

Cognitive Remediation Therapy (CRT) in a specialist inpatient eating disorder service for children and adolescents: CAN-CRT study protocol for a pilot randomised controlled trial

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Registration

Protocol full title: Pilot Randomized Controlled Trial of Cognitive Remediation Therapy in a specialist inpatient eating disorder services for children and adolescents.

Protocol Short Title/ Acronym: CAN-CRT (Children and Adolescent with Anorexia Nervosa Cognitive Remediation Therapy).

Trial registration: ISRCTN81736780

Ethics approval has been granted by London - Camberwell St Giles Research Ethics Committee, NHS England (17/LO/0876).

Abstract

Introduction: Research on treatments for young people (YP) with anorexia nervosa (AN) is scarce. Evidence supports the use of Cognitive Remediation Therapy (CRT) to improve central coherence and set-shifting; inefficiencies which can negatively impact on prognosis.

Objective: The study aims to evaluate the feasibility of individual CRT in an inpatient setting for YP aged 10-18 with AN, and to qualitatively examining YP's experiences and their parents' views.

Methods: In a single-centre, pilot, randomized controlled trial (RCT), 80 patients aged 10-18 with AN will be randomly allocated to the immediate CRT group or to the delayed CRT group, in addition to standard treatment. A repeated measures design will be conducted across three time-points.

Discussion: The data will provide evidence regarding the feasibility of individual CRT in YP with AN, and will inform directions of further development of the intervention. The study is in preparation for a future definitive RCT. The aim of this manuscript is to describe the study protocol.

Keywords: anorexia nervosa, cognitive remediation therapy, RCT, children and adolescents, treatment

Introduction

Anorexia nervosa (AN) is a life-threatening eating disorder (ED) with a lifetime prevalence of up to 3.6 to 4 %, according to DSM-5 criteria (APA, 2013; Mustelin, Silén, Raevuori, Hoek, Kaprio, & Keski-Rahkonen, 2016; Smink, Van Hoeken, & Hoek, 2013). Incidence is highest for female adolescents and it is the third most common chronic disorder affecting adolescent girls (Steinhausen, 2002). There is still an insufficient evidence base for treatment efficacy in young people (YP) suffering from AN. Best available evidence recommends family therapy and initial outpatient management for YP with AN (NICE, 2017).

The cognitive-interpersonal maintenance model (Treasure & Schmidt, 2013) outlines four components contributing to the development and maintenance of AN. In addition to perfectionist and obsessive-compulsive personality traits (Lloyd, Yiend, Schmidt, & Tchanturia, 2014), the thinking styles component of the model outlines a neuropsychological profile in AN that is characterised by inefficiencies in set-shifting (Westwood, Stahl, Mandy, & Tchanturia, 2016; Lang, Stahl, Espie, Treasure, & Tchanturia, 2014) and central coherence (Lang, Lopez, Stahl, Tchanturia, & Treasure, 2014; Lang et al., 2015; Lang et al., 2016), which manifests as rigid thinking and difficulty seeing the ‘bigger picture’. This is supported by empirical evidence in adults and YP diagnosed with AN, although only a limited number of studies have focused on exploring cognitive performance in YP (for reviews Lang & Tchanturia, 2014; Lang et al., 2015).

Cognitive Remediation Therapy (CRT) is an intervention that targets cognitive training of inefficiencies identified in eating disorder populations. It has been an intervention of choice in the treatment of several mental health conditions, such as schizophrenia (Thorsen, Johansson, & Løberg, 2012), bipolar disorder (Strawbridge et al., 2016) and autism (Okuda et al., 2017). It has also been adapted for the use, as an adjunct intervention, in the treatment of AN, specifically focusing on flexibility and bigger picture thinking (Tchanturia, 2015; Tchanturia, Giombini, Leppanen & Kinnaird, 2017).

Overall, quantitative and qualitative research indicates that CRT is an effective, feasible and acceptable intervention for AN in individual and group formats, and positive evaluations have been gathered from service users and clinicians in adult and child populations (Tchanturia, Lounes, & Holttum, 2014). In addition, recent randomised treatment studies in adult AN populations have shown that CRT enhances cognitive flexibility (Tchanturia, 2015), abstract thinking and is associated with an improvement in quality of life.

