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**Does Cognitive Remediation Therapy (CRT) Improve the Neuropsychological Function in Patients with Anorexia Nervosa?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences-Physician Assistant

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## ABSTRACT

**OBJECTIVE:** The objective of this selective EBM review is to determine whether or not cognitive remediation therapy (CRT) improves the neuropsychological function in patients with anorexia nervosa.

**STUDY DESIGNS:** Review of two randomized controlled trials and one non-randomized case series, published in 2012, 2013 and 2014.

**DATA SOURCES:** The three studies used in this review were published in English and found in PubMed.

**OUTCOMES MEASURED:** For all studies, neuropsychological function, such as memory, attention, and cognitive flexibility, were measured using pre- and post-treatment questionnaires. One study used a computerized task-shifting paradigm to determine cognitive flexibility.

**RESULTS:** Brockmeyer *et al.* and Lock *et al.* compared CRT to other forms of treatment, and Abbate-Daga *et al.* investigated the effects of CRT pre- and post-CRT. All three studies revealed statistically significant improvements in patient's neuropsychological function following CRT. Brockmeyer *et al.* measured patients' reaction times as an indication for cognitive flexibility during computerized exercises and found that reaction times were decreased in the CRT group compared to the group receiving non-neuropsychological therapy. In the study conducted by Lock *et al.*, patients who received 8 sessions of CRT as compared to those who received cognitive behavioral therapy, showed enhanced cognitive flexibility and central coherence. Abbate-Daga *et al.* demonstrated an improvement in patient decision making from baseline measurements.

**CONCLUSIONS:** The results presented in these three studies suggest that cognitive remediation therapy is an effective treatment approach to improving the neuropsychological function in patients with anorexia nervosa.

**KEY WORDS:** anorexia nervosa, cognitive remediation therapy

## INTRODUCTION

Anorexia nervosa, a serious physical and psychiatric illness, is characterized by restricted eating, obsessive thoughts about thinness and body image, and an extreme fear of weight gain.<sup>1</sup> In turn, this results in a body weight less than 85% of the expected weight for height and a body mass index (BMI) less than 17.5 kg/m.<sup>2,3</sup> There are two types of anorexia, defined as (1) restricting, where the patient eats very little and (2) binge eating and purging, where there are episodes of bingeing followed by purging.<sup>4</sup>

The onset of illness is usually bimodal, with the first peak in early adolescence and the second peak in late adolescence or young adulthood.<sup>5</sup> Among females, the lifetime prevalence rates of anorexia are approximately 1%, and of all the affected individuals, more than 90% are female.<sup>4</sup> Globally, the disorder is most common in the United States, Canada, Europe, Australia, and Japan.<sup>4</sup>

Though the exact cause of anorexia is not well understood, many experts postulate that the disorder has a primary psychiatric origin.<sup>2</sup> Characteristically, the patient comes from a family that is achievement-oriented with parents who are extremely concerned with their children's body shape, physical activity and dietary intake.<sup>2</sup> Additionally, pressures from outside the family can also play a significant role in shaping an individual's self-image. Western cultures over-emphasize thinness and the "perfect" body through the media<sup>4</sup>, thereby influencing unrealistic ideals and unhealthy behaviors. Patients with anorexia can present with a variety of signs and symptoms: severe emaciation, cold intolerance, hypotension, bradycardia, constipation, dry or scaly skin, lanugo, loss of body fat, possible parotid gland enlargement, and amenorrhea.<sup>2</sup> They may also display habitual behaviors, such as counting calories, frequent weighing and excessive exercise.<sup>4</sup>

Because of the severity of the illness and the recommendation for inpatient care, the economic impact of anorexia nervosa is rather substantial. The total number of annual visits to the hospital for this disorder is unclear; however, a recent study estimated that a patient admitted to the hospital will stay on average 37.9 days with a direct hospital cost of \$1355 per day.<sup>6</sup> Indirect costs to the patient's caregiver, calculated by determining lost work days and leisure time, are approximated at \$95 per day.<sup>6</sup>

