BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-036093
Article Type:	Protocol
Date Submitted by the Author:	29-Nov-2019
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Keywords:	Child & adolescent psychiatry < PSYCHIATRY, Depression & mood disorders < PSYCHIATRY, Clinical trials < THERAPEUTICS, NEUROPHYSIOLOGY

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Study protocol for a randomized-controlled study on emotion regulation training for adolescents with major depression: the KONNI study

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Word count: 4.221 (3.927 excluding the Discussion)

Abstract

Introduction: Major depression (MD) often has its onset during adolescence and is associated with significant morbidity and mortality. One important factor for the development and maintenance of adolescent MD are disturbances in emotion regulation and the underlying neural processes. Cognitive reappraisal (CR) is a particular adaptive emotion regulation strategy. Previously, it has been shown in healthy adults that a task-based training in CR is efficient to reduce negative affect, and that these effects translate into everyday life.

The present randomized-controlled trial examines for the first time whether a task-based training in CR proves effective in MD adolescents. Specifically, we will investigate whether the CR training improves the ability to down-regulate negative affect in MD individuals as assessed by behavioral and neurobiological indices, and whether training effects generalize outside the laboratory.

Methods and analysis: Adolescents with MD will be randomly allocated to a group that either receives a task-based training in CR or control training. Both involve four training sessions over a time period of two weeks. In the CR training, participants will be instructed to down-regulate negative affective responses to negative pictures by means of CR, while the control training involves picture viewing. During the training sessions, the Late Positive Potential, gaze fixations on negative picture aspects and affective responses to pictures will be collected. Before and after the training programs, and at a two-week follow-up, overall negative and positive affect, rumination and perceived stress will be assessed as primary outcomes. ANOVAs will be conducted to test the effectiveness of the CR training with regard to both primary outcomes and task-based behavioral and neurobiological parameters.

Ethics and dissemination: The study was approved by the institutional review board of the local ethics committee. The results will be published in peer-reviewed journals and disseminated through conferences, social media and public events.

Trial Registration: Clinical Trials NCT03957850, registered Mai 21st 2019; URL: https://clinicaltrials.gov/ct2/show/NCT03957850.

Strengths and limitations of the study:

- This study is the first to examine the effectiveness of a targeted CR training in youths with major depression.
- A randomized-controlled design is employed including an active control group.
- In addition to behavioral and questionnaire data, objective neurobiological indices will be collected to assess the effectiveness of the CR training.
- If proven effective, the CR training can be a promising and cost-effective approach to complement and enhance the efficacy of established treatments for adolescent MD.
- As the follow-up is limited to two weeks, the long-term effectiveness needs to be explored in future studies.

Introduction

Major depression (MD) is among the most debilitating, costly and common psychiatric disorders worldwide.[1] The risk of suffering from a depressive episode sharply rises during adolescence, with point prevalence rates of up to 7%.[2] Adolescents with MD show deficient emotion regulation (ER),[3] i.e., they have difficulties to modulate emotional responses by initiating appropriate regulatory processes.[4] Disturbances in ER and the underlying neural processes have been suggested to be an important risk factor for the development and maintenance of MD.[3, 5] Thus, the development of training regimens that target deficient ER in MD is an important research avenue.

Cognitive-behavioral therapy (CBT) belongs to the gold standard treatments in juvenile MD. However, less than 50% of MD adolescents respond to CBT and only about one third enter remission after treatment.[6, 7] Given the debilitating consequences of adolescent MD,[8] there is an urgent need to enhance the efficacy of established intervention. Recent findings in adults with MD suggest that an additional training of ER might be a promising approach to improve treatment effects.[9, 10] To date, it remains unclear whether these findings can be transferred to juvenile MD. In this regard, the present study takes a first step and systematically investigates the effects of a focused ER training in adolescent MD.