More recently, preliminary data has emerged supporting the use of CRT for YP with AN (Lang, Stahl et al., 2014, Westwood, et al., 2016; Brockmeyer, Friederich, & Schmidt, 2017; Giombini, Moynihan, Turco, & Nesbitt, 2016; Giombini et al., 2017; Tchanturia et al., 2017), although more robust efficacy studies are needed. This is an important population to consider, as the peak age of AN onset during adolescence is between 15 and 19 years old (Smink et al., 2013), which overlaps with critical periods of brain maturation and associated plasticity (Telman, Holmes, & Lau., 2013). Early and effective interventions are therefore fundamental to improve the prognosis for YP with AN (Stice, Becker, & Yokum, 2013).

Objectives

The aim of this paper is to describe the study protocol.

The present study is a pilot randomized control trial (RCT) aimed at evaluating the feasibility of individual CRT delivered in an inpatient setting to YP aged 10 to 18 years with AN, and to assess the methodology of the study (i.e. recruitment and study retention, integrity of study protocol and selection of outcome measures).

A second aim of the study is to explore at what stage of the treatment programme it is most feasible to deliver CRT and whether CRT has a positive impact on the management of eating disorder symptomatology. Additionally the study will consider the effect of CRT in participants who report the presence of autistic symptoms. This will be identified by administering self-report questionnaires on social communication and responsiveness skills to parents. Furthermore, the study will qualitatively examine YP's experiences of participating in CRT and their parents' views and attitudes towards the intervention using a systematic and

thorough approach. Qualitative data, gathered through participant satisfaction questionnaires completed at the end of CRT and parent focus groups, will inform directions of further development of the intervention. The data will lead to a future definitive RCT to investigate the effectiveness of CRT for YP with AN.

Research questions

The research questions being tested in this pilot RCT trial are:

- 1) Will it be feasible to recruit 80 participants over the planned 36-month recruitment phase;
- 2) Will the neuropsychological measures employed in the current study be suitable for use in evaluating individual CRT in a child and adolescent sample (i.e. sensitive to change pre-/post intervention and produce similar variability as found in previous research);
- 3) Will the Treatment as usual (TAU) with the addition of CRT be potentially superior to TAU alone for the improvement of set-shifting and central coherence. Will significant differences, reflecting positive change, be demonstrated between pre/post measures at Time 0 and Time 1 for participants receiving individual CRT in addition to TAU at the start of the treatment programme, relative to those receiving delayed individual CRT in addition to TAU;
- 4) Will potential longer-term effects of CRT be found when assessing those who received individual CRT at the start of the treatment programme at Time 2.

Methods

The protocol of this trial and CONSORT checklist are available as supporting information (see Checklist S1 and Protocol S1). Extension of CONSORT 2010 to pilot trials (Eldridge et al., 2016) is specifically observed in reporting this study.

RCT design

This is a single-centre, pilot, randomised, controlled, blind, superiority study with two crossover groups with a 1:1 allocation. Stratified randomization will be implemented. The study design is shown in Figure 1. Consenting patients who meet the eligibility criteria will be randomly allocated to the immediate CRT group receiving TAU with the addition of eight, twice weekly individual CRT sessions at the start of the treatment programme (Week 2 to Week 5) and TAU only for rest of the duration of the programme; or to the delayed CRT group receiving TAU only at the start of the programme and TAU with the addition of eight, twice-weekly individual CRT in the second part of the programme (Week 7 to Week 10). A repeated measures design will be conducted at three time-points: Time 0: Week 1; Time 1: Week 6; Time 2: Week 11.

INSERT FIGURE 1

Participants

The study will be conducted at Rhodes Wood Hospital (RWH) (Elysium Healthcare), a specialist non- National Health Service (NHS) inpatient eating disorder private service commissioned by NHS England, sited in London (UK). The service treats children and adolescents aged between 10 and 18 years who require hospital treatment for an eating disorder, independently from Weight for Height percentage (WfH %), as a specialist

community-based treatment was not available or was not effective and they can no longer safely remain in the community due to compromised physical health. Patients are referred by child and adolescent mental health services, general practitioners or privately.

Patients eligible for the trial must comply with all of the following at randomisation: 1) Participants' parents written informed consent and participants' informed assent (if below 16 years of age) or informed consent (if above 16 years of age); 2) Males or females; 3) Aged 10 to 18 years; 4) Diagnosis of AN or atypical AN (according to DSM-5 criteria; APA, 2013); 5) Newly referred to RWH; 6) Fluency in English; 7) No visual impairment; 8) No cognitive impairment; 9) No drug or alcohol abuse; 10) Absence of severe comorbidity at the time of intake (e.g. psychosis, severe learning disability, brain injury). Consultant psychiatrists and senior clinical psychologists will assess eligibility criteria at the RWH admission visit through a medical assessment and clinical interview.

