Published in final edited form as:

Int J Eat Disord. 2013 September ; 46(6): 567–575. doi:10.1002/eat.22134.

Is Outpatient Cognitive Remediation Therapy Feasible to Use in Randomized Clinical Trials for Anorexia Nervosa?

James Lock, M.D., Ph.D.¹, W. Stewart Agras, MD¹, Kathleen Kara Fitzpatrick, Ph.D.¹, Susan W. Bryson, MA¹, Booil Jo, Ph.D.¹, and Kate Tchanturia, Ph.D.²

¹Stanford Department of Psychiatry and Behavioral Sciences, 401 Quarry Road, Stanford, CA 94305

²Department of Psychological, Institute of Psychiatry, Denmark Hill 103, De Crespigny Park, London SE58AF

Abstract

Objective—There are limited data supporting specific treatments for adults with anorexia nervosa (AN). Randomized Clinical Trials (RCTs) for adults with AN are characterized by high attrition limiting the feasibility of conducting and interpreting existing studies. High dropout rates may be related to the inflexible and obsessional cognitive style of AN patients. This study evaluated the feasibility of using Cognitive Remediation Therapy (CRT) to reduce attrition in RCTs for AN.

Method—Forty-six participants (mean age of 22.7 years and mean duration of AN of 6.4 years) were randomized to receive 8 sessions of either CRT or CBT over 2 months followed by 16 sessions of CBT for 4 months.

Results—During the two month CRT vs. CBT treatment, rates of attrition were lower in CRT (13%) compared to CBT (33%). There were greater improvements in cognitive inefficiencies in the CRT compared to the CBT group at the end of two months. There were no differences in other outcomes.

Conclusion—These results suggest that CRT is acceptable and feasible for use in RCTs for outpatient treatment of AN. CRT may reduce attrition in the short term. Adequately powered future studies are needed to examine CRT as an outpatient treatment for AN.

Keywords

anorexia nervosa; cognitive remediation; treatment; cognitive flexibility; attention to detail

Anorexia Nervosa (AN) is a serious psychiatric disorder associated with high morbidity, mortality, and cost.(1, 2) Unfortunately, no treatments for adults with AN have been shown to be effective in systematic randomized studies.(3) This may be because treatment studies of adults with AN are plagued with difficulties recruiting and retaining participants.(3, 4) Most attrition occurs within the first two months of treatment and may reflect a mismatch between therapist and patient goals, especially in treatments emphasizing weight gain and changing eating related cognitions.(5)(6) However, many clinicians and researchers attribute

Corresponding Author: James Lock, Tel: 650-723-5473, FAX: 650-723-5511, Jimlock@stanford.edu.

CONFLICT OF INTEREST AND FINANCIAL DISCLOSURE STATEMENT

The authors report no conflicts of interests. This study was supported by NIH grants K24 MH074467-065 and MH082706 to Dr. Lock. All authors confirm they have no financial involvement or affiliation with any organization whose financial interests may be affected by material in the manuscript or which might potentially bias it.

part of these difficulties to the inflexible and obsessional cognitive style common in AN patients(7) because these cognitive features allow only limited acceptance and adherence to standard treatment procedures.(6) Treatments such as Cognitive Remediation Therapy (CRT) that address problematic cognitive style are effective in improving cognition and psychosocial function in other treatment resistant psychiatric disorders (e.g. schizophrenia), (8, 9) thus, it is possible that this approach may be useful in AN. The current study examines the feasibility of using CRT in an outpatient study of AN.

Neuropsychological research has established that patients with AN have a cognitive style characterized by inflexibility (set-shifting difficulties)(10–12) and excessively detailed information processing (i.e., weak central coherence).(13–15) Set shifting involves the ability to move back and forth between operations and strategies.(16) Individuals with AN take significantly longer to set-shift than participants with similar IQs who do not have AN. In adults, these set-shifting difficulties persist even after weight restoration.(11, 13, 16) suggesting that these impairments are not solely due to acute starvation. In addition, when compared to healthy controls, patients with AN display a piecemeal approach to copying, re-constructing, and recalling the Rey-Osterrieth Complex Figure (Rey-O) demonstrating central coherence inefficiencies.(14) Other data suggest this cognitive style affects not only core psychopathology of AN, but also other areas of patients' lives leading to diminished psychosocial functioning.(17)

Cognitive processing difficulties associated with a range of psychiatric disorders (e.g., schizophrenia, autism spectrum disorder, obsessive-compulsive disorder) are responsive to CRT.(8, 9, 18, 19) It appears that by improving inefficiencies and impairments in cognitive process through CRT, not only are distorted cognitive processes addressed, but related behavioral and other psychosocial problems also improve.(8, 9) Preliminary data from an iterative case series of severely underweight adult inpatients with AN treated with CRT found statistically and clinically significant changes on key neuropsychological measures related to set-shifting and central coherence with moderate to large effect sizes (ES), suggesting the approach may be useful with this treatment resistant population.(18, 20)

