Author’s response to reviews

Title: Cognitive Remediation Therapy (CRT) as a Pretreatment Intervention for Adolescents with Anorexia Nervosa during Medical Hospitalization: A Pilot Randomized Controlled Trial Protocol

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Author’s response to reviews:

To: Susana Dodd
From: C. Alix Timko
Re: PAFS-D-17-00164

Cognitive Remediation Therapy (CRT) as a Pretreatment Intervention for Adolescents with Anorexia Nervosa during Medical Hospitalization: A Pilot Randomized Controlled Trial Protocol

Thank you for the opportunity to revise the aforementioned manuscript. We have addressed the reviewers’ and editor’s comments. Below we noted the comment in bold and then followed with our response. All co-authors have reviewed the manuscript and have approved it in its current form. Please let me know if you have any questions about revisions or would like us to make any other changes or address other points.

Sincerely,

C. Alix Timko
Reviewer 1:

Re-organizing the Methods/Study Design section in line with other manuscripts that have been published in this journal may help clarify which of the many measures are assessing feasibility and acceptability versus outcome.

We reviewed protocols published in the journal and reorganized the methods section in the following fashion:

Ethical Considerations
Setting
Participants
Study Design
Recruitment and Screening Procedures
Description of Intervention
Blinding and Randomization
Measurement Strategy
Outcomes
Data Management and Analysis plan

We believe that this helps the flow of the manuscript. As per suggestion of the editor, the “outcomes” section links the specific outcome to the aims.

Also in the Discussion, it would be helpful to clarify which aspects of the study will specifically determine if the intervention is feasible to warrant a large scale RCT.

We have included this in the first paragraph of the discussion.

Abstract:

1. Background: Criteria for AN not fully accurate based on DSM-5.

We added the additional body-specific criteria to our description of AN and fleshed them out in more detail in the introduction (see comment below).
2. Method and Design: State number of participants, i.e. "a total of XX participants will be recruited…"

We have added the target sample size to the abstract.

Background:

1. First line of Background section, which defines AN, is inaccurate; it only refers to first criterion. Suggestion to revise to reflect DSM-5 criteria for AN.

We have added a description to reflect the other two criteria to the beginning of the introduction.

2. "AN is associated with significant morbidity" What do you mean? Mortality, psychiatric co-morbidity, medical complications?

We have clarified that it is both physical and psychiatric morbidity and added examples of each.

3. Sentence starting with "Severe starvation…" needs a reference.

We have provided references that support this statement.

4. Sentence starting "Results from longitudinal studies of brain functioning…" This sentence is speculative as there is not conclusive evidence of long term neurocognitive "deficits" or an endophenotype. Some problems with executive functioning that do not rise to the level of clinical deficits are found in adults and may remit, at least somewhat, with weight restoration. Please revise with "may."

We have revised this statement to include the word “may.” We have also added another reference that lends support to neurocognitive inefficiencies existing premorbidly.

5. Include abbreviation "CRT" after introducing Cognitive Remediation Therapy at end of p. 3.

Abbreviation included. Thank you for pointing out that we missed adding it.
6. The term neurocognitive "deficits" is used throughout the article to discuss possible neurocognitive difficulties. Suggestion to replace "deficits" with "problems," "difficulties," or "weaknesses." "Deficits" implies clinically significant levels of problems when in fact the literature has only found statistically significant levels.

This addresses a concern of the editor and other reviewer as well. We have opted to use the term "neurocognitive inefficiencies" in the manuscript as we feel this best captures what has been found in the literature to date. We agree that these inefficiencies are not deficits per se (though they are often referred to as such – as noted by the editor). We agree with the point that these are not usually clinically significant difficulties; however, they are often an area of significant personal weakness in an overall cognitive profile. In this way, they are intrapersonal deficits.

7. Revise sentence beginning "It has demonstrated reduction…” on p.4 to convey your meaning in a grammatically correct manner.

We have revised the sentence to read “CRT can reduce memory failure, reduce anxiety, improve self-esteem and sense of self, and improve social relationships.”

8. Use abbreviation AN consistently throughout instead of "anorexia" (ex. p. 4-5).

We have replaced anorexia or anorexia nervosa with “AN” throughout the manuscript.

