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Cognitive Remediation Therapy Does Not Enhance Treatment Effect in Obsessive-Compulsive Disorder and Anorexia Nervosa: A Randomized Controlled Trial

Boris van Passel[a, b] Unna N. Danner[c, d] Alexandra E. Dingemans[e, f] Emmeke Aarts[g] Lot C. Sternheim[c, d] Eni S. Becker[b] Annemarie A. van Elburg[c, d] Eric F. van Furth[e, h] Gert-Jan Hendriks[a, b, i] Daniëlle C. Cath[d, j, k]

[a]Overwaal Center for Anxiety Disorders, OCD, and PTSD, Pro Persona Institute for Integrated Mental Health Care, Nijmegen, The Netherlands; [b]Behavioral Science Institute, Radboud University, Nijmegen, The Netherlands; [c]Altrecht Eating Disorders Rintveld, Zeist, The Netherlands; [d]Department of Clinical Psychology, Utrecht University, Utrecht, The Netherlands; [e]Rivierduinen Eating Disorders Ursula, Leiden, The Netherlands; [f]Institute of Psychology, Leiden University, Leiden, The Netherlands; [g]Department of Methodology and Statistics, Utrecht University, Utrecht, The Netherlands; [h]Department of Psychiatry, Leiden University Medical Center, Leiden, The Netherlands; [i]Radboud University Medical Center, Department of Psychiatry, Radboud University, Nijmegen, The Netherlands; [j]Altrecht Academic Anxiety Center, Utrecht, The Netherlands; [k]GGz Drenthe, Department of Specialist Training, Rijksuniversiteit Groningen and University Medical Center Groningen, Department of Psychiatry, Groningen, The Netherlands

Keywords
Cognitive remediation therapy · Obsessive-compulsive disorder · Anorexia nervosa · Randomized controlled trial

Abstract
Background: Guideline-recommended therapies are moderately successful in the treatment of obsessive-compulsive disorder (OCD) and anorexia nervosa (AN), leaving room for improvement. Cognitive inflexibility, a common trait in both disorders, is likely to prevent patients from engaging in treatment and from fully benefiting from existing therapies. Cognitive remediation therapy (CRT) is a practical augmentation intervention aimed at ameliorating this impairing cognitive style prior to disorder-specific therapy. ***Objective:*** To compare the effectiveness of CRT and a control treatment that was not aimed at enhancing flexibility, named specialized attention therapy (SAT), as add-ons to treatment as usual (TAU). ***Methods:*** In a randomized controlled multicenter clinical trial, 71 adult patients with OCD and 61 with AN were randomized to ten twice-weekly sessions with either CRT or SAT, followed by TAU. Patients were evaluated at baseline, post-CRT/SAT, and after 6 and 12 months, with outcomes being quantified using the Yale-Brown Obsessive Compulsive Scale for OCD and the Eating Disorder Examination Questionnaire for AN. ***Results:*** Across study groups, most importantly CRT+TAU was not superior to control treatment (SAT)+TAU in reducing OCD and AN pathology. Contrary to expectations, SAT+TAU may have been more effective than CRT+TAU in patients being treated for OCD. ***Conclusions:*** CRT did not enhance the effect of TAU for OCD and AN more than SAT. Unexpectedly, SAT, the control condition, may have had an augmentation effect on TAU in OCD patients. Although this latter finding may have been due to chance, the effect of SAT delivered as a pretreatment add-on intervention for adults with OCD and AN merits future efforts at replication.

karger@karger.com
www.karger.com/pps

Boris van Passel, MD
Overwaal Center for Anxiety Disorders, OCD, and PTSD
Pro Persona Institute for Integrated Mental Health Care
Pastoor van Laakstraat 48, NL–6663 CB Lent (The Netherlands)
b.van.passel@propersona.nl

Introduction

Obsessive-compulsive disorder (OCD), which is characterized by intrusive thoughts, images, or urges (i.e., obsessions) and repetitive behaviors performed to relieve obsessional distress (i.e., compulsions) [1], affects 1–3% of the population worldwide [2, 3]. The eating disorder anorexia nervosa (AN) affects up to 4% of the population (predominantly women) [4]; it is characterized by a severe restriction of energy intake leading to a significantly low body weight, associated with an intense fear to become fat, and inadequate cognitions about body shape [1]. Of all mental disorders, AN is among those with the highest mortality rates [5]. Both OCD and AN are associated with impaired quality of life (QoL) [6–8].

Interestingly, OCD and AN share several phenotypic, epidemiological, and neuropsychological features [9]. Both patient populations show excessive habit formation, cognitive rigidity, and repetitive and ritualistic behaviors [10]. Moreover, several studies have demonstrated an increased risk of co-occurrence of the two disorders [9, 11], with rates of AN varying between 11–13% in clinical OCD populations and rates of OCD between 9.5 and 62% in patients with a primary diagnosis of AN. Patients with OCD and AN also share specific inefficiencies in executive functioning, most commonly in set-shifting/cognitive flexibility, visuospatial abilities, processing speed, motor inhibition, and working memory [12–19]. These inefficiencies have been associated with frontostriatal abnormalities in functional neuroimaging studies [20–22]; they are assumed to be central to the development and maintenance of obsessive thoughts and compulsive behaviors in both OCD and AN [23, 24] and thought to interfere with a patient's ability to acquire and use concepts trained in psychotherapy, most particularly cognitive therapies [25], where the traits negatively affect treatment motivation and outcomes.

The first-line treatment for OCD is cognitive-behavioral therapy in combination with pharmacotherapy, especially selective serotonin reuptake inhibitors. In case of nonresponse, specialized intensive interventions are advised, including residential treatments [26–29], but despite efficient treatment regimens the rates of incomplete recovery and treatment resistance remain relatively high [30]. While two-thirds of patients receiving (cognitive-) behavioral therapy and/or pharmacotherapy respond to these therapies, only about 50% of individuals diagnosed with OCD achieve complete remission [31].

The first-choice treatment for adult AN is a combination of psychotherapy, including family therapy for younger patients, and dietary management [32]. Longitudinal studies have shown that <50% of patients recover fully, while 20–30% experience residual symptoms, 10–20% remain significantly ill, and 5–10% die from their illness [33].

Clearly, current treatment strategies for OCD and AN warrant optimization, but this poses a real challenge to clinicians worldwide. Potentially, therapy results can be improved in both populations if the underlying inefficiencies in neurocognitive functioning are tackled before targeting the core symptoms of the disorders.