Because RCTs for adults with AN often fail to yield meaningful results due to difficulties in participant recruitment and attrition, it is imperative to address these problems if we are to make progress in conducting RCTs in this population.(6) CRT appears to be acceptable to patients and may help address these problems either because of its focus on neurocognitive process rather than weight gain and eating related thoughts; or, alternatively because it improves cognitive flexibility and global processing allowing for increased ability to see the need for change. To systematically examine the feasibility of using CRT as an initial outpatient treatment strategy for AN with the primary aim of examining treatment acceptance, and reducing participant driven attrition, we conducted a small RCT that compared 8 sessions of CRT over eight weeks to 8 sessions of CBT over eight weeks. The main outcome of this study is participant driven attrition rate at 8 weeks. Secondary outcomes are changes in cognitive process and weight at 8 weeks. After the initial 8 week period of randomized treatment, both groups received follow-up treatment consisting of 16 weeks of CBT to assess any continuing effects of a short course CRT during CBT. Assessments after follow-up treatment with CBT included attrition, neurocognitive processes, weight and eating related psychopathology. These assessments were also conducted after an additional 6 month open follow-up (no planned treatment) period. We hypothesized that CRT would be more effective in reducing participant driven attrition during the initial 8 week treatment period than CBT. We also predicted that neuropsychological changes related to cognitive flexibility and central coherence would be greater in CRT than CBT at the end of the initial 8 week period.

METHOD

We obtained IRB approval prior to initiating the study. A site based independent Data Safety and Monitory Board (DSMB) provided ongoing approval of participant safety and assurance of data quality.

Participants: Participants for this study were recruited through colleagues, organizations, and clinics treating eating disorders, and by publicizing in the local media. Participants were medically stable(21) > than 16 years of age and met diagnostic criteria for AN (excluding the amenorrhea criteria) within the past year and currently were at or below 90% of mean percentile BMI for gender and height using Center For Disease Control norms at the time of recruitment.(22) Participants were eligible if they were on a stable dose of psychotropic medications (antidepressants and antipsychotics) for a minimum of 2 months while still meeting study entry criteria. Potential participants were excluded if any of the following were present: current psychotic disorder; history of significant brain injury; current dependence on drugs or alcohol; physical conditions (e.g., diabetes mellitus, pregnancy) known to influence eating or weight; self-reported previous CBT or CRT for AN. All participants were required to be followed by outpatient physicians to insure they were medically stable for outpatient treatment throughout the study. Decisions about medical stability and medical hospitalization were made by the participants' physicians independent from study personnel. Participants were withdrawn by study personnel if they required any of the following: psychiatric hospitalization for greater than 72 hours, hospitalization for medical problems associated with AN for greater than 14 days or on more than 2 occasions, if they met any of the other exclusion criteria described above at any point during the study; missing more than 3 consecutive scheduled sessions unless hospitalized.

Assessment Protocol: Initial participant contact was through a clinic referral or telephone inquiry. Telephone screening was used to identify those likely to meet entry criteria for the study. Participants meeting the study criteria were invited for an interview. If the potential participant was eligible and interested in participating, consents were obtained and assessment procedures initiated. The main assessment points were baseline and at the end of the randomized treatment period (8 weeks). Additional follow-up assessments were conducted at the end of treatment (6 months) and after open follow-up (1 year) A blind assessor trained in the Eating Disorder Examination conducted all assessment interviews.

Study dropout: Study dropout, the primary outcome, was defined as a participant refusing further treatment and assessment. Participants who were withdrawn by study personnel for medical reasons were not counted as dropouts.

Neurocognitive Measures

Wechsler Adult Intelligence Scale, 3rd Edition (WAIS-III).(23) The WAIS-III was used as a measure of general intelligence. Two broad index scores, verbal and performance, were summed to create a full-scale intelligence quotient.

Delis-Kaplan Executive Functioning System (D-KEFS).(24) The D-KEFS provides a normative assessment tool for the evaluation of executive functioning. The D-KEFS taps key domains of cognitive flexibility, concept formation, problem solving, planning, impulse control and inhibition, verbal and spatial tasks are sensitive to strengths and weaknesses across the full profile of executive functioning. For the purposes of the current study, the following selected subtests were administered: Trail making, verbal fluency, color-word interference, and towers.

Rey-Osterrieth Complex Figure.(25) The Rey-Osterrieth is a complex figure used in the evaluation of visual-spatial memory and organization. Participants are asked to copy a complex figure design using colored pencils that are alternated at certain intervals(26). This allows for assessment of the process and integration of elements from the design gestalt, providing a measure of central coherence and level of detail focus.