9. Sentence starting "This is especially salient for individuals with anorexia…” - the purpose of CRT is not to guide away from a "perfection based or task oriented perspective." Rather it is to improve cognitive flexibility in terms of 1) set shifting and 2) central coherence. Cognitive inflexibility may be a feature found in a perfectionistic personality style but they are not the same thing.

We respectfully disagree with the reviewer regarding the purpose of CRT for AN. We agree that cognitive inflexibility and perfectionism are not the same thing. Research and clinical anecdotes support the idea that adolescents with AN have a more cognitively rigid or inflexible approach to problem solving. In the research literature (and in the popular vernacular) this has been approached or discussed through the concept of perfectionism. Many patients and their families will describe them as “perfectionistic.” We also know that set-shifting difficulties in older adolescents and adults are associated with perfectionism in childhood. In our view, perfectionism is salient as it overlaps with the CRT tasks used in this approach. In session with adolescents, we do work to guide them away from a more perfectionistic approach – we want them not to focus
on the outcome (i.e., doing it perfectly or correctly), but rather to think and reflect on their thinking style.

10. Point 9 above relates to a more major issue that the constructs of set shifting (a type of executive functioning) and central coherence, which are the two cognitive targets of CRT for AN, are not clearly or adequately defined. The set-shifting definition is okay (bottom p.4) but needs a reference. The definition of central coherence (p. 5) is not clear - weak central coherence has two aspects: difficulty with global processing AND over focus on detail. This definition also needs a reference. The sentence starting "CRT for anorexia was developed…” (p. 5) implies that central coherence is a form of executive functioning, which it is not. Switching from detail to global processing contains an element of set-shifting, but central coherence itself is not a form of executive function. The sections on pp. 4-5 would benefit from clearer explanation of the specific cognitive targets of CRT (set-shifting and central coherence), definitions of each construct, and how cognitive inflexibility (a thinking style) may contribute to cognitive and behavioral manifestations of AN.

We have reorganized and edited this section. We expanded our definition of set shifting and of central coherence. We clarified that central coherence is an information processing style as opposed to an aspect of executive functioning. We provided references for the definition of set shifting and central coherence. Finally, we linked both of them to some of the behavioral and cognitive manifestations of AN.

11. "Thinking style" is not mentioned until the last paragraph on p. 5. Suggestion to explicitly make the connection between this term and "cognitive inflexibility" earlier in the Background section.

Thank you for this suggestion. We have done so in our reorganization and editing of the section on set shifting and central coherence.

12. Incorrect use of ; after "behavioral flexibility" on p. 6.

Thank you for pointing out this typo. We have corrected it.


Likewise, that you for pointing this out.
Methods/Study Design:

1. Participants/Study Population: The sample includes sub-threshold AN participants yet the title, abstract, and paper as a whole refer to "AN" only. Wording should reflect that the sample included participants who did not meet full criteria for AN.

One of the reasons we included those with subthreshold AN is that adolescents who are eligible for this study are often in hospital unexpectedly. That is, this is often the first time they are diagnosed with AN or a diagnosis of AN is suspected. Some adolescents will deny symptoms and, in our clinical experience, will tell different members of the care team different things. In our experience, adolescents will often not report/display any elements of Criterion B (fear of gaining weight, becoming fat, or engagement in behavior that interferes with weight gain) until nutritional rehabilitation has begun. Thus, it may take a number of days of nutritional rehabilitation for strict DSM-5 criteria to be met. Waiting for this would reduce the amount of time adolescents would be able to receive CRT should they decide to participate. Because of this, we left the wording the same throughout the manuscript and added a footnote explaining our reasoning. In the manuscript describing results of the study, we will be explicitly clear on the diagnosis at recruitment and the diagnosis at discharge.

2. Description of Investigational Intervention: If set-shifting and central coherence are the cognitive targets of the intervention, which tasks or sessions relate to each of these? Suggestion to include the cognitive function targeted by each task in Table 1.

We have added this information to Table 1 and provided a table note with greater description of some of the tasks vis a vis their relationship to set shifting and central coherence. We have also clarified (see below) that all tasks occur in each session.