Cognitive remediation therapy (CRT) specifically aims at modifying cognitive inflexibility and organizational inefficiencies [34]. The intervention was originally designed to treat patients with schizophrenia [35, 36] but has since been adapted to treat individuals suffering from eating disorders [37]. CRT uses cognitive exercises to moderate people's adaptive thought processes about their daily routines and to promote a more flexible behavioral repertoire (by expediting a shift from habitual to more goal-directed behaviors) and a more global rather than a detail-focused style of processing information. Case series and randomized trials looking at CRT for AN found that the intervention improved the participants' cognitive flexibility [38, 39], QoL [40], motivation to change [41], and AN-specific pathology [40]. However, to date, no studies in eating disorders have compared the effect of CRT on treatment outcome using an active control condition. Since the randomized controlled trials compared the treatment under investigation with waiting-list conditions, a design which is known for its risk of overestimating treatment effects [42, 43], a logical next step would be to compare CRT to an active control condition.

Although to date CRT has, as such, not been evaluated in randomized designs with an active control arm, two studies, both from 2006, did compare cognitive remediation-like approaches to OCD with a control condition. In one randomized controlled trial [44], 35 adults with OCD who received a single-session training designed to help them augment their organizational skills in terms of memorizing and replicating complex visuospatial information improved more than 36 unaffected controls who did not receive this training. The second randomized controlled trial [45] likewise found that the 15 patients with OCD who received nine 60-min training sessions focused on enhancing visual-organizational and problem-solving strategies in everyday life improved more in both areas as well as in OCD symptoms than 15 peers who did not receive the treatment modality. Based on these preliminary results, we thought it worthwhile to evaluate

the effects of CRT and an active control arm prior to guideline OCD and AN treatment.

The primary aim of the present study then was to compare the efficacy of ten CRT sessions delivered prior to treatment as usual (TAU) in patients with OCD and AN with ten sessions of a newly developed control intervention (specialized attention therapy [SAT]; see below) in improving disorder-specific psychopathology and QoL, hypothesizing that CRT+TAU would be more effective in reducing OCD and AN symptoms and improving QoL than SAT+TAU.

Methods

Design

Full details of the study methods and patient selection can be found elsewhere [46]. Briefly, the present study comprises a randomized controlled multicenter trial with two treatment arms: CRT and SAT, a newly developed add-on intervention of similar duration and structure without the elements assumed to train flexibility and central coherence (see below for details). Both interventions comprised ten twice-weekly sessions of 45 min that were delivered prior to TAU for OCD and AN. Power calculations revealed that with an effect size f(V) of 0.25 and an alpha level of 0.05, 113 patients would be sufficient to achieve a power of 0.80 to detect significant between-group differences. In both conditions, patients were evaluated at baseline (T0), after 6 weeks (T1), after 6 months (T2), and after 12 months (T3).

Patients

The trial was carried out in four Dutch tertiary treatment centers specialized in the treatment of anxiety and OCD spectrum or eating disorders. Patients with OCD were recruited from Altrecht Academic Anxiety Center, Utrecht and Overwaal Center for Anxiety Disorders, OCD, and PTSD, Nijmegen. Patients with AN were recruited from Altrecht Eating Disorders Rintveld, Zeist and Rivierduinen Eating Disorders Ursula, Leiden. To be eligible for the study, patients had to be between 18 and 60 years of age and fulfil the DSM-IV criteria for OCD or AN (or an eating disorder not otherwise specified but clinically referred to as AN). DSM-IV-TR diagnoses were verified with the structured clinical interview for DSM-IV-TR axis I disorders (SCID-I) [47] and for patients suspected of AN diagnoses were additionally confirmed with the Eating Disorder Examination Questionnaire (EDE-Q) [48]. For patients with OCD to qualify for the study, a Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score ≥16 was required. Comorbidity with either AN (for OCD patients) or OCD (for AN patients) was allowed.

Patients were excluded if they had severe neurological illness (including a history of seizures, stroke, or Parkinson's disease), severe comorbid psychiatric disorders (clinically significant bipolar disorder, current psychosis, or substance dependence/abuse), intellectual impairment (defined as an IQ <80 estimated with the Dutch Adult Reading Test) [49], or an inability to speak or read Dutch adequately. Antidepressants and antipsychotics were allowed provided that dosages were kept constant during the experimental part of the study. Since benzodiazepines can dampen the effect of cognitive treatments [50], only sleep medication was allowed, restricted to a daily dose of up to 20 mg for temazepam or an equivalent dosage. Differences in the use of prescribed psychotropic drugs were recorded for both groups. During TAU, changes in psychotropic drugs were allowed. Separate analyses were performed to test for differences in psychotropic drug use and in the response trajectories of the two groups (CRT+TAU and SAT+TAU).

Measures

Primary Outcome Measures. We decided not to use generic instruments to gauge treatment outcomes across groups. Instead, we opted for widely used disease-specific measures to ensure optimal responsiveness to changes specific to each condition. The primary outcome measure for the OCD group was OCD symptom severity as assessed with the Y-BOCS [51, 52], a semi-structured interview that has strong internal consistency and excellent interrater reliability [52, 53] as well as a good test-retest reliability in clinical samples [54]. The primary outcome measure for the AN group was eating disorder severity as assessed with the self-report version of the EDE-Q [55–57], which weighs attitudinal and behavioral aspects of adults coping with eating disorders over a 28-day period. The EDE-Q contains 36 items of which 22 are rated on 7-point Likert scales; the remaining 14 items chart core eating disorder behaviors (i.e., binge eating, overeating, self-induced vomiting, use of laxatives, and excessive exercising). The EDE-Q has excellent internal consistency and test-retest reliability over a 2-week period [58].

Secondary Outcome Measures. The Eating Disorders Quality of Life questionnaire (EDQOL) [59] consists of 25 items assessing eating behaviors/body weight and has four subscales: psychological, physical/cognitive, financial, and work/school, together generating a QoL score. The EDQOL has good internal consistency (Cronbach α = 0.84–0.95) and test-retest reliability [59]. For the purpose of this study, we composed the Obsessive-Compulsive Disorder Quality of Life self-report questionnaire (OCDQOL) based on the EDQOL, with the same four subscales gauging the influence of OCD on the respondent's QoL. The 24-item self-report Detail and Flexibility questionnaire (DFlex) [60] has two subscales: cognitive rigidity and attention to detail, which both have shown high internal consistency (Cronbach α = 0.90–0.95). Construct validity has to be strong for cognitive rigidity (r = 0.72) but moderate for attention to detail (r = 0.26) [60].

Procedure

The study procedure has been described in detail in van Passel et al. [46]. In brief, recruitment was based on consecutive referrals to the participating clinics in the period between November 2013 and August 2015 (Fig. 1) and selection was done by interview. Patients satisfying the inclusion criteria were subsequently randomized to one of the two study conditions by an independent researcher not involved in the therapies or assessments using a randomization sequence stratified by treatment center, with a 1:1 allocation using random block sizes of 4.