Wisconsin Card Sort Task.(27) The computerized version of WCST is a well-normed measures of set-shifting ability and problem-solving. Alternative versions were used at follow-up to minimize practice effects.

Eating Disorder Related Measures

Weight Change. Weight and height was assessed at each of the three main assessment points by an independent assessor. The participant was gowned and weighed on a balance beam scale that was regularly calibrated.

Eating Disorder Examination (EDE).(28) The EDE is a standardized investigator-based interview that generates operational definitions of eating disorder diagnoses and measures the severity of the characteristic psychopathology of eating disorders.

Beck Depression Inventory (BDI).(29) The BDI is a 21-question scale with each answer rated 0–3. This scale has been used in numerous studies of adolescent depression, particularly in psychotherapy trials.

Rosenberg Self-Esteem Scale (RSE).(30) The RSE is a widely used self-report instrument of 10 items measuring an individual's overall self-esteem.

Therapy Suitability and Patient Expectancy (TSPE). Participants' perceptions of the suitability of the treatment provided was rated on a visual analogue scale (0–10) at the end of session 1.

Helping Relationship Questionnaire (HRQ).(31) This 11-item questionnaire is used to measure the quality of the therapist-patient relationship across the two treatments and was completed by participants just prior to each of the first eight sessions.

Treatments Used in the Study

Cognitive Remediation Therapy (CRT).(7, 32) Tchanturia and colleagues developed a cognitive flexibility module for the treatment of AN, providing remediation exercises targeting these domains, adapted from Wykes, Reeder, Delahunty, Morice & Frost's (1993) flexibility module for schizophrenia(33). Bigger picture thinking tasks were added to address piecemeal processing of thinking (i.e., weak central coherence). There is no direct focus on weight, eating, or eating related psychopathology. CRT in this study employed a manual.(7) In first 2–3 sessions cognitive exercises are introduced. In further sessions the therapist encourages the patient to reflect on the performance in cognitive exercises and link it to behaviors they are using in real life. During these sessions, discussion focuses on the patients developing cognitive skills and how using these skills can be helpful in their lives. The content of these sessions is tailored to the progress of the participant. In later sessions explicit behavioral tasks are discussed and agreed between therapist and patient to test out obtained skills in the real environment. The CRT manual for this trial consists of eight sessions conducted across a two month time span. The initial session lasts for one hour, while remaining sessions are approximately forty-five minutes in length. Session structure consists of eight to ten tasks, followed by a conversation between therapist and participant, with a focus on eliciting patterns of thinking and minimizing performance based assessment.

Cognitive-Behavioral Therapy (CBT). CBT for AN used in this study is a slightly modified version of CBT for AN used in a previous RCT.(5) The treatment takes place in 24 sessions over 6 months and has four stages. Stage 1 (8 sessions) focuses on assessment, formulation, challenging distorted eating related cognitions, and weight restoration. Sessions take place once per week throughout treatment except during the first week of treatment, when there are 2 meetings to promote therapeutic engagement. Stage 2 (8 sessions) focuses primarily on the treating the participant's interpersonal difficulties and enhancing social problem-solving skills while continuing to confront food/weight phobia. Stage 3 consists of 5 sessions and prepares the patient for autonomous functioning from the therapist. Stage 4 consists of 4 sessions dealing with termination. The treatment is the same for participants who receive CRT prior to CBT, except they have only 16 sessions (approximately 6 sessions in Stage 1, 6 sessions in Stage 2, and 4 sessions in Stage 3) of over 4 months.

Therapist Training and Supervision. Six therapists treated participants in this study. Each conducted treatments in both arms of the study to minimize non-specific therapist effects. Therapists were Ph.D. clinical psychologists or psychiatrists with experience in treating eating disorders. Therapists were systematically trained in both CBT and CRT as follows: 1) Therapists reviewed the manuals by reading specified preparatory materials (manuals and chapters describing CBT and CRT; 2) Experts in each treatment approach conducted three-day intensive workshops at the start of the study on the treatments which included role-play and active rehearsal of the treatments; 3) Each therapist treated four pilot cases using the two treatment types under weekly supervision; 4) A second workshop was conducted six-months later to discuss therapists' adherence to the two treatments prior to the initial recruitment of study patients. Once the study was underway, the therapists had an hour of ongoing supervision each week by experts (CBT-WSA; CRT-KT, KF) in each treatment condition in person, by telephone, and review of audiotaped sessions.