3. Description of Investigational Intervention: Is the intervention delivered in an individual or group modality? Please specify.

We have specified that they receive individual sessions in the description of the intervention on page 13.

4. Description of Investigational Intervention: Six sessions are considered treatment completion, but based on Table 1 it unclear how you will ensure that each participant receives the same, or even similar form of the intervention. How are the tasks rotated? Each task has "1-8" in the session number on Table 1. What does that mean? Please clarify to
show how you plan to standardize the CRT intervention (same 6 sessions/tasks for each participant?). Also, suggestion to include "minimum of 6 CRT sessions" in Table 4.

Tasks are delivered in a standard order (that which is listed in Table 1). Each task is given in the session specified. We clarified this in the text on pages 13-14.

We did not alter the “up to 8 sessions” to “minimum of 6” as adolescents may discharge after 4 days of CRT. Adolescents who are in hospital for a longer period of time may not be discharged until days after session 8 of CRT. Thus, adolescents can receive up to 8 sessions. In order to be considered a treatment completer, they need to complete at least 6 sessions.

5. Teach the Parent (TTP). First sentence p. 12: tense of pronouns is incorrect - "their" should be "she/he/.

We changed “parental” to “parents’” to address this error.

Reviewer #2: This is an exciting study with great potential to positively influence current treatment protocols for adolescent Anorexia Nervosa (AN). The authors have been very thorough and ethical in the design of the study and are adhering to the highest standards of scientific rigor.

Thank you.

One recommendation I have is that the authors reconsider their use of the term "deficit" when referring to difficulties in set-shifting (SS) and central coherence (CC) in patients with AN. Although the term "deficit" is frequently used this way in the current literature, if you examine the data in most studies, including those cited by the authors in this manuscript, AN participants most often fall within the normal range on tests of SS and CC although frequently perform more poorly than controls. The findings in studies with adolescent participants with AN show participants are even more likely to be in the average to above average range. While I understand talking about these difficulties as deficits strengthens arguments for supporting research in this area I believe it distorts the picture of what we are looking at which is more relative individual weaknesses rather than stark deficits.

Thank you for your thoughtful. The other reviewer agreed and we have replaced the term “deficits” with “cognitive inefficiencies” throughout the manuscript.
Editor: Thank you for submitting this well-written protocol. I have some minor comments relating to details given in this protocol regarding randomisation, analysis, blinding and outcomes:

Randomisation: It is not good practice to disclose the block size within the study protocol - please remove reference to the block size (6) in the Randomisation section.

We have removed this.

Efficacy Analysis: Pilot studies should focus on confidence interval estimation, rather than hypothesis testing or complex statistical modelling, due to a lack of power. I would recommend that you rephrase your analysis section, stating the primary aim of the analysis will be confidence interval estimation (for example, to inform future studies) and that any modelling will be considered entirely exploratory in nature.

We have added CI to the analysis plan.

Blinding: Might it be possible to include any blinding of outcome assessors or statistical analysts?

We noted that assessment at T1 is blind and that assessment at T3 – while not blind is also not specifically unblinded. We have specified that the PI and statistician will be blind to group for all analyses.

Outcomes: Please add an "Outcomes" section, which clearly sets out the primary and secondary feasibility/efficacy outcomes, which relate in turn to the primary and secondary objectives of the study.

We have added this in the suggested location.

Minor comments:

Use "AN" rather than full words ("anorexia nervosa") for all instances where it appears in the manuscript (eg p6 lines 15, 22; p12 line 60; p16 line 60; p17 line 11; p18 line 6)

We have replaced all instances of “anorexia nervosa” and “anorexia” with AN.
The following minor corrections were noted:

p8 line 36: replace semi-colon with comma; replace "are" with "will"

p10 line 34: replace "recruitment" with "being informed about the trial" (or something similar)

p10 line 53: add "of" to the statement "The outside the envelope"

p11 lines 20/22: remove hyphen from "in-hospital"

p13 line 51: remove semi-colon before 'discharge'

p15 line 7: add closed bracket after "hypothesis"

These have all been addressed.