The principles of informed consent and participants' right to withdraw from the study at any time will be reiterated throughout the study.

Interventions

Treatment as usual (TAU)

TAU consists of a 12-week stepped programme. All patients receive adequate nutrition to meet their needs (either a weight gaining or maintenance prescription according to Weight for Height percentage), and are expected to gain weight via eating or nasogastric feeding conducted under the Mental Health Act (2007).

A multi-disciplinary treatment is offered, by including a combination of medical risk management, nursing input, dietetic support, psychological interventions, and provision of school education. Patients receive the following psychological interventions: weekly individual Cognitive Behavioural Therapy for Eating Disorders (CBT-ED)-ED, fortnightly family therapy and psycho-educational group therapy on nutrition, eating disorders, anxiety, and relapse prevention strategies. As well as attending family therapy, parents/carers can access a monthly parent's support group.

Cognitive Remediation Therapy

In this trial, CRT will adhere to the CRT Manual developed by Tchanturia, Davies, Reeder, & Wykes, (2010) and manualised group programme (Maiden, Baker, Espie, Simic, & Tchanturia, 2014). Adherence to the Manual will be assessed through a thorough supervision conducted by KT. CRT involves 8, twice weekly, 45 minute sessions which are delivered by assistant psychologists trained by first and principal authors of the study (KT, LG). During the sessions, facilitators will encourage patients to complete board games, pen and paper activities and computerized activities with the aim of exploring and eliciting cognitive domains such as central coherence and set-shifting. The games are developmentally appropriate and suitably challenging for the age group (Tchanturia et al., 2017; Giombini et al., 2017). Specifically, the first and fifth sessions will focus on central coherence, the second and sixth sessions on switching, the third and seventh sessions on multitasking, and the fourth and eighth sessions on summarising previous content. For a more detailed description of the exercises, see Tchanturia et al., (2010) and Maiden et al., (2014).

Outcomes

The primary outcome is to determine if it will be feasible to recruit 80 participants over the planned 36 month recruitment phase and if the neuropsychological measures employed in the current study will be feasible for use in evaluating individual CRT in a child and adolescent sample (i.e. sensitive to change pre-/post intervention and produce similar variability as found in previous research).

The secondary outcomes are: to examine if TAU, with the addition of CRT, is superior to TAU alone for the improvement of set-shifting and central coherence; to determine if CRT contributes to a decrease in eating disorder symptomatology, anxiety and depression, and to

an increase in motivation to change; and to explore the social skills of the population investigated by considering parents' response to specific questionnaires.

The process outcome is to explore service user satisfaction of the intervention and parents' views towards the intervention in order to inform further development and implementation of CRT for children and adolescents.

Outcome measures

The assessment will be conducted at three different time-points: Time 0: Week 1, Time 1: Week 6 and Time 2: Week 11. The assessment battery consists of self-report questionnaires and neuropsychological measures suitable for children and adolescents and already used in previous studies (Lang et al., 2015). Onsite assistant psychologists will administer the assessment battery under the supervision of LG.

Primary outcome measures

The Wisconsin Card Sorting Test, Computer version 4 [(WCST) Heaton, 1993): participants must match a number of stimulus cards to one of four category cards. Cards can be matched by colour, number or shape, and the rule must be worked out by trial and error based upon the feedback received. Once the participant has correctly matched the card for 10 consecutive sorts, the sorting rule changes and the participant must shift their response to work out the new sorting rule. The rule changes up to five times throughout the task, and every time a participant correctly completes a sort, it is termed 'completing a set'. Detailed description of this measure and large dataset comparing HC and ED groups can be found in Tchanturia et al., 2012.

The most commonly reported outcome from the WCST is the number of perseverative errors made by the participant. However, in line with previous CRT research (Tchanturia et al., 2012) the current study will also report measures of general performance, perseveration, conceptual ability and response consistency.

The Brixton test (Burgess & Shallice, 1997): the participant is asked to predict the movements of a blue circle, which changes location after each response. A concept (rule) has to be inferred from its movements to make correct predictions. Occasionally, the pattern of movement changes and the participant has to abandon their old inferences. Parallel version of the Brixton test will be used to avoid learning effect (Tchanturia et al., 2012).