Cognitive reappraisal in depressed individuals

Cognitive reappraisal (CR) is a frequently studied ER strategy and involves the reinterpretation of a situation such that the emotional response is changed. The habitual use of CR has been shown to relate to good interpersonal functioning and well-being.[11] Questionnaire studies have found that depressive symptoms are associated with less habitual use of CR.[12-14] To experimentally investigate CR in MD, studies applied a well-established CR paradigm during which participants are instructed to reappraise negative pictures. This regulation condition is compared to an unregulated condition, during which participants are asked to simply attend to negative stimuli. Within the framework of this paradigm, a number of studies in MD collected behavioral measures of self-reported affect to assess regulation success. Contrary to expectation, some studies found no group differences between depressive and healthy participants in this index of CR.[15, 16, but see 17] However, these results might be biased due

to social desirability which probably obscures group differences. Moreover, complex ER disturbances are unlikely to be captured using simple affect ratings,[18, see also 19] highlighting the importance of additionally assessing objective and more sensitive parameters when studying CR, including neurobiological indices.

A commonly studied neurobiological index of CR is the Late Positive Potential (LPP). Studies in healthy samples show that the LPP is reduced when individuals are instructed to reappraise unpleasant stimuli compared to attending to unpleasant pictures.[e.g. 20, 21, 22] This decrease is thought to reflect a reduction of the emotional response following CR, which may result from a shift in stimulus meaning.[23, 24] Depressive psychopathology has been shown to be associated with a smaller reduction of the LPP during CR.[23, 25, 26] However, to date, no study has investigated whether this neurobiological disturbance can be normalized by a repeated training of CR.

Besides the LPP, a number of studies in healthy individuals have investigated gaze fixation patterns to gain insight into the mechanisms underlying CR.[e.g. 27, 28, 29] They found that a greater regulation success is paralleled by less gaze fixations directed towards negative picture cues. This suggests that the regulatory effects of CR may partly be attributed to gaze deployment, highlighting the importance of also assessing gaze fixation when examining CR.

Trainability of cognitive reappraisal

Evidence from a randomized controlled trial (RCT) in adult MD suggests that systematically training ER skills in addition to standard CBT improves treatment efficacy.[9, see also 10] As the ER training of this RCT aimed at enhancing general ER skills and included CR among other ER strategies, the unique contribution of CR remains to be investigated. A recent investigation addressed this issue experimentally in healthy adults,[30] demonstrating that a task-based CR training resulted in less perceived stress in daily life. Beneficial effects of a task-based CR training have recently also been shown in healthy and anxious adolescents.[31] While these results are encouraging, it needs to be examined whether the findings can be extended to MD samples.

Aim of the study

The aim of the study is to assess whether in MD adolescents, a task-based CR training results in an improved downregulation of negative affective responses as assessed by behavioral and neurobiological indices. Moreover, the study aims to investigate whether the training effects generalize outside the laboratory, i.e., lead to affect-related changes and a reduction in perceived stress.

It is hypothesized that over the course of the CR training, MD adolescents show improvements in the downregulation of negative affective responses as assessed by task-based behavioral[30] and neurobiological indices. Based on prior research,[30, 31] it is further hypothesized that the CR training results in improvements in affect- and stress-related symptoms in daily life.

Methods and analysis

The study (Public and scientific Title: Cognitive Reappraisal in Adolescents with Major Depression: From Neurobiological Mechanisms to Intervention; German acronym: KONNI) was prospectively registered on ClinicalTrails.gov (NCT03957850) before recruitment start. The study protocol and the template informed consent/assent forms (including two amendments) were approved by the institutional review board of the local ethics committee (Ludwig-Maximilians-University Medical Division Ethics Committee, Munich, Germany; study ID: 63-16) on 30th January 2019 and are reported in line with the Standard Protocol Items: Recommendations for Interventional Trials Statement (SPIRIT 2013). Important modifications to the study protocol would require an additional amendment, which would have to be approved by the Ethics Committee before implementation. The trial registry (ClinicalTrials.gov) would then be updated.

Design

This interventional study is designed as a short-term randomized controlled, participant-blind clinical superiority trial including two parallel groups of MD adolescents. Participants will be randomly assigned to a group that receives task-based training in CR or to a control training. All participants will take part in one diagnostic assessment (T0), four training sessions (T1-4) over the course of two weeks, and a follow-up two weeks after T4. All questionnaires and test procedures are summarized in Table 1. During

the training sessions, task-based indices of CR will be continuously assessed based on behavioral affect ratings and the LPP. Moreover, eye gaze will be recorded during the task-based training. The KONNI study design is depicted in Figure 1.