Data Analysis

We used a computer generated block randomization approach to allocate participants to treatment groups. Participants were notified of their treatment assignment prior to session 1. Participants were considered entered when they were told their treatment allocation. Those who decided not to continue with the study before being randomized were regarded as study refusals and included in the determination of retention rates. Participants who dropped out after randomization were regarded as treatment dropouts and included in the retention analysis. Retention status was assessed at two time points: the end of 8 sessions (corresponding to the end of the CRT phase) and at end of CBT for both groups (6 months). Participants who were withdrawn by study personnel were not considered dropouts unless the reason was non-attendance. A chi-square analysis was used to compare retention rates between treatments of our primary hypothesis. Effect sizes (ES) were calculated for all outcomes as the study is a small feasibility design.

An independent t-test was used to compare baseline measures across treatment groups. Preliminary analyses to check the data for input errors and inconsistencies, to check the success of randomization, and to generate a description of the population sampled were conducted. Analyses designed to check the assumptions of all analytic procedures were also completed. For outcomes (other than retention rates) at session 8 and EOT we used mixed effects modeling(34, 35) to compare the outcome trajectories of the two groups. For maximum likelihood estimation of our longitudinal mixed effects models, we employed Mplus program.(36) We used a quadratic trend to model each participant's trajectory, which shows considerably nonlinear trends for some outcomes. This approach utilizes the repeated measures for each participant to reduce the unreliability of the outcome measure and to better manage missing data and dropout.(37) All 46 participants were included in longitudinal mixed effects analyses. We incorporated the MacArthur framework for the

exploratory moderator/mediator analysis(38, 39) in this longitudinal modeling framework to effectively assess moderator and mediator effects utilizing session 8 neuropsychological outcomes. A moderator variable determines on whom or under what conditions particular treatments work better than the others. A mediator variable determines how or why particular treatments achieve their effects on the primary outcome measure. Understanding these mechanisms can help identify heterogeneous subpopulations that may benefit differently from different treatments. For the six month open follow-up examining only BMI, we conducted an ANCOVA controlling for baseline differences in BMI.

RESULTS

Forty-six participants were recruited within the planned time line. The mean age of participants was 22.7 (SD 5.9) years with an average duration of AN of 6.4 (SD 5.8) years. According to self-report of racial and ethnic grouping, seventy-two percent of the participants were White; 11% were male, 57% had prior or current use of psychotropic medications, and 64% had been previously hospitalized for AN. The mean BMI of the group was 17.5 (SD 1.2) at baseline. Details of the baseline characteristics of the groups are available as an online appendix. Despite randomization, participants randomized to CRT had lower mean BMI ($t(1,44) = 2.1$ $P = .042$), lower scores on the WAIS similarities subscale ($t(42) = 2.4$ $p = .024$) and were more likely to be married ($\chi^2(1) = 5.6$ $p = .018$). Our analysis controlled for these baseline differences in WAIS and BMI. There was no difference on therapeutic suitability (CBT = 7.2 (2.7); CRT + CBT = 7.00 (2.7), $T(43) = 0.28$, $p = 0.78$, Cohen's $d = 0.08$) or therapeutic expectancy (CBT = 5.41 (2.1); CRT + CBT = 6.43 (2.5), $T(43) = 1.5$, $p = 0.15$, Cohen's $D = 0.44$) between the groups.

There were 7 dropouts (33%) by session 8 who were treated by CBT alone and 3 dropouts (13%) by session 8 that had received only CRT to this point. A two-tailed test with continuity correction of $\chi^2(1) = 1.5$, $p = 0.21$ Odds Ratio = 0.30, 95% Confidence Interval (.07 = 1.4), and ES of NNT = 5. There were two drop outs in participants under the age of 16, one from CRT and one from CBT. One of these drops occurred before session 8 (CRT) and one after session 8 (CBT). There were no withdrawals in this younger age group. Three participants (two in the first 8 sessions and one after 8 sessions) were withdrawn by study personnel according to protocol (all required medical or psychiatric hospitalization greater than allowed in the protocol) and not included as treatment dropouts. One of these three was from the CRT group. Withdrawals were not considered participant driven attrition because removal from the study was by study personnel based on exclusion criteria described above and not under participant control. During the follow-up period when CBT was given to both groups, the rate and amount of attrition from group that had previously received CRT increased and ultimately matched that of group that had initially received CBT.

The results of our longitudinal analyses using mixed effects modeling were converted to group effect (difference in change from the baseline) at each assessment point for each outcome variable. These results are illustrated in Figure 2 and detailed results on Table 2 in the online appendix). Effect sizes (ES) were calculated for group effect estimates from mixed effects modeling based on the standard deviation of the estimated change in outcome. Raw scores on neuropsychological outcome are used in these analyses because they are the norm for reporting amongst adult studies(11–13) and are most frequently used when the goal is group performance comparisons rather than comparisons of the individual to a normative sample. In addition, some of these tasks exist in multiple forms and do not have transformed normative scores.