The Rey-Osterrieth Complex Figure test [(ROCFT) Osterrieth, 1944] is a pen and paper task measuring global processing ability. Participants are required to accurately copy a complex figure and the drawing strategy adopted by the participant is used as a measure of central coherence. The ROCFT is scored according to Booth's 2006 scoring method, which incorporates both the order in which the participant chooses to draw the elements (whether preference is shown to global or detailed elements) and the style in which they are drawn in (fragmented or coherently). Order index (OI) and style index (SI) are computed and combined to give the Central Coherence Index (CCI). For more details, see Lang, Lopez, et al., 2014 and Lang et al, 2016.

The Detail and Flexibility questionnaire [(DFLEX) Roberts, Barthel, Lopez, Tchanturia, & Treasure 2011] is a self-rated 24-item scale assessing cognitive rigidity/detail focused processing.

Secondary outcome measures

Eating Disorder Examination Questionnaire [(EDEQ) Fairburn & Beglin, 1994] is a self-rated 36-item scale assessing attitudinal and behavioural aspects of EDs over a 28-day period. It has four subscales assessing concerns about shape, weight, eating, and restraint. It consists of subscale scores and a total score. It has excellent internal consistency (Cronbach α 0.78-0.93). The subscales also have excellent test-retest reliability over a two week period (Pearson r ranging from 0.81 to 0.94) (Luce & Crowther, 1999). Global scores higher than 2.7 are considered clinically significant (Mond, Hay, Rodgers, & Owen, 2006).

The Revised Child Anxiety and Depression Scale [(RCADS), Chorpita, Morfitt, & Gray, 2005] is a 47-item, self-report questionnaire, with subscales including: separation anxiety

disorder (SAD), social phobia (SP), generalized anxiety disorder (GAD), panic disorder (PD), obsessive compulsive disorder (OCD), and major depressive disorder (MDD). It also yields a Total Anxiety Scale (sum of the 5 anxiety subscales) and a Total Internalizing Scale (sum of all 6 subscales). Items are rated on a 4-point Likert-scale from 0 (“never”) to 3 (“always”).

The Motivational Ruler uses visual analogue scales (0-10) to assess the importance of and confidence to change.

The Social Communication Questionnaire [(SCQ) Rutter, Bailey, & Lord, 2003] is an instrument used to screen for autism in individuals over the age of 4, with a mental age over 2 years. The SCQ contains 40 yes/no items, which can be completed in less than 10 minutes by a parent or other caregiver. The SCQ has two forms: the Lifetime Form, which focuses on behaviour throughout development, and the Current Form, which focuses on behaviour during the most recent three months. In the present study, parents are asked to complete the Current Form. The instrument yields a Total Score that can be compared with defined cut-off points.

The Social Responsiveness Scale [(SRS); Constantino & Gruber, 2005] is a 65-item rating scale asking about characteristic autistic behaviour. Each item is scored from 0 (‘never true’) to 3 (‘almost always true’) as best describes the child’s behaviour in the past 6 months. Total scores can range from 0 to 195. It will be completed by parents.

Intelligence Quotient (IQ): Wechsler Abbreviated Scale of Intelligence [(WASI) Wechsler & Hsiao-pin, 2011]: The WASI produces an estimate of general intellectual ability based on two subtests, Vocabulary and Matrix reasoning. Administered in approximately 15 minutes, the WASI is a quick estimate of an individual level of intellectual functioning with higher scores indicating greater intellectual ability. The WASI is linked to both the Wechsler Intelligence Scale for Children and Wechsler Adult Intelligent Scale and it has been normed for individual’s ages 6 to 89 years. Raw scores are calculated for each subscale and then scaled, correcting for age.

Demographic (age, sex, ethnicity, family structure) and clinical (height, weight, duration of illness, lowest weight, medications, number of previous hospital admissions) will be collected through a structured interview.

Process outcome measures

The Individual Satisfaction Questionnaire is a self-report measure created *ad hoc* for completion at the end of the intervention. This measure will be adapted to include an 'open feedback' section in order to enable participants to expand on their thoughts and feedback about the CRT intervention. Participants are asked to provide their views regarding: what they found beneficial and/or challenging, what they enjoyed and/or did not like, the transferability of CRT skills into their routine, and suggestions for further improvements of the intervention.

Focus groups: A group of eight parents of YP within the immediate CRT group and the delayed CRT group will be invited to attend a focus group with the aim of exploring their views and perceptions of intervention outcomes, barriers to change and suggestions for improvement.

