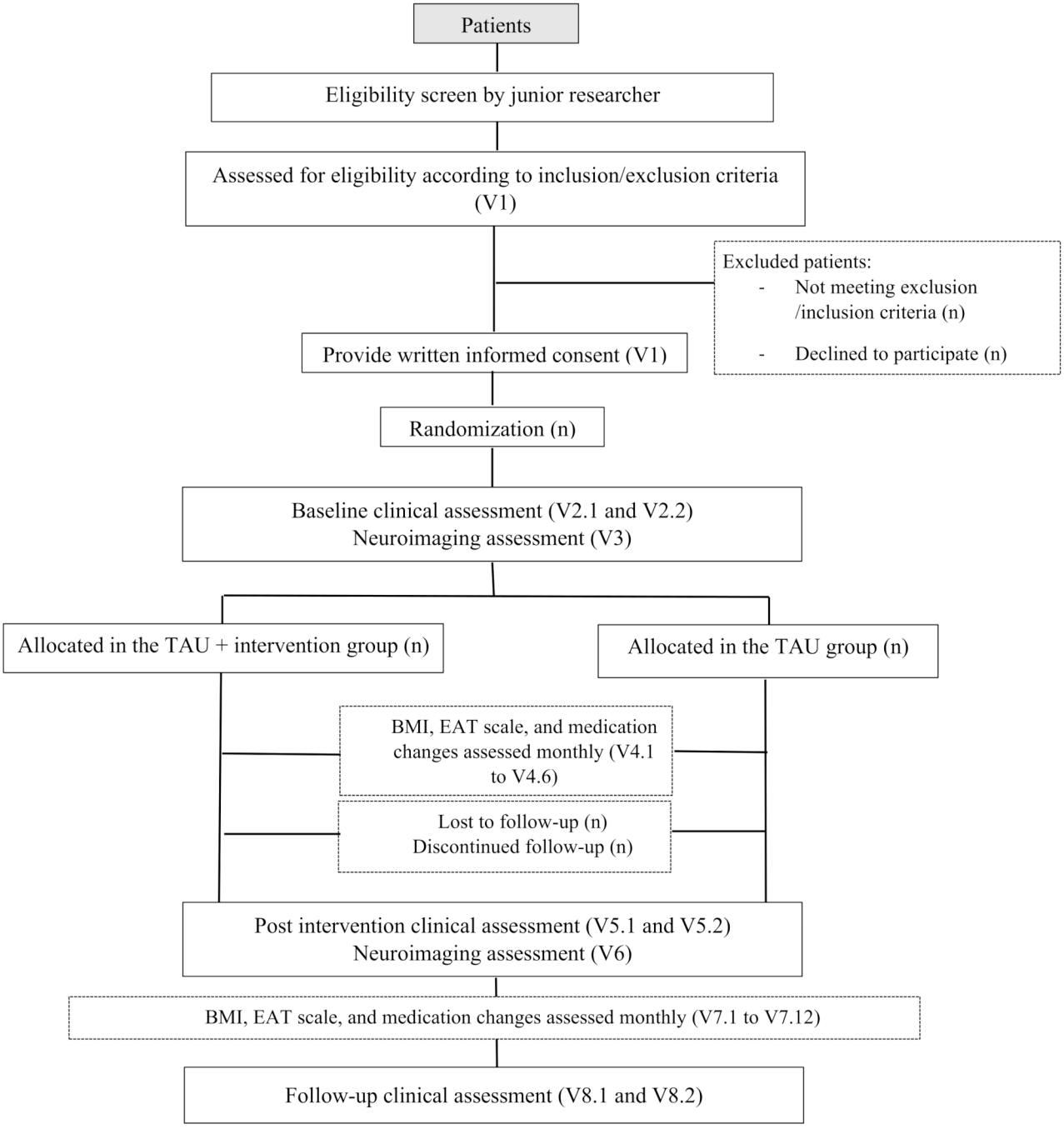

Fig. 1 Flow of participants through the study

Demographic and clinical assessment

- Demographic variables: age, sex, gender, marital status, employment status, and maximum educational level.
- Clinical variables: Type of AN, BMI, severity and clinical course (including previous treatments, years of disease, maximum and minimum BMI), presence of comorbidities with other psychiatric or medical disorders not considered in exclusion criteria, family history of EDs or other psychiatric disorder, and current pharmacological treatment if present.
- Verbal Comprehension Index from Wechsler Adult Intelligence Scale version-IV (WAIS-IV).
- Structured Clinical Interview for text revised fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) Axis II Personality Disorders [27].