Interventions

CRT. CRT for OCD and AN was based on the original practitioner's manual for patients with AN [37]. The intervention uses a range of cognitive exercises to modify cognitive inflexibility and

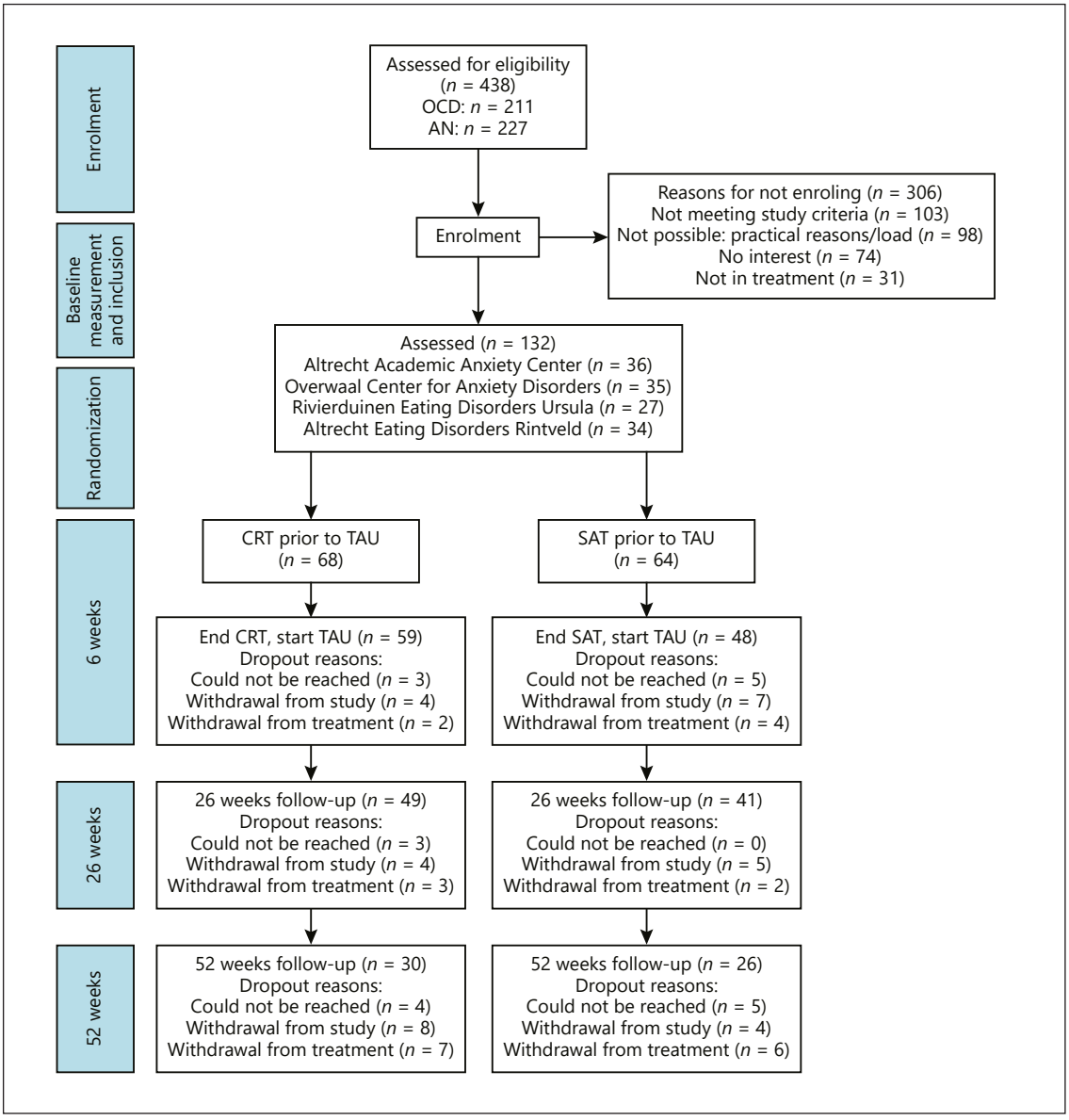

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Fig. 1. Patient flowchart. AN, anorexia nervosa; CRT, cognitive remediation therapy; OCD, obsessive-compulsive disorder; SAT, specialized attention therapy; TAU, treatment as usual.

overdetailed information processing. The exercises encourage patients to reflect on the nature of their thinking styles. To help them recognize the effect of these thinking styles on their daily lives, patients are given home assignments comprising real-life cognitive-behavioral tasks in addition to the ten twice-weekly 45-min sessions.

SAT. SAT was specifically developed for this trial [61]. The design was similar to that of CRT with respect to its structure, duration (ten twice-weekly 45-min sessions), and inclusion of homework assignments, but cognitive flexibility, central coherence, perfectionism, and awareness training of thinking styles were not addressed expressly. Patients were told that SAT was aimed at helping them focus on positive experiences by means of "exercises." Addressing the same principles as the CRT modalities, the exercises comprised board games tapping into motor, visual, and verbal skills, luck games, collaborative games, including e.g. Djenga, Mikado, Game of the Goose, Ludo, and Snakes and Ladders, and reading poems (for an overview, see van Passel et al. [46]).

TAU. TAU contained all the essential elements as recommended in the Dutch OCD and AN guidelines [62–64], which closely follow the international guidelines [65, 66]. TAU for the patients with OCD comprised cognitive-behavioral therapy delivered in weekly or twice-weekly 45- to 90-min sessions in which exposure with response prevention forms a key element. In line with the lit-

erature, the OCD protocol was flexible and encompassed patient-tailored psychoeducation, cognitive therapy, in vivo exposure to anxiety-provoking thoughts and situations, combined with response prevention, psychiatric consultation, and, in case of severe symptoms, pharmacotherapy. TAU for the patients with AN entailed normalization of adverse eating behaviors, goal setting, discussion of daily problems, psychoeducation, cognitive-behavioral therapy, and – when indicated – art therapy, psychomotor therapy, social skills training, family therapy, psychiatric consultation, and pharmacotherapy.

Therapist Training, Treatment Integrity, and Treatment Fidelity

Both CRT and SAT were delivered by trained psychologists together with clinical nurses and psychology students (at the MSc level) under the supervision of the treating psychologist. All practitioners had been trained by experienced CRT therapists (U.N.D., B.v.P., L.C.S., D.C.C.) who had received their training from Dr. Tchanturia. Supervision/intervision sessions were conducted on a regular basis in each center.