Sample size

No formal size calculation was completed because this is a pilot RCT and will be used to obtain information on the likely effect size, variability and other aspects of outcome data for a future definitive trial sample size calculation. However, the sample size was defined on the basis of two previous studies that investigated the effectiveness of CRT in improving central coherence in YP with AN (Giombini et al., 2016; Van Noort et al., 2016). In Van Noort et al., (2016) twenty inpatients and outpatients with AN aged 12 to 18 years received individual CRT, matched with healthy controls who did not receive CRT. In Giombini et al., (2016) a within-subjects design was used to compare the performance of 92 female participants

diagnosed with AN aged between 11 and 17 on several neuropsychological measures administered before and after a course of CRT, in a specialist inpatient unit.

Given due consideration to previous studies, the researchers aim to recruit a total of 80 male and female patients who meet the eligibility criteria.

Over the course of the study, all the participants' parents will be invited to attend a focus group. Based on the rate of their participation the methodological appropriateness of conducting a qualitative analysis will be decided.

Inductive Thematic Analysis (Braun & Clarke, 2006) will be used to identify key themes relating to patients and parents experiences of the intervention and help guide future development.

Randomisation

Trial participants will be randomised between the two groups at a 1:1 ratio within 24 hours of collection of informed consent. After receiving coded and anonymised data, stratified randomisation using date of birth and severity of the illness (Weight for Height, WfH %), and minimisation with a random component will be performed. For the first n cases (n is not disclosed), the randomisation will be performed within each stratum using random permuted blocks with varying block sizes. A database will hold the basic details required for randomisation [i.e. date of birth, severity of illness (WfH %), initials, and unique patient number]. Randomisation will be facilitated by the Department of Mathematics, Royal Holloway University of London, by TS, who is not involved in delivering the assessments or interventions, and who will hold the details needed for randomisation.

Blinding

TS is individually responsible for managing the randomization of the selection of participants, and will not disclose group allocation to participants and assessors at Time 0 Assessment.

Blind analysis will be conducted by removing data labels and group indication so as to reduce confirmation bias. Opaque and sealed envelopes will be used for allocation concealment. Research assistants conducting the assessment will be unaware of the treatment conditions at Time 0 assessment. The research assistant who administers the assessment at each time period will not deliver the intervention. This is order to decrease bias.

Given the nature of the study design, all patients and therapists are aware of the treatment condition. Patients are informed that both treatment arms are being investigated as to their potential to enhance TAU.

Statistical methods

All main analysis will follow the 'intention to treat' principle; that is, patients will be analysed in the groups to which they were randomised irrespective of treatment received.

The first part of analysis will include an assessment of methodology, including calculation of the recruitment rate, study retention, and assessment of the logistics of running the study. The latter includes the evaluation of study protocol integrity, data collection forms and selection of appropriate outcome measures.

Appropriate tools of general linear modelling will be used to evaluate the differences in performance on the neuropsychological measures for Time 0 (Week 1), Time 1 (Week 6), and Time 2 (Week 11). Each group will be compared to investigate if there is an effect of CRT on performance.

Additionally, Time 0 (Week 1) and Time 2 (Week 11) assessments will be compared to investigate the longer-term effects of CRT.

Furthermore, qualitative data collected through participant satisfaction questionnaires and parent focus groups will be analysed adopting The Framework Method (Braun & Clarke, 2006; Gale, Heath, Cameron, Rashid, & Redwood, 2013). This is appropriate for thematic analysis of textual data, such as written feedback reports and interview transcripts. It facilitates thematic comparisons across data cases, whilst also contextualising individual perspectives by taking into account other aspects of each individual's view.

Discussion

Inefficiencies in cognitive flexibility and central coherence are problematic in psychiatric disorders. CRT aims at addressing these inefficiencies, aiming to enhance treatment outcome. To our knowledge, this is the first pilot RCT investigating the feasibility of CRT in a specialist inpatient setting for children and adolescents with AN. The study aims to investigate CRT's potential to enhance TAU, alongside exploring qualitatively the experience of CRT in both patients and their parents.

This study will also enable us to explore at what stage of the treatment programme it is most feasible to deliver CRT and whether CRT has a positive impact on the management of eating disorder symptomatology.

A limitation of this trial is that it is conducted in a single centre, impacting on the generalisability of the data. However, the findings from this study could determine the parameters required to execute a definitive trial.

Conclusion

This paper outlines the protocol for a study that will add to the limited literature base on interventions for children and adolescents with AN.

We have outlined the components of the CAN-CRT intervention and clearly stated the research methodology in accordance with recommendations that aim to improve reporting and replication of treatment evaluations (Schulz, Altman, & Moher, 2010).

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