Participants

Participants aged 12-18 years with a current ICD-10 diagnosis of MD,[32] an IQ of ≥80 and sufficient German language skills will be included. The following exclusion criteria will be applied: acute suicidality, neurological disorders, schizophrenic disorder, pervasive developmental disorder, bipolar disorder, borderline personality disorder, substance dependence disorder and gender dysphoria. Participants with other psychiatric comorbidities are included if MD is the primary diagnosis.

Recruitment

MD adolescents will be primarily recruited from the Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital of the LMU Munich, Germany. Currently untreated MD patients from the waiting list, and in-and outpatients are enrolled in the study. The first participant was enrolled in May 27th, 2019. The planned completion of participant enrollment is in April 2021. Since the start of the study n=15 subjects were enrolled.

Procedure

Adolescents and one parent/legal custodian (for participants <18 years) will be contacted by a study nurse and will be informed about the study details, including the fact that the allocation to the training groups will be made based on a predefined randomization list. In case of interest in participation, their written informed consent/assent will be collected. In the written informed consent/assent, participants and their parent/legal custodian are asked for their permission that the data can also be used for an ancillary case-control study on neurobiological underpinnings of ER in MD. The participants and the parent/legal custodian will be blinded regarding allocation to the CR/control training group until study completion and only unblinded prior to study completion if they terminate participation prematurely. At the first session (T0), a diagnostic interview and other baseline measures (see below) will be applied to

the adolescent and will last ~2,5 hours. The diagnostic session will be conducted by psychologically trained staff.

If the participant is eligible for the study, the following session appointments will be scheduled and the participant will be randomly allocated to the CR or the control training group. To ensure allocation concealment, the random allocation to one of the groups is implemented after completion of baseline measurements; i.e., neither the recruiter nor the person conducting the baseline session know to which group the participant will be assigned after T0. Randomization stratifying for age (<15 years vs. ≥15 years of age)[1] and sex will be performed by a statistician, who is neither involved in recruitment nor in testing of participants. The randomization will be performed with a 1:1 allocation. A follow-up session will take place two weeks after completion of the forth training session. After the follow-up, participants are unblinded regarding group allocation. As expense allowance for study participation (~10 hours including follow-up), the participants will receive 100€. Participation is voluntary and can be discontinued at any time for any reason. Participation is discontinued in case of acute suicidality during the study. No other criteria for discontinuation are defined. Treatment fidelity concerning the training is assured by standardized oral and written instructions and by comprehensive training of the experimenters. The concomitant treatment as usual is permitted during the ongoing study and information on the type of treatment during the study will be assessed along with any spontaneously reported adverse effects.

Cognitive Reappraisal Training

The CR training task is well-established and is adapted from previous studies.[e.g. 22, 33-35] An exemplary illustration of an experimental trial is depicted in Figure 2. Participants will be presented emotional pictures which are preceded by a condition specific cue signaling the appropriate strategy (attend vs. reappraise) during picture presentation. Following each picture, participants are instructed to indicate their affective response to the image on the portrait version of the nine-point self-assessment manikin scale for valance.[SAM; 36, for the portrait version see 37, 38] A higher score on this scale

[1] Based on prior studies in MD adolescents conducted in our department, 15 is the expected approximate median age of MD participants.

indicates a more positive valence rating. The task involves four conditions: 1) **Negative-reappraise:** participants are asked to view negative pictures and to decrease their affective response by reappraising the negative event. Participants are explicitly instructed to use the reinterpretation tactic during CR, which involves "mentally changing the meaning of the actions, context and/or outcome depicted in a stimulus".[30] 2) **Negative-attend,** 3) **Neutral-attend and** 4) **Positive-attend:** participants are asked to view the pictures and to respond naturally to them without trying to alter their affective response. Comparison of the negative-reappraise and the negative-attend conditions allows assessing behavioral and neural indices of reappraisal success. The neutral-attend and the positive-attend conditions are included to avoid slight changes in negative affect due to the exclusive presentation of unpleasant pictures.[39]

The training task will be repeated over four training sessions. Before the first session, participants will complete a comprehensive practice training, during which a trained experimenter will provide standardized oral instructions regarding the task and the two strategies (attend, reappraise).[30] Thereafter, walk-through images are presented to confirm the appropriate use of the strategies. Task instructions will be briefly summarized before each training session.