By session 8 (main outcome point) there was a significant treatment effect for improving set-shifting and central coherence associated with moderate to large effect sizes. That is, by

session 8 the group receiving CRT (see Figure 2) improved more in these domains than those receiving CBT. Specific improvements favoring CRT at session 8 were found on the following neuropsychological tests related to set-shifting: DKFS Color-Word Interference Inhibition Raw Score-Condition 3 (see Table 2 in the appendix and Figure 2). In addition greater improvements favoring CRT at session 8 were found on the following specific measures of central coherence: Rey-O Central Coherence-Style Index; Rey-O Central Coherence-Coherence Index. However, after the 16 week CBT only treatment phase in both groups, there were no differences on any outcomes at the 6 month or 1 year follow-up assessments on these measures. In addition, there were no significant differences at any time points on the EDE, RSE, or HRQ.

During the initial 8 weeks comparison period, BMI increased 0.226 BMI points in CBT and 0.574 BMI points in CRT. After the next 4 months when both groups received CBT, BMI had increased to a total of .686 BMI points in the CBT only group and had decreased slightly to a gain of only .514 in the group initially randomized to CRT and followed by CBT. Thus, although both groups significantly improved in terms of BMI statistically, there were no significant group differences in change in BMI in the randomized groups at any time point (see Table 2 in the online appendix). In addition we found no differences in BMI between groups (CBT only $N = 14$, CRT followed by CBT $N = 17$) based on data collected at the end of an open follow-up (1 year) ($F(1,27) = .3$ $p = .57$).

None of the six variables explored as potential moderators (age, duration of AN, co-morbidity, prior or current use of medications, weight, or EDE at baseline) met the eligibility and analytical criteria for moderators. According to the MacArthur model with respect to moderation, a baseline variable is considered to be a moderator of treatment response if 1) the baseline measure of the potential moderator precedes treatment; 2) the baseline measure of the potential moderator is not correlated with treatment assignment; 3) and the response to treatment differs depending on the values of this potential moderator (i.e., treatment $\times$ potential moderator interaction is significant). For example, one of our exploratory hypotheses is that the baseline EDE will moderate the treatment effect. The conditions 1) and 2) are satisfied (i.e., met the eligibility criteria) since the study was randomized and baseline measure was estimated before randomization. However, the condition 3) was not satisfied (i.e., did not meet the analytical criteria) since the treatment $\times$ baseline EDE interaction effect was very small and insignificant. However, we identified one non-specific predictor—use of medication (prior or current) predicted poorer verbal cognitive flexibility outcome based on a worse DKEFS Color Word Interference Task performance score at session 8 ($p = .032$).

We also explored early changes (from baseline to session 4) in BMI, Rosenberg Self-esteem, and EDE restraint subscale score as potential mediators. According to the MacArthur model with respect to mediation, a post-randomization variable is considered to be a mediator of treatment response if the 1) treatment assignment precedes the measurement of the post-randomization variable; 2) the potential mediator is significantly correlated with treatment assignment, and 3) there is either a main effect of this potential mediator on the outcome and/or an interactive effect between the potential mediator and treatment assignment. Based on these criteria, none of the post randomization variables we explored as potential mediators were identified as mediators of outcome on the neuropsychological differential outcomes at session 8.

There were significant improvements from baseline to EOT at 6 months in EDE global score within groups for CBT (-0.771 , $p = .006$) and for CRT followed by CBT (-0.853 , $p = .004$). There were also significant improvements from baseline to EOT for BDI in the CRT followed by CBT group (-6.075 , $p = .003$), but not for the CBT alone group. However, there

were no between group differences on change from baseline to 6 months on global EDE (group difference = -0.081 , $p = 0.813$, $ES = 0.06$) or BDI (group difference = -2.086 , $p = 0.462$, $ES = 0.21$).

DISCUSSION

This study examined the feasibility of conducting an RCT for AN using CRT, a novel treatment for AN directly addressing cognitive style, compared to a treatment that emphasized weight gain and eating related cognitions (CBT) in reducing participant driven dropout. Secondly we explored differential changes in cognitive flexibility and overly detailed processing, eating related psychopathology, and weight. There are three important findings from this study.