Treatment of anorexia is centered on a multidisciplinary approach with a primary goal of gradual weight restoration to at least 90% of the predicted weight.<sup>4</sup> To determine the need for inpatient care, the patient's weight and severity of complications are considered.<sup>2</sup> Fluid and electrolyte disturbances are corrected, and calories are replenished at 1200-1800 kcal/day for the severely underweight.<sup>2,4</sup> Outpatient treatment consists of cognitive behavioral therapy, family therapy, and supervised weight gaining programs.<sup>2</sup> These therapies should continue for at least one year to help maintain weight gain and healthy behaviors.<sup>4</sup> Adjunctive antidepressants, second generation antipsychotics, and lithium are beneficial, especially in patients with comorbid depression or psychosis.<sup>4</sup> Additionally, olanzapine has been shown to improve weight gain and fluoxetine is used in the prevention of relapse in some patients.<sup>4</sup>

Despite the multifaceted approach and advancements in treatment, 75% of anorexic patients are unable to overcome their weight-related concerns and unrealistic body image, and many researchers attribute this failure to the inflexible and obsessional cognitive function characteristic of the disorder.<sup>4,5</sup> Thus, alternative methods have been hypothesized as new treatment modalities. Cognitive remediation therapy (CRT) is designed to increase awareness of one's cognitive weaknesses and strengthen those weaknesses through repetitive cognitive exercises.<sup>1,5,7</sup> This therapy was initially developed for patients with brain lesions and

schizophrenia; however, initial findings in studies have suggested that CRT may be effective in improving cognitive function, thought processing and flexibility in anorexic patients.<sup>7</sup> CRT in anorexia nervosa is structured in a way to improve the rigid neurocognitive function in patients.<sup>7</sup> This paper utilizes 2 randomized controlled trials and 1 case series evaluating the efficacy of CRT as a method for improving neuropsychological functioning in patients with anorexia nervosa.

## **OBJECTIVE**

The objective of this selective EBM review is to determine whether or not CRT improves the neuropsychological functioning in patients with anorexia nervosa.

## **METHODS**

Two randomized controlled trials (RCT) and 1 case series were used in this review. The population included male and female patients with anorexia nervosa, ages 16 and older. In the study conducted by Brockmeyer *et al.*, 126 participants were recruited from two specialized inpatient units for eating disorders and an outpatient center.<sup>7</sup> Of the 126 patients selected, 40 met DSM-IV criteria for eating disorders and were randomly assigned to the intervention group, which involved 30 sessions of CRT or to the control group, which involved 3 weeks of non-neuropsychological therapy.<sup>7</sup> CRT and non-specific neurocognitive therapy (NNT) are similar in that they both focus on memory, attention and deductive reasoning; however, CRT adds the component of cognitive flexibility.<sup>7</sup> Both groups participated in 21 computer-based sessions and 9 face-to-face sessions with therapists.

The RCT studied by Lock *et al.* randomly assigned 46 participants to either 8 sessions of CRT over a 2 month period plus 16 sessions of CBT or 24 sessions of cognitive behavioral

therapy (CBT) over a 6 month period.<sup>5</sup> CBT is divided into stages where the goal of treatment changes from stage to stage.<sup>5</sup>

The intervention conducted by Abbate-Daga *et al.* involved 20 participants recruited from a center for eating disorders in Italy.<sup>1</sup> Each participant met DSM-IV criteria and after agreeing to be part of the study, was assigned to 10 sessions of CRT only.<sup>1</sup> The primary outcome measured across all 3 studies was improvement in neuropsychological function.

Key words used in the search included “anorexia nervosa” and “cognitive remediation therapy”. The chosen articles were all written in English and published in peer-reviewed journals between the years 2012 and 2014. Literature searches were conducted using PubMed, and the articles were chosen based on their relevance to my clinical question and the presence of patient oriented outcomes. The inclusion criteria for article selection consisted of randomized controlled trials or case series utilizing participants that met the diagnostic criteria for anorexia. Exclusion criteria consisted of articles published before 1999 and medically unstable patients. Data obtained from the studies were recorded as continuous and could not be converted to dichotomous. The statistics reported included P-values and changes in mean from baseline. Table 1 summarizes the demographics and characteristics of each study.