All therapists filled in a session form after each CRT/SAT session to document the exercises and homework assignments completed/discussed. All sessions were video- or audiotaped. To determine treatment integrity, 5.5% of the taped sessions were randomly selected and judged by trained raters who were blinded to the treatment outcome. Following the instructions of Hagermoser Sanetti and Kratochwill [67] and Perepletchikova [68], three categories of treatment integrity were scored on a standardized scoring form: treatment adherence, treatment competence, and treatment differentiation. Scores for treatment adherence ranged from 0 (inadequate) to 2 (good) as based on the number of essential predetermined items addressed in the session: adequate explanation of the rationale of the intervention, >20 min dedicated to CRT- or SAT-specific components, the (number and type of) exercises completed during therapy, adequate discussion of the exercises, and preparation and discussion of homework assignments. Treatment competence was rated for both the therapist and the patient, with eight therapist factors and four patient factors being rated from 0 (inadequate) to 2 (good); the total score was the mean score for these factors. Treatment differentiation was rated as yes/no, where no was recorded if a session contained elements of the other condition (i.e., CRT elements in a SAT session or vice versa).

Statistical Analyses

All analyses were conducted using SPSS version 25.0 [69]. Potential demographic and clinical between-group differences at baseline were analyzed using χ^2 or Fisher's exact tests for categorical variables and independent-sample *t* tests for continuous variables.

For the primary outcome measures, a reliable change index was calculated to detect clinically meaningful changes using the procedure described by Jacobson and Truax [70].

To anticipate the possibility that patients would drop out from the study nonrandomly, we used linear mixed-effects modeling (LMM) for repeated-measures data, which implies that all available data of all patients are entered into the analyses, in this case the data of all cases with more than one assessment. Twenty-three patients (9 OCD, 14 AN) for whom the data of only one assessment were available were excluded. We evaluated the differences in the effects of CRT and SAT and between OCD and AN based on predicted means from the three-way LMM. To facilitate overall outcome analyses across the two outcome measures (i.e., Y-BOCS and EDE-Q) for both study groups (OCD and AN) at four time points, we constructed *z*-scores using all available data on the primary outcome and QoL measures (i.e., EDQOL and OCDQOL). The *z*-scores were calculated by subtracting the mean outcome score per diagnostic group from the individual score, divided by the standard deviation of the group using the formula

$$z = \frac{x - \text{mean}}{\text{standard deviation}}.$$

The LMM was fitted, regressing the main outcome variable *z*-score on the group indicators (CRT+TAU vs. SAT+TAU) and (OCD vs. AN), using four time indicators (baseline, post-CRT/SAT, 6- and 12-month follow-up). We analyzed the corresponding time indicator by group interaction terms as fixed effects and person identification as random effects.

Although differences were nonsignificant between diagnoses and conditions, education level, age, and illness duration were included in the model-fitting procedures to enhance statistical power and correct for potential nonsignificant bias [71, 72]. Multicollinearity for these three covariates were checked and found to be absent. The data of these measurements were used and fitted by LMM with random effects at the individual level and the following fixed effects: diagnosis (OCD or AN), condition (CRT or SAT), linear time, time × time, age, illness duration, years of education, two-way interaction time × diagnosis, two-way interaction time × condition, two-way interaction diagnosis × treatment, and three-way interaction time × diagnosis × treatment.

Between-group effect sizes were calculated based on predicted means from the LMM and standardized using pooled baseline standard deviations (according to the PPC2 method) [73]. Effect sizes are reported as Cohen's *d*.

Results

Participants

Participants were recruited between November 2013 and August 2015, with the final 12-month follow-up assessment being conducted in August 2016. As can be seen in Table 1, at baseline the demographic and clinical characteristics of the participants in the two conditions did not significantly differ from each other, albeit the average duration of illness was >7 years for the patients with OCD and >4.6 years for the patients with AN.

Adherence to the treatment protocol was rated as satisfactory to good in 95% of all cases reviewed. Therapist and patient performance was rated as competent in 97 and 100% of session deliveries, respectively. Treatment differentiation was good in that in the CRT sessions no SAT interventions were detected and vice versa.

Dropout

Dropout and Adverse Events during CRT and SAT. Of the 132 patients included in the study, 9% (n = 12; CRT:

Table 1. Baseline demographic, clinical, and neurocognitive characteristics of the treatment groups in frequencies, percentages, means, and standard deviations, and statistical analyses

Characteristics	OCD subgroup		Statistics	AN subgroup		Statistics	OCD+AN CRT vs. SAT
	CRT group (n = 37)	SAT group (n = 34)		CRT group (n = 31)	SAT group (n = 30)		
Sex			$\chi^2(1) = 0.24$, $p = 0.62$			$\chi^2(1) = 1.14$, $p = 0.29$	$\chi^2(1) = 0.70$, $p = 0.40$
Female	27 (73%)	23 (68%)		30 (97%)	27 (90%)		
Male	10 (27%)	11 (32%)		1 (3%)	3 (10%)		
Years of education	8.35 (2.01)	8.35 (2.23)	$t(41) = 0.00$, $p = 1.00$	8.77 (1.83)	9.23 (1.45)	$t(54) = -1.04$, $p = 0.25$	$t(97) = -0.69$, $p = 0.49$
Psychological treatments			$\chi^2(4) = 2.10$, $p = 0.72$			$\chi^2(3) = 2.68$, $p = 0.44$	$\chi^2(4) = 0.52$, $p = 0.97$
0	7 (21%)	9 (21%)		13 (42%)	8 (27%)		
1–5	13 (38%)	8 (24%)		10 (32%)	13 (42%)		
6–10	2 (6%)	1 (3%)		2 (7%)	4 (13%)		
>10	9 (26%)	11 (33%)		5 (16%)	3 (10%)		
Unknown	3 (9%)	4 (12%)		0 (0%)	0 (0%)		
Age at onset, years	28.48 (10.95)	23.66 (8.78)	$t(58) = 1.88$, $p = 0.07$	20.10 (7.11)	19.76 (7.40)	$t(58) = 0.18$, $p = 0.86$	$t(118) = 1.53$, $p = 0.13$
Age, years	34.78 (10.57)	33.09 (11.39)	$t(69) = 0.65$, $p = 0.52$	25.19 (7.66)	24.60 (6.98)	$t(59) = 0.32$, $p = 0.75$	$t(130) = 0.72$, $p = 0.48$
Duration of illness, years	7.52 (8.95)	9.79 (12.93)	$t(58) = -0.80$, $p = 0.43$	5.10 (7.50)	4.66 (4.35)	$t(58) = 0.28$, $p = 0.78$	$t(118) = -0.55$, $p = 0.58$
Current BMI	25.01 (4.62)	23.33 (4.27)	$t(62) = 1.51$, $p = 0.14$	15.87 (1.64)	16.26 (1.99)	$t(58) = -0.83$, $p = 0.41$	$t(122) = 0.70$, $p = 0.49$
Concurrent medication	8 (25%)	6 (20%)	$\chi^2(1) = 0.29$, $p = 0.59$	22 (59%)	18 (53%)	$\chi^2(1) = 0.31$, $p = 0.58$	$\chi^2(1) = 0.60$, $p = 0.44$
EDE-Q – total	1.42 (1.62)	1.20 (1.24)	$t(50) = 0.56$, $p = 0.58$	4.00 (1.31)	4.12 (1.23)	$t(52) = -0.34$, $p = 0.74$	$t(104) = 0.54$, $p = 0.59$
Y-BOCS – total	23.81 (7.15)	24.41 (5.68)	$t(66) = -0.38$, $p = 0.71$	5.60 (9.39)	5.80 (9.98)	$t(58) = -0.08$, $p = 0.94$	$t(126) = -0.06$, $p = 0.95$
EDQOL or OCDQOL – total	2.62 (0.65)	2.57 (0.59)	$t(65) = 0.31$, $p = 0.76$	2.86 (0.54)	2.93 (0.68)	$t(52) = -0.46$, $p = 0.65$	$t(98.9) = -1.50$, $p = 0.13$
DFlex – rigidity	45.20 (13.51)	41.78 (12.06)	$t(65) = 1.09$, $p = 0.28$	42.52 (11.84)	46.96 (10.08)	$t(51) = -1.45$, $p = 0.15$	$t(118) = -0.01$, $p = 0.99$
DFlex – attention	40.69 (13.10)	41.38 (12.78)	$t(65) = 0.21$, $p = 0.83$	38.86 (11.88)	38.75 (12.02)	$t(51) = 0.034$, $p = 0.97$	$t(118) = 0.17$, $p = 0.87$