In each training session, 144 pictures will be presented in 3 blocks, each containing 12 positive-attend, 12 neutral-attend, 12 negative-attend, and 12 negative-reappraise trials. Pictures are taken from the International Affective Picture System (IAPS),[40] Besançon Affective Picture Set-Adolescents,[BAPS-Ado; 41] and Besançon Affective Picture Set-Adults,[BAPS-Adult; 42] with the latter two sets being derived from the Besançon Attachment Pictures Set. Each picture will be presented twice over the course of the training.[30] To ensure adherence to task instructions, participants will fill in a questionnaire after each training session to indicate which strategies they used during the task.

Control training

The control training is implemented to account for unspecific effects and the task employed is similar to the CR task except that it involves no "negative-reappraise" condition. Instead, the control task only involves attend conditions (negative-attend, neutral-attend, positive-attend). To keep the total number of trials involving negative pictures constant across the two groups, the control task involves twice as

many negative-attend trials as the CR training group. Mirroring the CR training procedure, the control training is repeated over four sessions and preceded by standardized oral instructions and a practice session. Participants of the control training group will also fill in a questionnaire on how they resolved the task after each training session.

Measures

Information about psychometric properties of all measures described in the following paragraph are summarized in Table 1 along with the respective assessments points.

Diagnostic measures

A diagnosis of MD and potential comorbidities will be assessed using a well-established German standardized semi-structured diagnostic interview (Kinder-DIPS).[43, 44] The interview will be administered by experienced, psychologically trained staff. IQ will be estimated based on the first part of the CFT-20-R.[45] For some patients, results from other established IQ tests [e.g. WISC-V; 46] will be available from routine care, which will be used instead.

Outcome measures

Primary outcomes

The primary outcomes of the study are (1) change in rumination from baseline (T0) to post-training (directly after T4) and follow-up [assessed by the scales "self-focused rumination" and "symptom-focused rumination" of the German short version of the Response Styles Questionnaire; RSQ-D; 47]; (2) change in depressive symptoms [assessed by the German version of the Beck Depression Inventory – Second Edition; BDI-II; 48] from baseline (T0) to post-training (directly after T4); (3) change in perceived stress over the course of the four training sessions and at follow-up [assessed by the German translation of the Perceived Stress Scale 10; PSS-10; by Prof. Dr. Arndt Büssing; 49][2]; (4) changes in negative and positive affect [assessed by the Negative Affect Scale and Positive Affect Scale for

[2]In the PSS-10, items were reworded to “in the past few days” instead of “in general” to better allow assessing changes of the course of the training.

Children Shortened Version; PANAS-C-SF; 50] over the course of the four training sessions and at follow-up.

Secondary outcomes

One secondary outcome is the change in the downregulation of affective behavioral responses to negative pictures by means of CR. Affective behavioral responses to negative pictures will be continuously assessed during each of the four training sessions using the SAM rating scale.[36, with the portrait version from 37, 38]

Another secondary outcome is the change in the downregulation of the early and late LPP amplitude to negative pictures by means of CR. The LPP elicited to pictures in the negative-attend and the negative-reappraise condition will be continuously assessed during each of the four training sessions. Additionally, changes in the percent duration of gaze fixations within a-priori defined emotional interest areas of negative pictures[3] will be assessed during both the negative-attend and negative-reappraise condition over the course of the four training sessions.

All secondary outcome measures will only be assessed in the CR training group, as participants in the control training group are not instructed to apply CR. However, these measures will also be assessed in the control training group during the negative-attend condition to allow additional exploratory analyses.

Confounding variable

Participants will complete the Social Desirability Scale.[SES-17; 51] The rationale for assessing this confounding variable is that behavioral ratings of affective responses to pictures will be assessed, which are prone to response biases.[18]

Mediators

State rumination during the training will be treated as a potential mediator as ruminative thoughts might hamper beneficial training effects.[52] After completion of each training session, participants in the CR

[3]Emotional areas of interest of negative pictures will be defined based on a separate validation study.

and control training group rate state rumination during the task on a scale from 0 “not at all” to 10 “exactly” based on a 5-item questionnaire applied in a previous study.[53]

We will also assess a potential mediating role of executive function abilities, which are thought to be critically involved in ER.[54] Individual baseline differences in executive function abilities might thus prove important mediators of training outcome. Therefore, set-shifting, working memory and inhibition [55, 56] as the three core components of executive functions will be assessed based on the TAP 2.3.[Testbatterie zur Aufmerksamkeitspruefung; 57]

Moreover, we will treat habitual ER as a potential mediator, which will be assessed based on the FEEL-KJ [58]. The FEEL-KJ is a self-report questionnaire assessing habitual adaptive and maladaptive ER strategies.