Table 2 Schedule of enrolment, intervention, and assessments of participants throughout the study

	Enrolment	Allocation	Intervention	Post-intervention	Follow-up	Endpoint
Corresponding visit (*)	V1, V2.1, V2.2 and V3		V4.1, V4.2, V4.3, V4.4, V4.5 and V4.6	V5.1, V5.2, and V6	V7.1, V7.2, V7.3, V7.4, V7.5, V7.6, V7.7, V7.8, V7.9, V7.10, V7.11 and V7.12	V8.1 and V8.2
Time point			(30 weeks)	+ 34 weeks	(48 weeks)	+ 82 weeks
Enrolment						
- Eligibility screen	X					
- Explanation of the study and informed consent	X					
- Allocation		X				
Intervention						
- TAU			X			
- TAU + RO-DBT			X			
Assessments						
- Demographic	X			X		X
- Clinical	X			X		X
- Neuroimaging	X			X		
- Outcome measures	X			X		X
- Neuropsychological	X			X		X
- BMI, EAT scale, pharmacological treatment			X (monthly)		X (monthly)	

(*) Activities included in each visit: V1 (eligibility screening, providing IC), V2.1 and V2.2 (baseline demographic, clinical and neuropsychological variables), V3 (baseline neuroimaging), V4.1 to V4.6 (BMI, pharmacological changes and EAT scale monitoring), V5.1 and V5.2 (post-intervention demographic, clinical, neuropsychological and outcome variables using CRD), V6 (post-intervention neuroimaging), V7.1 to V7.12 (BMI, pharmacological changes and EAT scale control), V8.1 and V8.2 (follow-up demographic, clinical, neuropsychological and outcome variables)

- Childhood Trauma Questionnaire– Short Form, CTQ-SF [28].
- Zuckerman-Kuhlman Personality Questionnaire, ZKPQ [29].

Outcome measures

Principal outcome measure: Quality of Life Enjoyment and Satisfaction Questionnaire, Q-LES-Q [30]. This questionnaire explores patient's satisfaction in eight areas: physical health status, mood, work, home activities, academic tasks, leisure activities, social relationships, and general activities. This was selected as the primary outcome as it may reflect a more comprehensive measure of recovery in patients with AN. While EDs symptoms are important, they often do not capture the broader psychosocial and functional impairments that significantly affect these patients' lives, even after weight restoration. Besides this, the impact of RO-DBT on domains such as social connectedness, emotional well-being, and overall functioning, will also be evaluated. This decision aligns with recent calls in the field to prioritize patient-centered outcomes that go beyond symptom reduction [31].

Secondary clinical outcome measures: Summarized in Table 4.

Neuroimaging variables: All the patients will be scanned two times: within two weeks before the first TAU or TAU + RO-DBT session (MRI1) and at 1-month follow-up after completion of the treatment protocol (MRI2). A 3.0-T Siemens MAGNETOM Prisma scanner (Munich, Germany) equipped with a 32-channel head coil will be used to acquire structural, functional, and metabolic magnetic resonance imaging.

- High-resolution T1-weighted anatomical sequence with repetition time, 2500 ms; echo time, 4.37 ms; flip angle, 7°; field of view, 256 × 256 mm; matrix size, 256 × 256 pixels; in-plane resolution, 1 × 1 mm^2; slice thickness, 1 mm; 176 slices; acquisition time, 3:47 min.
- High-resolution T2-weighted anatomical sequence with repetition time, 3200 ms; echo time, 405 ms; flip angle, 120°; field of view, 256 × 256 mm; matrix size, 256 × 256 pixels; in-plane resolution, 1 × 1 mm^2; slice thickness, 1 mm; 176 slices; acquisition time, 3:42 min. This sequence will be used to discard brain pathology.
- Diffusion-weighted multiband and multi-shell imaging sequence (repetition time, 3000 ms; echo time, 113 ms; flip angle, 90°; field of view, 224 × 224 mm; matrix size, 112 × 112 pixels; in-plane resolution, 2 × 2 mm^2; slice thickness, 2 mm; 76 slices; acquisition time: 7:40 min) with an