Values are presented as n (%) or mean (standard deviation). AN, anorexia nervosa; BMI, body mass index; CRT, cognitive remediation therapy; DFlex, self-report Detail and Flexibility questionnaire; EDE-Q, Eating Disorder Examination Questionnaire; EDQOL, Eating Disorders Quality of Life questionnaire; OCD, obsessive-compulsive disorder; OCDQOL, Obsessive-Compulsive Disorder Quality of Life self-report questionnaire; SAT, specialized attention therapy; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

n = 5; SAT: n = 7) never started CRT/SAT therapy, while 11% (n = 14; CRT: n = 4; SAT: n = 10) terminated CRT/SAT prematurely (Fig. 1). The treatment completers and dropouts did not differ regarding all but one of their baseline variables (i.e., age, number of previous treatments, baseline Y-BOCS score or baseline EDE-Q score, age at onset, QoL scores, and psychotropic drug use), with illness duration being significantly longer in the patients dropping out (mean illness duration: 6.2 years for completers vs. 9.9 years for dropouts; $t[122.17] = 2.972$, $p < 0.01$). There was no difference in the number of patients dropping out from CRT and SAT ($\chi^2[1, n = 132] = 3.30$, $p = 0.07$). All completers of both interventions participated in the first follow-up assessment. As mentioned, the data of the dropouts remained included in the analyses if they concerned more than one assessment. No adverse events were reported for either intervention. Applying the Jacobson and Truax [70] method for the calculation of reliable change indices, we found that during the experimental phase 4 patients (2 OCD in CRT and 2 OCD in SAT) showed a reliable deterioration, 82 no change, and 14 a reliable improvement. Table 2 shows the total number of patients with reliable deterioration, no change, or reliable improvement.

Dropout at 6 and 12 Months. Of the 120 patients having started CRT or SAT, 23% (n = 28) did not complete the follow-up assessment at 6 months. There were no differences in the number of patients dropping out from the CRT and SAT condition at this first follow-up ($\chi^2[1, n = 120] = 0.54$, $p = 0.46$). Finally, 49% (n = 59) never completed the second follow-up assessment (12 months), with no differences for the two treatment arms ($\chi^2[1, n = 120] = 0.47$, $p = 0.52$). Moreover, the last available z-scores of the primary outcome measure from patients who dropped out during TAU were not significantly higher or lower than the z-scores of patients who stayed in the study until 52 weeks ($t[12.20] = -1.54$, $p = 0.15$).

Table 2. Number of patients with reliable deterioration, no change, or reliable improvement on primary outcome measures (Y-BOCS or EDE-Q)

		Reliable deterioration		No change		Reliable improvement	
		CRT	SAT	CRT	SAT	CRT	SAT
T0–T1	OCD (n = 57)	2	2	26	20	4	3
	AN (n = 43)	0	0	20	16	5	2
	Total (n = 100)	4		82		14	
T0–T2	OCD (n = 51)	0	0	19	13	11	8
	AN (n = 34)	0	0	16	9	3	6
	Total (n = 85)	0		57		28	
T0–T3	OCD (n = 25)	2	3	4	3	5	8
	AN (n = 21)	3	0	2	3	10	3
	Total (n = 46)	8		12		26	

AN, anorexia nervosa; CRT, cognitive remediation therapy; EDE-Q, Eating Disorder Examination Questionnaire; OCD, obsessive-compulsive disorder; SAT, specialized attention therapy; T0, baseline; T1, after 6 weeks; T2, after 6 months; T3, after 12 months; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

Table 3. Means and standard deviations of the scale scores at T0–T3

	T0		T1		T2		T3	
	CRT	SAT	CRT	SAT	CRT	SAT	CRT	SAT
z-score, Y-BOCS and EDE-Q	0.37 (57) 0.93	0.41 (47) 0.77	0.15 (58) 0.96	0.03 (49) 0.81	–0.17 (49) 0.95	–0.42 (40) 1.01	–0.47 (30) 1.05	–0.78 (26) 1.10
Y-BOCS	24.25 (32) 7.10	24.25 (28) 5.67	23.06 (33) 6.78	21.57 (28) 5.93	18.80 (30) 7.42	16.55 (22) 6.98	17.56 (18) 7.42	11.64 (14) 7.31
EDE-Q	3.93 (25) 1.36	4.05 (19) 1.19	3.50 (25) 1.50	3.43 (21) 1.23	3.49 (19) 1.33	3.18 (18) 1.61	2.75 (12) 1.73	3.10 (12) 1.60
z-score, OCDQOL and EDQOL	0.35 (54) 0.75	0.38 (44) 0.87	0.38 (55) 1.03	–0.09 (46) 0.95	–0.22 (39) 0.93	–0.21 (34) 0.98	–0.17 (28) 1.15	–0.43 (23) 1.03
OCDQOL	2.63 (30) 0.62	2.54 (26) 0.61	1.90 (30) 0.80	2.03 (26) 0.70	2.21 (20) 0.77	2.29 (17) 0.73	2.45 (16) 0.77	1.92 (12) 0.75
EDQOL	2.77 (24) 0.48	2.88 (18) 0.67	2.41 (25) 0.68	2.73 (20) 0.64	2.33 (19) 0.57	2.28 (17) 0.67	2.09 (12) 0.80	2.31 (11) 0.77
DFlex total score	83.16 (55) 23.97	84.24 (45) 21.99	77.00 (54) 21.75	77.66 (47) 24.22	79.03 (39) 21.26	79.66 (35) 25.20	83.42 (28) 27.22	79.46 (24) 22.93
OCD subgroup	85.16 (30) 25.90	84.69 (26) 23.34	75.31 (29) 23.05	73.23 (26) 25.94	77.80 (20) 25.87	81.76 (17) 26.73	90.13 (16) 28.05	77.58 (12) 23.32
AN subgroup	80.76 (25) 21.71	83.63 (19) 20.62	78.96 (25) 20.43	83.14 (21) 21.25	80.32 (19) 15.64	77.67 (18) 24.28	74.50 (12) 24.35	81.33 (12) 23.42