Moderators

As anxiety disorders/symptoms frequently co-occur with MD,[59] state and trait anxiety will be assessed based on the State-Trait-Anxiety Inventory (STAI).[60] Moreover, symptoms of psychopathology will be screened using the Child Behavior Checklist (CBCL 6-18R).[61] Both variables will be treated as potential moderators.

Eye-tracking apparatus

During the four training sessions, eye-movements will be continuously recorded using the Eyelink 1000 Plus SR Research eye-tracker. At the beginning of the training, participants are seated at the viewing distance of approx. 55 cm from the monitor and a 9-point calibration is performed. Prior to each experimental trial, a drift correction is conducted.

Electroencephalogram recording and preprocessing

The electroencephalogram data is recorded using the Electrical Geodesic Inc. 128-channel system with 500 Hz sampling rate and Cz as reference electrode. Impedance is kept below 50 kΩ during recording. The further preprocessing and analyses steps will be performed with Brainvision Analyzer 2.1 (Brain Products GmbH, Germany). After filtering, removal of electro-oculographic artefacts based on

Independent Component Analysis and exclusion of other artefacts, the signal will be re-referenced. Data will be segmented into epochs, baseline-corrected and averaged separately for each participant and condition. The LPP will be measured as the mean amplitude at a centro-parietal region-of-interest within early (<300ms) and late time windows (≥300 ms) following picture onset.[33, 62]

Data management and confidentiality

All data will be entered electronically in IBM SPSS statistics by a scientific assistant. Plausibility and completeness checks will be regularly performed by E.G., L.F., C.P. to promote and monitor data quality. Original documents will be maintained for 15 years in the department. All original and electronic data is stored on the hospitals server under a pseudorandomized coded ID, which does not contain names or birth dates of the participants. Only the project leader and her deputies have access to the participants' names and the corresponding allocation to the encryption code and the original documents, which are kept in locked cabinets. The records containing names and other personal identifiers (e.g., informed consent/assent forms) will be stored in locked cabinets separately from the study records which are identified by the coded ID. The participants' study information will not be released outside the study, except in case of threat to self or threat to others. The final cleaned data sets will be provided to all investigators of the study. To adhere to principles of open science and to facilitate further use of aggregated data in meta-analytic approaches, we will consider making raw data available to other researchers if this can be achieved along with protecting sensitive patient information, such as sociodemographic information. Since patients could possibly be identified by making our raw data publicly available, ethical principles of protecting patient confidentiality would be breached. Aggregated group data can be made available upon request.

Calculation of sample size

A rough approximation of the requested sample size targeted at rumination as one of the primary outcomes can be achieved by referring to a previous study.[63] This study investigated the effects of a task-based cognitive control training compared to treatment as usual in adult MD. The training aimed at improving ER skills indirectly by targeting mechanisms thought to underlie ER. This study reported a

large effect size in the training group from pre to post (Cohen's d=1.42) on a measure related to negative affect (rumination). Based on a conservative assumption, a large effect size of d=0.85 is expected with regard to changes in rumination for the CR training from pre to post. For the control training, a small effect size (d=0.2) is expected from pre to post due to unspecific "positive" effects of the control intervention. This effect size is based on prior evidence[4] on the effects of a similar control training in young adults.[30]

Based on these assumptions, calculation of the required sample size to detect a significant 2(group) x 2(time: T0=pre, T4=post) interaction for rumination using a repeated measures ANOVA with a 5% level of significance (alpha=0.05) and 80% statistical power (1–beta=0.80) revealed an N=47 for the total group (assuming a 0.7 pre-post correlation). The drop-out rate for the study is estimated at approx. 33%. Thus, n=35 adolescents will be enrolled in each group. The necessary sample size was calculated with G*power 3.1. Statistical power of analyses that involve more measurements, such as the analysis of affect, will have more than 80% statistical power if effect sizes are similar.