Table 3 Summary of each skill training session content

Lesson nº	Lesson plan:
1	*Radical Openness*
2	*Understanding Emotions*
3	*Activating Social Safety*
4	*Enhancing Openness and Social Connection via Loving Kindness*
5	*Engaging in Novel Behavior*
6	*How Do Emotions Help Us?*
7	*Understanding Overcontrolled Coping*
8	*Tribe Matters*
9	*Social Signaling Matters!*
10	*Using Social Signaling to Live by Your Values*
11	*Mindfulness Training, Part I*
12	*Mindfulness Training, Part II*
13	*Mindfulness Training, Part III*
14	*Mindfulness Training, Part IV*
15	*Interpersonal Integrity, Part I*
16	*Interpersonal Integrity, Part II*
17	*Interpersonal Effectiveness*
18	*Being Assertive with Open Mind*
19	*Using Validation to Signal Social Inclusion*
20	*Enhancing Social Connectedness, Part I*
21	*Enhancing Social Connectedness, Part II*
22	*Learning from Corrective Feedback*
23	*Mindfulness Training, Part I*
24	*Mindfulness Training, Part II*
25	*Mindfulness Training, Part III*
26	*Mindfulness Training, Part IV*
27	*Envy and Resentment*
28	*Cynicism, Bitterness, and Resignation*
29	*Learning to Forgive*
30	*RO Integration Week*

acceleration factor = 4 and 3 diffusion-weighted shells at b-value = 500 s/mm^2 (6 volumes), b-value = 1000 s/mm^2 (64 volumes), and b-value = 2000 s/mm^2 (64 volumes). The sequence will include 14 interspersed b-value = 0 s/mm^2 volumes. A reverse phase-encode polarity sequence will be acquired for susceptibility distortion correction.

- Resting-state multiband functional sequence with acceleration factor, 8; repetition time, 800 ms; echo time, 37 ms; flip angle, 52º; field of view, 208 × 208 mm; matrix size, 104 × 104 pixels; in-plane resolution, 2 × 2 mm^2; slice thickness, 2 mm; 72 slices; 595 volumes; acquisition time, 8:06 min. A reverse phase-encode polarity sequence will be acquired for susceptibility distortion correction.
- Single-voxel Point-Resolved Spectroscopy sequence with repetition time, 2000 ms; echo time, 32 ms; 128 averages; acquisition time, 4:24 min. Unsuppressed water scans (16 averages) will be acquired alongside each scan. A total of 2048 data points will be collected over a spectral width of 2000 Hz. The volumes of interest will be adjusted to the individual left and right insula anatomy (37 × 13 × 21 mm^3), based on the theoretical background previously exposed.

End of study and discontinuation criteria

The study will end 18 months after the inclusion of the last patient. No need for early discontinuation of the study is anticipated beyond: (i) ineffectiveness of the treatment, (ii) appearance of adverse events unknown to date or unrelated, (iii) insufficient number of patients included in the study. Following the closure of the study, it is planned to call participating patients in the future to determine the long-term effects of the intervention.

Data analyses

Withdrawal from the trial will be triggered if a trial subject misses two or more consecutive therapy sessions or four or more non-consecutive therapy sessions, and they will be promptly notified via phone or email. However, these individuals will continue to receive follow-up care as deemed appropriate by medical professionals. Trial subjects will not be replaced, except in cases where they have not yet started treatment and are still in the phase of evaluation and MRI. Likewise, the absence at two or more control visits or four or more non-consecutive assessments will also be considered a withdrawal criterion in the case of participants assigned to the TAU group. The withdrawals in each group will be explicitly analyzed.

We will use the statistical package SPSS 27.0 for Windows for statistical analyses. The following statistical tests will be carried out to evaluate the efficacy of the RO-DBT on quality of life and its impact on relapse prevention, EDs symptoms, ASD symptoms, executive function, and other psychological well-being variables. Two-factor mixed ANOVA tests will be performed with time as an intra-group variable and the different clinical scores as between-group variables. A statistical significance level of $p < 0.05$ (Family-Wise Error corrected) will be used. We will do both intention to treat and per protocol analysis.