Values are presented as mean (n) followed by standard deviation. AN, anorexia nervosa; CRT, cognitive remediation therapy; DFlex, self-report Detail and Flexibility questionnaire; EDE-Q, Eating Disorder Examination Questionnaire; EDQOL, Eating Disorders Quality of Life questionnaire; OCD, obsessive-compulsive disorder; OCDQOL, Obsessive-Compulsive Disorder Quality of Life self-report questionnaire; SAT, specialized attention therapy; T0, baseline; T1, after 6 weeks; T2, after 6 months; T3, after 12 months; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

CRT+TAU versus SAT+TAU across Diagnostic Groups

Table 3 shows the time course for the primary and secondary outcome measures comparing the combined CRT+TAU group with the combined SAT+TAU group from baseline to follow-up.

Primary Outcome Measures

Mixed model analyses revealed a significant effect of time (t[257.63] = –11.01, p < 0.01) for the total group. A quadratic relation over time was significant and therefore kept in the model (t[251.61] = 2.74, p = 0.01). Next, having added the covariates age, illness duration, and education years to the model followed by condition, we found no significant group effect on condition, which means there was no difference in the baseline primary outcome scores between the two treatment groups. To test for baseline differences between CRT and SAT for the OCD and AN groups, we subsequently added the diagnosis × condition interaction to the model, which was nonsignificant (t[70.34] = –0.04, p = 0.97). As can be seen in Table 4, when the two-way interactions time × diagnosis

Table 4. Predicted mean scores and within-group effect sizes for the primary outcome measures based on LMM at the different time points for CRT versus SAT (top part), and estimates for the condition × time interactions (bottom part)

	Condition	T0	T1	T2	T3
		Predicted mean scores	Predicted mean scores	Predicted mean scores	Predicted mean scores
OCD (Y-BOCS)[1]	CRT	23.46	21.92	17.84	15.02
	SAT	24.81	22.82	17.25	12.48
AN (EDE-Q)[2]	CRT	4.37	4.21	3.84	3.78
	SAT	4.60	4.36	3.74	3.35
		Predicted mean *z*-scores	Predicted mean *z*-scores	Predicted mean *z*-scores	Predicted mean *z*-scores
Total group[3]	CRT	0.31	0.19	–0.12	–0.30
	SAT	0.40	0.24	–0.19	–0.52
Within-group ES	CRT	reference	0.23	0.88	1.38
Y-BOCS	SAT	reference	0.26	1.02	1.67
Within-group ES	CRT	reference	0.20	0.73	1.08
EDE-Q	SAT	reference	0.23	0.87	1.36
Between-group effects		*z*-scores CRT vs. SAT	*z*-scores CRT vs. SAT	*z*-scores CRT vs. SAT	*z*-scores CRT vs. SAT
	estimate	reference	0.44	–0.06	–0.21
	95% CI		–0.15, 0.24	–0.26, 0.13	–0.45, 0.04
	p value		0.65	0.51	0.10
	ES		0.4	–0.1	–0.2

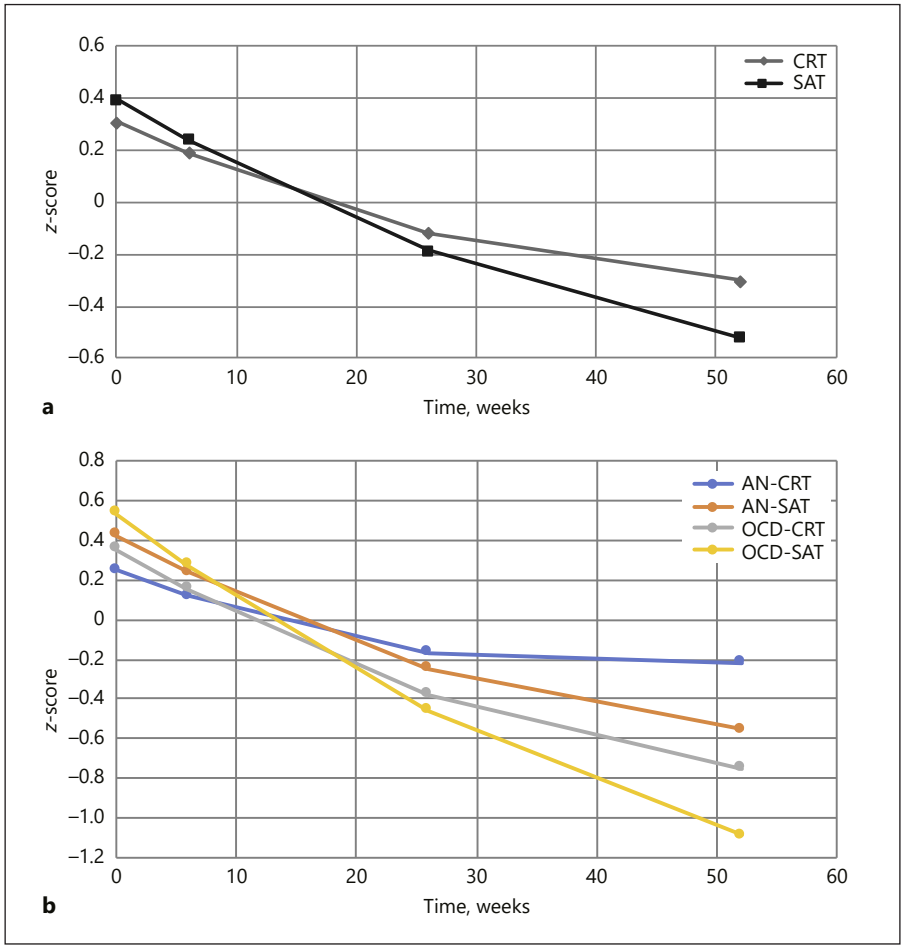
[1] Time × condition: $t(70.0) = -2.97$, $p < 0.01$. [2] Time × condition: $t(101.7) = -0.82$, $p = 0.42$. [3] Time × condition: $t(174.18) = -2.37$, $p = 0.02$; time × diagnosis: $t(173.48) = -2.90$, $p < 0.01$. AN, anorexia nervosa; CRT, cognitive remediation therapy; EDE-Q, Eating Disorder Examination Questionnaire; ES, effect size; LMM, linear mixed-effects modeling; OCD, obsessive-compulsive disorder; SAT, specialized attention therapy; T0, baseline; T1, after 6 weeks; T2, after 6 months; T3, after 12 months; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