Statistical analysis

To test the hypotheses that the CR training results in a stronger decrease in depressive symptoms/rumination from baseline to post-training assessment compared to a control training, a mixed-model ANOVA with the factors group (CR vs. control training) and time (T0, T4) will be conducted for the BDI-II and the two RSQ-D scales "self-focused rumination", "symptom-focused rumination". To account for the fact that the RSQ-D will be reassessed at follow-up, a mixed-model ANOVA with the factors group (CR vs. control training) and time (T0, T4, follow-up) will additionally be conducted for the two rumination scales. Mixed modeling has the advantage over regular repeated measures ANOVA that all available data can be used, including data from incomplete cases, without using imputation techniques for missing data. To test the hypotheses that the CR training results in a a) stronger decrease in negative and b) stronger increase in positive affect from pre- to post-training and follow-up assessment compared to the control training, mixed-model ANOVAs with the factors group (CR vs.

[4] Detailed statistical information was derived from personal communication with corresponding author of this study; B. Denny, April 26th, 2017.

control training) and time (T1, T2, T3, T4, follow-up) will be conducted for the Negative Affect/ Positive Affect scale of the PANAS-C-SF. The same statistical model procedure will be applied for perceived stress (PSS-10).

To test the hypothesis that over the course of the CR training, MD adolescents show an increased downregulation of the early and late LPP amplitude via CR, a mixed-model ANOVA with the factors 2(condition: negative-reappraise, negative-attend) x 4(training session: T1, T2, T3, T4) will be conducted separately for early and late LPP time windows. The same statistical procedure will be conducted for the affective ratings of negative pictures and the percent of gaze fixation duration in emotional areas of negative pictures. Correlation analyses will be performed between the percent of gaze fixation duration in emotional areas of negative pictures and ER success (downregulation of the LPP and affective ratings of negative pictures via CR).

To examine changes of the LPP, affective ratings of negative pictures and gaze fixations for the negative-attend condition in the control training group over the course of the training, additional exploratory ANOVAs will be conducted. Likewise, for the control training group, exploratory correlation analyses will be calculated to examine relationships between these measures and gaze fixation duration in emotional areas of negative pictures. Finally, moderation and mediation analyses will be applied to examine the role of mediating and moderating variables.

Patient and public involvement

Participants or their parents were not involved in designing the study. However, we will present the results of the study to parent and participant representatives to include their suggestions in the dissemination plan. Moreover, parallel to publication of the results, all participants and their families will receive a letter summarizing the main findings and conclusions in comprehensible language.

Discussion

This study will for the first time elucidate whether in adolescents with MD, a CR training shows beneficial effects both in and outside the laboratory. If the training proves effective, this approach might be a promising resource-effective intervention for adolescents with MD. Such an intervention could,

e.g., be applied to bridge the often long waiting times for treatment of MD or as an adjunction to a treatment as usual. Moreover, after psychoeducation on CR and guided practice of this strategy in psychotherapy, the training could also be (online) applied as an adjunct to treatment as usual. In such a context, the psychotherapist could monitor difficulties and progress in the use of CR, and promote the transfer of strategy into everyday life of the patient.

Building on the results from the present RCT, future investigations could additionally consider transfer effects to CR tasks other than the training tasks or to CR abilities in daily life e.g., based on ecological momentary assessment. Moreover, as a next step, it would be worthwhile to assess whether this training might prove effective in patients with other psychiatric disorders which are also characterized by deficient ER abilities, such as anxiety disorders and eating disorders.[64]

The results of our study will be an important step towards larger scale, multi-center RCTs in MD adolescents to investigate whether a CR training increases the efficacy of standard treatments. Furthermore, the study will elucidate neurobiological changes that occur during training and whether these are linked to changes in training outcome. To this end, our protocol may also aid to identify potential biomarkers for monitoring and predicting treatment success and thereby spark further research into the direction of individualized treatment adaptation based on neurobiological parameters.