MRIs will be pre-processed using FreeSurfer (i.e., T1-weighted and diffusion-weighted images), fMRIPrep (i.e., resting-state functional images), and jMRUI (i.e., spectroscopy images) following standardized protocols. T1-weighted pre-processed images will be used to optimize both diffusion-weighted and resting-state functional pre-processing procedures. For diffusion-weighted images, we will extract four diffusion measures: Fractional Anisotropy, Mean Diffusivity, Axial Diffusivity, and Radial Diffusivity of 42 reconstructed white-matter pathways using global probabilistic tractography

Table 4 Secondary outcome measures

Outcome Measure	Time point	Instrument explanation
Clinical Relapse (*)	Intervention and follow-up	
Eating Attitudes Test, EAT-40 [32]	Enrolment, post-intervention and endpoint	Assesses symptoms and behaviours common in AN and bulimia nervosa (BN). Also provides an index of severity of the disorder.
Eating Disorder Inventory, EDI [33]	Enrolment, post-intervention and endpoint	Assesses psychological and behavioural traits common to AN and BN, in 8 domains: drive for thinness, bulimia, body dissatisfaction, ineffectiveness, perfectionism, interpersonal distrust, interoceptive awareness, and maturity fears.
Autism-Spectrum Quotient, AQ [34]	Enrolment, post-intervention and endpoint	Covers five different domains associated with the autism spectrum: social skills; communication skills; imagination; attention to detail; and attention switching/tolerance of change.
Rosenberg General Self-Esteem Scale, RGSE [35]	Enrolment, post-intervention and endpoint	Measures global self-worth by measuring both positive and negative feelings about the self.
Inventory of Interpersonal Problems, IIP-64 [36]	Enrolment, post-intervention and endpoint	Describes the types of interpersonal problems that people experience and the level of distress associated with them.
Social Connectedness Scale-Revised, SCS-R [37]	Enrolment, post-intervention and endpoint	Assesses the extent to which persons feel connected to others in their surrounding social area.
Questionnaire Envy in Adults, CEA [38]	Enrolment, post-intervention and endpoint	Assesses the construct of envy.
Depression Anxiety Stress Scales, DASS-21 [39]	Enrolment, post-intervention and endpoint	Measures the emotional states of depression, anxiety and stress.
Iowa-Netherlands Comparison Orientation Measure, INCOM-E [40]	Enrolment, post-intervention and endpoint	Measures the tendency to engage in social comparison and captures central aspects of the self, the other, and the psychological interaction between the two.
Overcontrol Trait Rating Scale [41]	Enrolment, post-intervention and endpoint	A measure for obsessive-compulsive personality disorder and overcontrolled disorders.
Clinical Outcomes in Routine Evaluation-Outcome Measure CORE-OM [42]	Enrolment, post-intervention and endpoint	A measure of psychological distress designed to be administered during a course of treatment to determine treatment response, with good sensitivity to change.
Trail Making Test, TMT [43]	Enrolment, post-intervention and endpoint	Neuropsychological test of visuomtor attention and task switching.
Neuroimaging variables	Enrolment and post-intervention	Structural and functional magnetic resonance.

(*) Defined by having a body mass index below 19 kg/m^2 during two or more visits and/or a punctuation above 21 in the Eating Attitudes Test

as implemented in TRACULA (TRActs Constrained by UnderLying Anatomy) on FreeSurfer. Resting-state functional networks will be analyzed using a group probabilistic independent component analysis approach in MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components) and computed at the individual level using a Dual Regression on FSL-FMRIB Software Library [44] (a comprehensive library of analysis tools for fMRI, MRI and diffusion brain imaging data). Spectra processing will calculate NAA and Glx insular concentrations using jMRUI. Linear mixed-effects models will be conducted to evaluate the impact of the two different treatment strategies (i.e., TAU and TAU + RO-DBT) on the neuroimaging measures using SPSS (i.e., diffusion-weighted and spectroscopy images) and FSL-FMRIB (i.e., resting-state functional images). In addition, multiple regression analyses on the TAU + RO-DBT group will be performed to evaluate the potential relationship between clinical and neuroimaging variables (i.e., predictive and response biomarkers). Statistical significance will be set at a threshold of $p < 0.05$ False Discovery Rate corrected.

Discussion

This study protocol presents the design of the first randomized controlled clinical trial evaluating the efficacy of RO-DBT in female weight-restored adults with AN. Despite extensive research on various psychological treatments for EDs and AN in adults and some clinical guidelines recommendations, achieving complete and comprehensive remission is still a challenge for some patients.

With this study, we aim to address a severe and not-yet-resolved health problem: the need for a more effective treatment for AN focused not only on weight restoration but also on quality of life enhancement. In addition to its scientific significance, this study is motivated by the desire to expand the understanding of the neural mechanisms underlying this psychological intervention by incorporating neurobiological biomarkers such as neuroimaging signatures. Other strengths of this study include the large battery of secondary outcome measures that will be used. Finally, the follow-up will extend up to one year after the intervention is finished, thus allowing the possibility to draw conclusions about mid to long-term

effects of RO-DBT in terms of relapse prevention and overall quality of life.