This study suggests that it is feasible to use CRT in an outpatient RCT for AN. We were able to recruit (48% of eligible participants were randomized), we retained 88% during the first two months of treatment and 67% were retained until the end of 6 months of treatment. We were able to collect clinical and neuropsychological outcomes on participants in a randomized study involving CRT. Only 3 eligible patients stated the reason for refusal to be randomized was due to CRT (see Figure 1). In addition, participant driven attrition rates were 13% during CRT compared to 33% in CBT, which though not statistically different, did show an NNT of moderate size(5) favoring CRT during that phase of treatment. It may be that not addressing weight and shape directly in CRT compared to CBT accounts for this difference because patients are allowed to avoid confronting problematic thoughts and behaviors in CRT. However, even compared to studies of other treatments for adults with AN, the rate of 13% is low.(4) For example, in a study that compared Interpersonal Psychotherapy (IPT), Supportive Clinical Management and CBT in a clinically similar outpatient population, attrition rates were 43%, 31%, and 37% respectively.(40) Most dropouts in treatment for AN occur early (within the first 2 months),(5) because patients reject the treatment approach but this was not the case for CRT.(41) Only after CRT ended and CBT began did attrition in these participants become substantially similar to the CBT group.

A second important finding is that a two month treatment period of CRT lead to significantly greater improvement on key neurocognitive measures of set-shifting and central coherence than those randomized to CBT. These differences were statistically significant and associated with medium to large effect sizes (see Figure 2 and Table 2 in the online appendix). Although in need of examination in an adequately powered RCT, this is nonetheless the first randomized study to demonstrate that CRT could be effective in addressing neurocognitive inefficiencies in AN.(18, 42) While speculative, it is possible that these improvements in neurocognitive style helped to diminish dropout while the participants were in CRT. At the same time, we did not find the effects of CRT to endure past the initial treatment period--an issue that was also considered a problem in early application of CRT to schizophrenia, but with subsequent refinement and study appears to have been overcome by refining the approach and adding additional CRT sessions.(8, 9, 43)

A third important finding is that there was no difference in weight gain or change in eating related psychopathology (EDE) in the group that initially received CRT compared to the group that received CBT throughout at any assessment point. The finding that there was not a difference between groups is not surprising given the limited course of CRT (8 sessions over 2 months) together with the fact that the majority of treatment offered over the study in both treatment groups was CBT. However, it is important to note that there do not appear to be harms in not initially emphasizing weight gain and eating related cognitions. This suggests that a period of focusing on cognitive process can be undertaken in the outpatient

setting without concern that this will lead to immediate weight loss in patients. On the other hand, a brief course of CRT does not appear to have substantive effects on BMI or eating related cognitions in the short term nor does it appear to improve outcome on these measures when followed by CBT in the longer term. These results emphasize the need to better understand the potential role of CRT in those with enduring AN.

The study has a number of important limitations. The study is an exploratory feasibility study and is underpowered. The study took place at a university clinic with a specialty eating disorder service and this may limit the generalizability of the findings. Participants in the study were outpatients and therefore not severely emaciated. The version of CBT for AN used in this study was manualized and used in another RCT;⁽⁵⁾ however, newer versions of CBT have been recently developed and are being evaluated.⁽⁴⁴⁾ The inclusion of older adolescents (> 16 years) might have affected outcomes. However, there were no differences in the numbers of dropouts between the groups in younger participants during the initial two months or at follow-up points. Psychotropic medication use might have affected outcome, but the 17 participants on psychotropic medications were almost equally distributed between the groups (8 in CRT and 9 in CBT) and any effects therefore likely equal in both groups. We focused on participant driven attrition, while overall study attrition (including withdrawals) might have also been considered. However, even if withdrawals were included in the analysis, the differences in total attrition rates were noteworthy (35% in CBT and 17% in CRT). Further, although no clinical harms of using CRT were detected, other than differences on attrition and neurocognitive measures, there was no evidence of substantial clinical improvements on AN specific variables such as weight and eating related cognitions; however, the study was not powered to detect these if they existed. Further, the addition of a quality of life change indicator and health care utilization index (i.e., number of physician visits, hospitalizations, etc.) would have been a helpful addition to future protocols as this is likely these are important areas to assess in patients being treated for persistent AN.

It is unclear at this time how best to incorporate CRT in the treatment of AN. Given our results, it appears that using a short course of CRT as a “lead in” therapy for other approaches (e.g., CBT) may not be the best approach.^(32, 45) One possibility would be to continue CRT for a longer or more with more frequent meeting or to incorporate CRT as an adjunctive treatment in the context of CBT or some other therapy. Unfortunately, the current study cannot shed light on this question except to note that participants initially randomized to CRT did as well as CBT on improving weight and eating related psychopathology, not only during the 2 month randomization period, but also at all follow-up assessments. The results of this study suggest that an RCT employing CRT for AN is indeed feasible. Further, CRT may be useful in preventing participant dropout, a key impediment that must be overcome if RCTs for adults with AN are to be successful. CRT also appears to lead to clinically meaningful changes in cognitive style related to central coherence and set shifting though these effects were not enduring. These findings suggest that further study of CRT in adequately powered studies is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Arcelus J, Mitchell A, Wales J, Nielsen S. Mortality rates in patients with anorexia nervosa and other eating disorders. *Archives of General Psychiatry*. 2011; 68:724–31. [PubMed: 21727255]
2. Streigel-Moore R, Leslie D, Petrill SA, Garvin V, Rosenheck RA. One-year use and cost of inpatient and outpatient services among female and male patients with an eating disorder: Evidence