Table 1 – Demographics and Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion criteria	Exclusion criteria	W/D	Interventions
Brockmeyer <sup>7</sup> , 2014	RCT	40	18+	Participants must meet criteria with anorexia nervosa currently receiving treatment as usual	Suicidal ideations, current substance abuse, current or past schizophrenia, bipolar, or organic mental disorder	1	30 sessions of CRT or non-specific neurocognitive therapy for 3 weeks
Lock <sup>5</sup> , 2013	RCT	46	16-29	Met diagnostic criteria for anorexia w/in last year, medically stable, at or below 90% of mean percentile BMI, on psychotic meds for at least 2 months	Current psychotic disorder, hx of brain injury, current alcohol or drug dependence, physical conditions known to influence eating/weight, self-reported previous CBT or CRT for anorexia	15	8 sessions of CRT plus 16 sessions of CBT or 24 sessions of CBT over 6 months
Abbate-Daga <sup>1</sup> , 2012	Case series	20	22.5 (mean age)	Met the DSM diagnostic criteria, female, normal IQ	Severe medical comorbidity, drug dependence, need of acute hospitalization	0	10 sessions of CRT

## OUTCOMES MEASURED

In Brockmeyer *et al.*, the main outcome measured was cognitive set-shifting, an indication of cognitive flexibility.<sup>7</sup> To measure this, researchers utilized a computer-based cued task-switching paradigm, which allows participants to view a diagram of 4 square boxes, with positions labeled in each box, an arrow pointing right or left, and the word “right” or “left” within each arrow.<sup>7</sup> Participants were either instructed to follow the direction of the arrow or the word, and the reaction times were measured during each session to estimate the level of cognitive flexibility.<sup>7</sup>

Lock *et al.* measured both neurocognitive outcomes and eating disorder related outcomes at baseline, session 8 and at the end of treatment.<sup>5</sup> The Wechsler Adult Intelligence Scale was

used to measure general intelligence. The Delis-Kaplan Executive Functioning System was used to assess cognitive functioning, particularly in the areas of cognitive flexibility, concept formation, problem solving, planning, impulse control and inhibition.<sup>5</sup> To assess visual-spatial memory, participants were asked to copy a complex figure design with colored pencils using the Rey-Osterrieth Complex Figure.<sup>5</sup> The computerized version of Wisconsin Card Sort Task measured set-shifting ability and problem-solving.<sup>5</sup>

The study conducted by Abbate-Daga *et al.* also assessed neurocognitive outcomes at baseline and post-CRT.<sup>1</sup> The Wisconsin Card Sorting Test (WCST) was used to assess abstract thinking and cognitive strategy in the presence of changing environments.<sup>1</sup> The Iowa Gambling Task (IGT) measures decision-making as the participant is instructed to select favorable or unfavorable cards from 4 different decks.<sup>1</sup> To assess attention and cognitive flexibility, the team implemented the Trail Making Test (TMT) which requires the participant to connect numbers and letters in ascending order.<sup>1</sup>

## **RESULTS**

The three studies in this review evaluated the effectiveness of CRT in improving neuropsychological functioning in patients with anorexia. Two of the studies selected were RCTs and one was a case series. All relevant data was presented in a continuous form and was not able to be converted to dichotomous data.

Brockmeyer *et al.* recruited participants with a mean age of 23. The original sample size for each group was  $n = 20$ ; however, the results were calculated using data from participants that completed each treatment with  $n = 11$  for CRT and  $n=14$  for NNT. Using a cued task-switching paradigm to evaluate cognitive flexibility, the researchers demonstrated that mean reaction times at post-assessment were significantly shorter in the CRT group as compared to the NNT group ( $p$

= 0.027) (Table 2).<sup>7</sup> Sixty percent of participants in the CRT and 43% in the NNT group reported feeling more flexible in their daily routines after the exercises.<sup>7</sup> There were no side effects noted from either form of treatment.

Table 2 Brockmeyer *et al.* Means and standard deviations for reaction times for treatment completers

	Pre-Assessment		Post-Assessment		ANCOVA	
	CRT (n = 11)	NNT (n = 14)	CRT (n = 11)	NNT (n = 14)	F	<i>p</i>
Variable	M ± SD	M ± SD	M ± SD	M ± SD		
Cognitive set-shifting	1194 ± 347.39	1191.18 ± 337.78	826.30 ± 172.48	1027.18 ± 342.62	5.59	0.027

Lock *et al.* conducted a randomized controlled trial with 46 male and female participants with anorexia between the ages of 16 and 29. The participants were randomly assigned to either the CRT plus CBT treatment group (n = 23) or the CBT only treatment group (n = 23). By the end of treatment, there were 7 dropouts from the CRT group (n = 16) and 8 dropouts from the CBT group (n = 15). At session 8, the group receiving CRT as compared to the group receiving CBT showed improved neuropsychological functioning, especially set-shifting (cognitive flexibility) measured by the DKFS Color-Word Interference (p = 0.001) and central coherence, measured by the Rey-O Central Coherence-Style (p = 0.005) and Coherence-Coherence Index (p = 0.008) (Table 3).<sup>5</sup> However, after 16 weeks of CBT only for both groups, there was no further improvement in set-shifting or central coherence at 6 months.<sup>5</sup> Patients did not report side effects or safety issues in this study.