However, several limitations should be acknowledged. First, as TAU + RO-DBT involves more treatment sessions compared to TAU alone. This study is implemented in a standard care treatment unit, where RO-DBT is implemented as an adjunctive treatment. Any observed superiority of TAU + RO-DBT could partially reflect the benefits of increased treatment frequency to standard care, but this is an important first step in assessing the potential added value of RO-DBT. Future studies could further disentangle the specific effects of RO-DBT by comparing it to other interventions matched for intensity and duration. Second, the study's inclusion criteria restrict participation to weight -restored female patients, which limits the generalizability of the findings to the broader population of individuals with AN, including males and those who are not yet weight-restored. These restrictions, while important for maintaining sample homogeneity, should be considered when interpreting the results and planning future studies to extend the findings to more diverse populations. Third, the use of concomitant medication is allowed, which may interfere with the results, but changes in the prescription will be monitored, aiming to control for those potential confounder factors in the analysis.

Cumulative evidence favoring RO-DBT for patients with AN may reduce the disorder-related costs by preventing relapse or modifying the tendency for the disorder to become chronic, generate new lines of research by applying it to a broader group of patients, and finally focus on patients' real-life worries not only symptom reduction or weight restoration.

Abbreviations

AN	Anorexia Nervosa
APA	American Psychiatric Association
AQ	Autism-Spectrum Quotient
ASC-WP	Assessing Styles of Coping– Word Pair
ASD	Autism Spectrum Disorder
BMI	Body Mass Index
BN	Bulimia nervosa
BPD	Borderline Personality Disorder
CBT	Cognitive Behavioral Therapy
CEA	Questionnaire Envy in Adults
CORE-OM	Clinical Outcomes in Routine Evaluation-Outcome Measure
CTQ-SF	Childhood Trauma Questionnaire– Short Form
DASS	Depression Anxiety Stress Scales
DBT	Dialectical Behavioral Therapy
dlPDC	Dorsolateral prefrontal cortex
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision
EAT	Eating Attitudes test
EDI	Eating Disorder Inventory
EDs	Eating Disorders
GAF	Global Assessment Functioning
Glx	Glutamate + Glutamine
HSCSP	Hospital de la Santa Creu i Sant Pau
IC	Informed Consent
IIP	Inventory of Interpersonal Problems
INCOM-E	Iowa-Netherlands Comparison Orientation Measure
MANTRA	Maudsley Model of Anorexia Nervosa Treatment for Adults
MRI	Magnetic resonance imaging
NAA	N-acetyl aspartate
RGSE	Rosenberg General Self-Esteem Scale
RO-DBT	Radically Open Dialectical Behavioral Therapy
SCS-R	Social Connectedness Scale-Revised
TAU	Treatment As Usual
TMT	Trail Making Test
WAIS-IV	Wechsler Adult Intelligence Scale version-IV
ZKPQ	Zuckerman-Kuhlman Personality Questionnaire

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-025-06854-9.

Supplementary Material 1

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Author contributions

AAP drafted the manuscript which was critically reviewed by CCF, MC, AMB and MJP. CCF designed the study with the collaboration of MJP, AMB, AAP, JS, and MCS. CCF, AAP, LG, MCS and NC were involved in the set-up of the study, providing information upon the availability of facilities and clinical settings. CCF, AAP and MC reviewed the theoretical rationale for manuscript preparation. CCF, MJP and AMB defined the statistical approach for the manuscript. MC and VPA defined the neuroimaging variables and its statistical evaluation. All authors read and approved the final version manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study is approved by the Ethical Committee for Clinical Research (in Spanish, Comité Ético de Investigación Clínica) from the *Hospital de la Santa Creu i Sant Pau*, project number IIBSP-TDC-2022-123. Protocol version 3, 14th July 2023.
Central Clinical Research and Clinical Trials Unit (CCRCTU), Research Institute of the Hospital de Sant Pau, will monitor through periodic visits the correct progression of the project, alerting from protocol deviations. They will be constantly aware of every single step of the project.
All participants will receive extended information about the study and must give their written informed consent prior to participate in the study. This study does not pose any risk to the participants.

Consent for publication

Written informed consent from participants will be obtained prior to the inclusion to the study.

Competing interests
The authors declare no competing interests.

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