- from a national database of health insurance claims. *International Journal of Eating Disorders*. 2000; 27:381–9. [PubMed: 10744844]
3. Bulik CM, Berkman N, Kimberly A, Brownly JS, JA, Lohr K. Anorexia nervosa: a systematic review of randomized clinical trials. *Int J Eat Disord*. 2007; 40:310–20. [PubMed: 17370290]
 4. Dejong H, Broadbent H, Schmidt U. A systematic review of dropout from treatment in outpatients with anorexia nervosa. *IJED*. 2012; 45:635–47.
 5. Halmi CA, Agras WS, Crow SJ, Mitchell J, Wilson GT, Bryson S, et al. Predictors of treatment acceptance and completion in anorexia nervosa: implications for future study designs. *Arch Gen Psychiatry*. 2005; 62:776–81. [PubMed: 15997019]
 6. Halmi CA. The perplexities of conducting randomized, double-blind, placebo-controlled treatment trials in anorexia nervosa patients. *American Journal of Psychiatry*. 2008; 165:1227–8. [PubMed: 18829874]
 7. Tchanturia K, Lock J. Cognitive remediation therapy (CRT) for eating disorders: Development, refinement, and future directions. *Current Topics in Behavioral Neuroscience*. 2011; 6:269–97.
 8. Bowie C, McGurk S, Mausbach B, Patterson T, Harvey P. Combined cognitive remediation and functional skills training for schizophrenia: Effects on cognition, functional competence, and Real-Word behavior. *American Journal of Psychiatry*. 2012; 169:710–8. [PubMed: 22581070]
 9. Wykes T, Huddy V, McGurk S, Czobor P. A meta-analysis of cognitive remediation for schizophrenia: Methodology and effect sizes. *AJP*. 2011; 168:472–85.
 10. Tchanturia K, Davies H, Roberts M, Harrison A, Nakazato M, Schmidt U, et al. Poor cognitive flexibility in eating disorders: Examining the evidence using the Wisconsin Card Sorting Task. *PloS ONE*. 2012; 7:e28331. [PubMed: 22253689]
 11. Tchanturia K, Harrison A, Davies H, Roberts M, Oldershaw A, Nakazato M, et al. Cognitive flexibility and clinical severity in eating disorders. *PloS ONE*. 2011; 6:e20462. [PubMed: 21698277]
 12. Tenconi E, Santonastaso P, Degortes D, Bosello R, Tittton F, Mapelli D, et al. Set- Shifting abilities, central coherence, and handedness in anorexia nervosa patients, their unaffected siblings and healthy controls: exploring putative endophenotypes. *World J Bio Psychia*. 2010; 11:813–23.
 13. Lopez C, Tchanturia K, Stahl D, Treasure J. Central coherence in eating disorders: a systematic review. *Psychol Med*. 2008; 38:1075–84. [PubMed: 18070369]
 14. Sherman B, et al. Strategic memory in adults with anorexia nervosa: Are there similarities to obsessive compulsive spectrum disorders? *Int J Eat Disord*. 2006; 39:468–76. [PubMed: 16715489]
 15. Southgate L, Tchanturia K, Treasure J. Information processing bias in anorexia nervosa. *Psychiatry Res*. 2008; 15:221–7. [PubMed: 18579218]
 16. Tchanturia K, Davies H, Harrison A, Roberts M, Nakazato M, Schmidt U, et al. Poor cognitive flexibility in eating disorders: Examining the evidence. *PloS ONE*. 2012; 7:e28331. [PubMed: 22253689]
 17. Tchanturia K, Hambrook D, Curtis H, Jones T, Davies H, Lounes N, et al. Work and Social Adjustment in patients with Anorexia Nervosa. *Comprehensive Psychiatry*. 2012
 18. Tchanturia K, Davies H, Lopez C, Schmidt U, Treasure J, Wykes T. Neuropsychological task performance before and after cognitive remediation in anorexia nervosa: a pilot case series. *Psychol Med*. 2008; 38:1371–3. [PubMed: 18578900]
 19. Buhlman J. Cognitive retraining for organizational impairment in obsessive compulsive disorder. *Psychiatry Research*. 2006; 144:109–16. [PubMed: 17007938]
 20. Easter A, Tchanturia K. Therapists' experiences of Cognitive Remediation Therapy for anorexia nervosa: Implications for working with adolescents. *Clin Child Psychology and Psychiatry*. 2011; 16:233–46.
 21. Golden N, Katzman D, Kreipe R, Stevens S, Sawyer S, Rees J, et al. Eating disorders in adolescents: position paper of the Society for Adolescent Medicine: Medical Indications for Hospitalization in an Adolescent with an Eating Disorder. *J Adolesc Health*. 2003; 33:496–503. [PubMed: 14642712]
 22. Control CfD. CDC Growth Charts for the United States: Development and Methods. Atlanta, GA: Center for Disease Control; 2002.