Table 3 Lock *et al.* Change from baseline to session 8 and end of treatment

	Session 8				End of Treatment			
	CBT		CRT		CBT (n = 15)		CRT + CBT (n = 16)	
DKFS	p = 0.074	95% CI = -4.819, 0.0023	p = 0.001	95% CI = -9.115, - 4.693	p = 0.027	95% CI = -6.077, - 0.365	p = 0.001	95% CI = -9.126, - 3.352
Rey-O Coherence- Style	p = 0.678	95% CI = -0.280, 0.182	p = 0.005	95% CI = 0.087, 0.503	p = 0.001	95% CI = 0.108, 0.438	p = 0.001	95% CI = 0.184, 0.522
Rey-O Cohoerence- Coherence	p = 0.696	95% CI = -0.228, 0.152	p = 0.008	95% CI = 0.041, 0.491	p = 0.001	95% CI = 0.094, 0.372	p = 0.001	95% CI = 0.125, 0.403

Abbate-Daga *et al.* performed a case series study to evaluate the effects of CRT on 20 female anorexic patients with a mean age of 22.5 years. A paired- sample t-statistic was utilized to determine if cognitive flexibility and decision making strategies differed before and after treatment.<sup>1</sup> Researchers found that neuropsychological performances improved from baseline, particularly on the WCST (p = 0.042), which evaluates abstract thinking and cognitive strategy, and the TMT (p = 0.031), which evaluates cognitive flexibility (Table 4). However, there were no changes noted in decision-making skills measured by the IGT (p = 0.109).<sup>1</sup> There were no safety concerns or side effects of treatment reported in this study.

Table 4 Abbate-Daga *et al.* Neuropsychological performances before and after CRT treatment

		Before CRT (n = 20)	After CRT (n = 20)	<i>t</i>	<i>p</i>
TMT	Trail A	44.99 ± 22.79	34.91 ± 11.77	2.335	0.031
WCST	Global Score	22.80 ± 23.56	11.35 ± 2.39	2.177	0.042
IGT	Net Score	1.30 ± 19.33	0.70 ± 29.58	0.113	0.109

## DISCUSSION

This systematic review evaluated 2 RCTs and one case series for the effectiveness of cognitive remediation therapy in improving neurocognitive function in anorexic patients. CRT is designed to strengthen cognitive weaknesses through repetitive exercises.<sup>1,5,7</sup> Because there is no evidence-based and successful psychological or pharmacological treatment for anorexic patients,

new treatment approaches are warranted.<sup>7</sup> Additionally, the obsessive and rigid characteristics of anorexia suggest the need for a cognitive-based treatment plan. Similar to preliminary findings, the 3 studies investigated in this review all found CRT to be effective in improving cognitive function in anorexic patients.

There were several limitations expressed by each study. Collectively, sample sizes were not large enough, and the use of older adolescents and young adults decreased the generalizability of the results. Additionally, only one study reported the inclusion of males, despite an increase in body image distortions in that gender.<sup>5</sup> The study conducted by Brockmeyer and colleagues noted that the inability to rule out effects from previous treatment (treatment as usual) could have skewed the results in a more positive direction.<sup>7</sup> Lock *et al.* noted that their findings may have been different if unstable or severely anorexic patients had not been excluded from the participant population.<sup>5</sup> Additionally, only 67% of the participants remained at the conclusion of their study. The study performed by Abbate-Daga *et al.* did not recruit a control group for comparison.<sup>1</sup> Finally, two of the three studies used questionnaires to gather data which could have allowed for reporting bias.

## **CONCLUSION**

The data assessed in this EBM systematic review revealed that cognitive remediation therapy improves neuropsychological functioning in patients with anorexia nervosa, thereby highlighting the potential beneficial outcomes of CRT as part of a treatment regimen for this disorder. More studies, especially RCTs, are necessary to further investigate the effects of CRT in anorexic patients with varying disease severity. Also, research involving a combined treatment approach, such as CRT with a pharmacological aspect, is warranted due to the combined psychological and physical nature of the disease.

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