and time × condition were added to the model, both interactions were significant ($t[173.48] = -2.901$, $p < 0.01$, and $t[174.18] = -2.37$, $p = 0.02$, respectively), implying that the main outcome variable *z*-scores of the patients in the SAT condition had declined more over time than those of the patients receiving CRT prior to TAU and that the main outcome variable *z*-scores of the patients with OCD had declined more than those of the patients with AN. Finally, the three-way time × diagnosis × condition interaction was nonsignificant: $t(205.45) = -1.16$, $p = -0.12$, i.e., there were no between-group differences over time for CRT and SAT. Therefore, the two-way interaction model (time × diagnosis and time × treatment) was the best-fitting model and is presented in Table 4 and in Figure 2.

The upper part of Table 4 demonstrates the time course of the Y-BOCS and EDE-Q scores and their combined *z*-scores comparing CRT+TAU with SAT+TAU between baseline and follow-up. We found time effects for the patients treated for OCD for both conditions, with large effect sizes at 26 and 52 weeks (Cohen's $d = 0.88$ for CRT+TAU and 1.02 for SAT+TAU at 26 weeks and 1.38 and 1.67 at 52 weeks, respectively). The time effects for the patients with AN showed medium to large effect sizes for both conditions, both at 26 weeks (Cohen's $d = 0.73$ for CRT and 0.87 for SAT) and at 52 weeks (Cohen's $d = 1.08$ for CRT and 1.36 for SAT).

Secondary Outcome Measures

QoL. The mixed-model analyses of QoL revealed a significant effect over time ($t[235.40] = -4.44$, $p < 0.01$) for the total group. A quadratic relation over time was significant and kept in the model ($t[226.84] = 3.64$, $p = 0.00$). The covariates age, illness duration, and education years were added to the model, with interactions proving nonsignificant, meaning there were no baseline differences between the two treatment conditions. Addition of diagnosis revealed that this predictor was also nonsignificant, showing there were no significant ($t[63.81] = -1.00$, $p = 0.32$) baseline differences in QoL scores between the OCD and AN groups. Since the interaction with treatment condition, which was added next, also was nonsignificant ($t[64.10] = -0.30$, $p = 0.98$), there were no significant differences in baseline QoL between CRT and SAT. The time × condition interaction was also nonsignificant, indicating that the treatment effect on QoL did not differ between groups over time ($t[169.40] = -1.85$, $p = 0.07$). However, the time × diagnosis interaction was significant ($t[166.87] = 2.88$, $p = 0.04$), indicating that QoL had improved more over time for the pa-



Color version available online

Fig. 2. Change over time of symptom severity. **a** CRT vs. SAT. **b** Two-way interaction model. AN, anorexia nervosa; CRT, cognitive remediation therapy; OCD, obsessive-compulsive disorder; SAT, specialized attention therapy.

tients with AN than it had for the patients with OCD. Finally, the three-way time × condition × diagnosis interaction was nonsignificant (t[217.43] = –1.24, p = 0.218); therefore, the previous model was the determinative model.

Cognitive Rigidity and Attention to Detail (DFlex). This model was constructed in the same way as the two previous models. First, a significant effect of time (t[231.12] = –2.01, $p < 0.05$) was found for the total group. A quadratic relation over time was significant and therefore kept in the model (t[226.74] = 2.01, $p < 0.05$). Having added the covariates age, illness duration, and education years to the model followed by treatment condition revealed no significant group effect for condition (t[70.42] = –0.20, p = 0.85), implying there was no difference in the baseline primary outcomes between the two treatment groups. As the diagnosis × condition interaction was nonsignificant (t[70.57] = –0.65, p = 0.51), indicating the absence of baseline differences between CRT and SAT for the OCD and AN patients, it was subsequently left out of the model. The two-way interactions time × diagnosis and time × condition were both nonsignificant (t[167.38] = –1.37, p = 0.17, and t[167.97] = –1.64, p = 0.10, respectively), signifying there was no significant difference in the main DFlex outcome scores of the patients in the SAT and those in the CRT condition. As the final three-way time × diagnosis × condition interaction was also nonsignificant (t[195.34] = –1.10, p = 0.27), denoting there were no between-group differences in the time course for the two treatment conditions, the two-way interaction model (time × diagnosis and time × treatment) proved the best-fitting model.

Psychotropic Medication. There were no differences in the proportion of patients using psychopharmaceuticals between the CRT+TAU and the SAT+TAU groups at each time point, except for the number of patients using benzodiazepine at time point 1 (6 weeks), which was significantly higher in the CRT+TAU group. Further-

more, the lower part of online supplementary Table 1 (see www.karger.com/doi/10.1159/000505733 for all online suppl. material) shows the number of patients with a significant change in pharmacotherapy between time point 1 (6 weeks) and time point 3 (52 weeks). Again, no differences were detected between the CRT+TAU group and the SAT+TAU group. As a next step, we examined the type of changes in pharmacotherapy (i.e., starting, increasing dose, decreasing dose, switching or stopping; online suppl. Table 2). There were no significant differences between the CRT+TAU and the SAT+TAU groups.

Finally, we applied the same procedure to detect differences between the CRT subgroup and the SAT subgroup in response trajectories on the primary outcome measures associated with pharmacotherapy. To detect differences in response trajectories between patients whose pharmacotherapy had been altered versus those whose drug regimen had remained the same, we constructed the model in the same way as with the primary research question, except that instead of comparing diagnostic groups (AN vs. OCD) we added the group of patients with versus without changes in pharmacotherapy. Both the two-way interactions time × medication change and time × treatment (CRT vs. SAT) were added to the model. The first interaction was nonsignificant (t[173.15] = 1.55, p = 0.12) and the second interaction was significant (t[175.06] = –2.40, p = 0.02), implying that the outcome z-scores of the patients receiving SAT prior to TAU had declined more over time than those of the patients receiving CRT prior to TAU and that medication change in the course of the study did not significantly influence the results. Finally, as expected, the three-way interaction time × medication change × condition was nonsignificant (t[210.83] = 0.95, p = 0.34), indicating no significant influence of medication change on the change trajectories recorded for the two interventions. Thus, the two-way interaction model time × treatment proved to be the best-fitting model.