23. Wechsler, D. WAIS-III Weschler Adult Intelligence Scale. 3. San Antonio: Psychological Corporation; 1997.
24. Delis, D.; Kaplan, E.; Kramer, J. Examiner's Manual: Delis-Kaplan Executive Functioning Systems (D-KEFS). San Antonio, TX: Psychological Coporation; 2001.
25. Osterrieth P. Test of copying a complex figures: contribution to the study of perception and memory. *Archives de Psychologie*. 1944; 20:206–356.
26. Strauss, E.; Sherman, EMS.; Spreen, OA. *Compendium of Neuropsychological Tests: Administration, Norms and Commentary*. New York: Oxford University Press; 2006.
27. Resources, PA. Computerized Wisconsin Card Sort Task, (WCST), version 4. 2003.
28. Fairburn, CG.; Cooper, I. The eating disorder examination. In: Fairburn, CG.; Wilson, GT., editors. *Binge eating: Nature, Assessment, and Treatment*. 12. New York: Guilford Press; 1993.
29. Beck, AT. Beck Depression Inventory. San Antonio, TX: The Psychological Corporation; 1987.
30. Rosenberg, M. *Conceiving the Self*. New York: Basic Books; 1979.
31. Luborsky, L. *Principles of psychoanalytic psychotherapy*. New York: Basic Books; 1984.
32. Tchanturia, K.; D, H. Cognitive Remediation. In: Grilo, C.; Mitchel, J., editors. *The Treatment of Eating Disorder: Clinical Handbook*. New York: Guilford Press; 2009. p. 130-50.
33. Wykes T, Dunn G. Cognitive deficit and the prediction of rehabilitation success in a chronic psychiatric group. *Psychol Med*. 1992; (22):389–98. [PubMed: 1615106]
34. Raudenbush, S.; Bryk, A. *Hierarchical linear models: applications and data analysis methods*. Thousand Oaks: Sage; 2002.
35. Singer, B.; Willett, J. *Applied longitudinal data analysis*. Oxford: Oxford University Press; 2003.
36. Muthén, L.; Muthén, BO. *Mplus user's guide*. Los Angeles: 1998–2011.
37. Little, R.; Rubin, D. *Statistical Analysis with Missing Data*. 2. New York: John Wiley; 2002.
38. Kraemer H, Wilson GT, Fairburn CG, Agras WS. Mediators and moderators of treatment effects in randomized clinical trials. *Arch Gen Psychiatry*. 2002; 59:877–84. [PubMed: 12365874]
39. Kraemer H, Kierman M, Essex M, Kupfer D. How and why criteria defining moderators and mediators differ between the Baron & Kenny and MacArthur Approaches. *Health Psychology*. 2008; 27(Supplement):S101–S8. [PubMed: 18377151]
40. McIntosh VW, Jordan J, Carter FA, Luty SE, McKenzie JM, Bulik CM, et al. Three psychotherapies for anorexia nervosa: a randomized, controlled trial. *Am J Psychiatry*. 2005; 162:741–7. [PubMed: 15800147]
41. Hay P, Touys W, Sud R. Treatment of severe and enduring anorexia nervosa: a review. *Australian and New Zealand Journal of Psychiatry*. 2012
42. Tchanturia K, Davies H, Campbell I. Cognitive Remediation for patients with Anorexia Nervosa: preliminary findings. *Annals of General Psychiatry*. 2007; 14:1–6.
43. Hogarty G, Flesher S. Cognitive remediation in schizophrenia: proceed...with caution! *Schizophrenia Bulletin*. 1992; 18:51–7. [PubMed: 1553500]
44. Fairburn, CG.; Cooper, Z.; Shafron, R. Enhanced cognitive behavioral therapy for eating disorders ("CBT-E"): An overview. In: Fairburn, CG., editor. *Cognitive Behavioral Therapy and Eating Disorders*. New York: Guilford; 2008.
45. Baldock E, Tchanturia K. Translating laboratory research into practice: foundations, functions, and future of cognitive remediation therapy for anorexia nervosa. *Therapy*. 2007; 4:1–8.

Figure 1.
Consort Diagram

Figure 2.
Longitudinal Trajectories of Cognitive Processing (based on observed means using all available cases at each assessment)