Discussion

To our knowledge, this is the first randomized controlled trial using an active control condition (i.e., SAT) evaluating the effectiveness of CRT as a treatment enhancer preceding TAU for AN and OCD. Previous controlled trials reporting promising effects of CRT had methodological limitations mostly because they lacked an active control condition. This study enabled us to specifically compare the anticipated treatment-enhancing effect of CRT with an active control condition, assuming that this control condition encompassed an intervention without therapeutic ingredients. The strength of our study lies in the use of an active control condition that was designed to resemble CRT in structure and form of procedures while not explicitly or deliberately training cognitive flexibility.

At the group level, both CRT+TAU and SAT+TAU were effective, with analyses revealing large effect sizes for both treatment combinations. In contrast to our initial hypothesis, CRT+TAU was not superior to SAT+TAU.

What is it that explains why CRT was not effective in augmenting TAU in our study? First and in line with previous studies [40, 74, 75], we found no additional effect of CRT on cognitive inflexibility and attention to detail (as assessed with DFlex), rendering the theoretical basis of the added value of CRT questionable. Hypothetically, CRT should have a positive effect on these inefficient traits that have, in and of themselves, face value with respect to enhancing treatment effects when trained in the two patient groups studied [45, 76]. Moreover, although research has shown patients with OCD and AN to achieve poorer performance results relative to healthy individuals on set-shifting and central coherence tasks, this underperformance may not be clinically meaningful. Although CRT is designed to improve these inefficient characteristics, any improvement might then also not be of clinical relevance [15]. It needs to be noted, however, that neither of the reasonings underlying the enhancing effects of CRT were formally tested in our study. As Danner et al. [77] proposed, other factors might explain how CRT achieves positive effects in functioning. The intervention might (also) (1) help enhance self-reflection on the dysfunctional behavior, (2) promote the implementation of behavioral changes in daily life, (3) create confidence that behavioral changes can be achieved, (4) boost the motivation to change, and (5) positively reinforce techniques trained during the sessions. In our trial all these operant factors might well have played a role in both treatment conditions.

Another potential explanation lies in our use of an active control condition as a comparator. To date, all but one study investigating the effectiveness of CRT in AN compared CRT+TAU to TAU only, a design that has the risk of resulting in an overestimation of positive results [38, 40, 78]. Brockmeyer et al. [39] were the only researchers to compare CRT+TAU to a nonspecific neurocognitive therapy combined with TAU. Arguably, the superior treatment effects for CRT+TAU in the previous studies

might have been partly attributable to a better-quality therapist-patient relationship resulting from the add-on sessions.

Unexpectedly, CRT+TAU was not superior to SAT+TAU. We deem it unlikely that these results stem from a "pure" placebo effect. Both in OCD and AN placebo effects are generally negligibly small when compared to the rates reported for other disorders [79, 80]. SAT and CRT share an explicit focus away from the symptoms of the two conditions. In CRT the focus is on improving dysfunctional thinking styles and in SAT on neutral non-goal-directed activities. This latter focus may, however, have unintentionally promoted the patients' engagement in and enjoyment of spending pleasurable time including time together with the family. Thus, although intended as a neutral control condition, SAT may have contained some elements of psychological well-being (through game-oriented homework assignments).

As to the limitations of our trial, we need to mention the 49% dropout rate at the 52-week time point in both treatment conditions, which, in AN, is at the higher end of the range [81] and also seems to be somewhat increased for patients with OCD. The high rates in our trial are possibly due to the relatively high symptom severity in both patient cohorts. Furthermore, 75% (36 of 48) of the patients who dropped out for measurement at the 52-week time point had already ended TAU and were no longer available for the study. The last available *z*-scores of the primary outcome measure from patients who dropped out during TAU were not significantly higher or lower than the *z*-scores of patients who stayed in the study until 52 weeks. Next, a more intensive CRT format than the protocol we used, with a wider time spread and more sessions, might have been more effective in training set-shifting and central coherence skills. To try and attain longer-lasting improvements in set-shifting, Brockmeyer et al. [39] opted for a thirty-session format for their patients with AN. Future studies may address either intensifying CRT and/or integrating CRT in TAU to investigate whether better results can be obtained.

Some methodological issues also warrant discussion [82, 83]. The first issue concerns potential pharmacological effects. Although prescriptions were not changed during the experimental phase of the study (T0–T1), we cannot rule out that during TAU (T2 and T3) outcomes were influenced by the recorded medication changes, nor can we rule out interaction effects with other treatment factors, as was pointed out by Fava et al. [82]. Still, post hoc analyses showed that there were no differences in proportion of patients using psychopharmaceuticals between the CRT+TAU and the SAT+TAU groups, and there were no differences in the number of patients with a significant change in pharmacotherapy between these two groups. Furthermore, we found no significant two-way interactions (time × medication change) and no significant three-way interactions (time × medication change × treatment condition). The number of patients using a benzodiazepine at baseline and the 6-week time point was higher in the CRT+TAU group. As dosages were relatively low (equivalent dosage of 1.9 mg diazepam) and benzodiazepines were only allowed as sleep medication, we deem it unlikely that this difference influenced the outcomes.

The second methodological issue concerns AN/OCD comorbidity. Twelve patients (11%) fulfilled the diagnostic criteria for both OCD and AN. However, age at onset, years of education, age, illness duration, body mass index, and QoL did not differ from the total sample. This makes it unlikely that comorbid AN and OCD affected the overall outcomes.

Third, the presented *p* values were not corrected for multiple comparisons and hence the probability of a type I error might be larger than the reported unadjusted *p* values. Therefore, it cannot be ruled out that the positive finding for an effect of SAT might be a consequence of a type I error.

In conclusion, the results of this study showed that CRT did not show an improvement in response relative to treatment as usual in OCD and AN. Unexpectedly, SAT, the control condition, might have augmented the effect of TAU in the OCD group. Although this finding might have represented a chance finding, given that we hypothesized a priori an effect in the opposite direction, and further that we used uncorrected *p* values which would inflate the type I error rate. Nevertheless, despite these cautions, the effect of SAT delivered as a pretreatment add-on intervention for adults with OCD and AN merits future efforts at replication.

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Statement of Ethics

The trial design was approved by the Medical Ethics Committee of the University Medical Center Utrecht (METC No. NL43751.041.13 v0.3). The trial was registered in The Netherlands Trial Register (www.trialregister.nl, identifier: 3865) prior to the start of data collection (registered February 20, 2013). All patients gave their written informed consent before enrolment after receiving oral and written information about the study.

Disclosure Statement

The authors have no conflict of interest to declare.

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Author Contributions

All authors were involved in the conception and design of the study and/or in the analysis and interpretation of the data reported in this paper. All authors contributed to the original draft of the manuscript and/or added important intellectual content during the revision process.

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