Abbreviations

BAPS-Ado: Besançon Affective Picture Set-Adolescents; BAPS-Adult: Besançon Affective Picture Set-Adults; BDI-II: Beck depression inventory; CBCL 6-18R: Child Behavior Checklist for the ages 6-18; CFT-20-R (revidierte Grundintelligenztest Skala 2): Culture fair intelligence test; CBT: Cognitive-behavioral therapy; CR: Cognitive reappraisal; DFG (Deutsche Forschungsgemeinschaft): German Research Foundation; FEEL-KJ (Fragebogen zur Erhebung der Emotionsregulation bei Kindern und Jugendlichen): Questionnaire for the assessment of emotion regulation in children and adolescents; IAPS: International Affective Picture System; ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision; IQ: Intelligence Quotient; Kinder-DIPS (Diagnostisches Interview bei psychischen Störungen im Kindes- und Jugendalter): Diagnostic interview for psychiatric disorders for children and adolescents; LMU: Ludwig-Maximilians University; LPP: Late Positive Potential; MD: Major depression; PANAS-C-SF: Negative Affect Scale and Positive Affect Scale for Children Shortened Version for Children Shortened Version; PSS-10: Perceived Stress Scale 10; RSQ-D: German Version of the Response Styles Questionnaire; SAM: self-assessment manikin rating scale; SES-17: Social Desirability Scale; SPIRIT: Standard protocol items: recommendations for interventional trials; STAI: State-Trait-Anxiety Inventory; TAP (Testbatterie zur Aufmerksamkeitsprüfung): Test battery for executive functions; WISC-V: Wechsler Intelligence Scale for Children - Fifth Edition.

Declarations

Ethics approval

Written informed consent/assent will be taken by the participating adolescents and their parents/legal custodians. The study protocol and the template informed consent/assent forms were approved (including two amendments) by the institutional review board of the local ethics committee (Ludwig-Maximilians-University Medical Division Ethics Committee, Munich, Germany; study ID: 63-16) on 30th January 2019.

Consent for publication

This manuscript does not contain any form of individual person's data, all data will be reported based on aggregated group data.

Availability of data and material

The datasets generated and/or analyzed during the current study are not publicly available due to sensitive patient information, such as sociodemographic information, birth date and comorbidities, but aggregated group data can be made available upon request.

Competing interests statement

The authors declare that they have no competing financial or non-financial interests.

Funding

This work was supported by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Grant GR4753/2-1 to E.G. The funding body played no role in the design of the study or writing of the manuscript or the decision to submit the report for publication.

Authors' contributions

EG, LF, GSK and CP contributed to the study design. Data management will be conducted by LF and EG and data analysis and interpretation will be performed by LF, EG, FO, GSK, JB, MSR and CP. EG

and LF wrote the study protocol. All authors read and critically revised the draft of the paper and approved the final version of this manuscript.

Acknowledgements

We are grateful to Carolin Zsigo for the assistance during the implementation of the experiment. We wish to thank Petra Wagenbüchler for her assistance in data collection. We further would like to thank Dr. Lauriane Vulliez and Dr. Monika Szymanska for providing BAPS-Ado and BAPS-Adult picture sets.

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References

1 Kessler RC, Bromet EJ. The epidemiology of depression across cultures. *Annu Rev Publ Health* 2013;34:119-38.
2 Avenevoli S, Knight E, Kessler RC, et al. Epidemiology of depression in children and adolescents. In: Abela JRZ, Hankin BL, editors. Handbook of depression in children and adolescents. New York: Guilford; 2008. p. 6-32.
3 Kovacs M, Yaroslavsky I. Practitioner review: Dysphoria and its regulation in child and adolescent depression. *J Child Psychol Psychiatry* 2014;55(7):741-57.
4 Ochsner KN, Gross JJ. The cognitive control of emotion. *Trends Cogn Sci* 2005;9(5):242-9.
5 Ahmed SP, Bittencourt-Hewitt A, Sebastian CL. Neurocognitive bases of emotion regulation development in adolescence. *Dev Cogn Neurosci* 2015;15:11-25.
6 Compton SN, March JS, Brent D, et al. Cognitive-behavioral psychotherapy for anxiety and depressive disorders in children and adolescents: an evidence-based medicine review. *J Am Acad Child Psy* 2004;43(8):930-59.
7 Curry J, Rohde P, Simons A, et al. Predictors and moderators of acute outcome in the Treatment for Adolescents with Depression Study (TADS). *J Am Acad Child Psy* 2006;45(12):1427-39.
8 Thapar A, Collishaw S, Pine DS, et al. Depression in adolescence. *Lancet* 2012;379(9820):1056-67.
9 Berking M, Ebert D, Cuijpers P, et al. Emotion regulation skills training enhances the efficacy of inpatient cognitive behavioral therapy for major depressive disorder: a randomized controlled trial. *Psychother Psychosom* 2013;82:234-45.
10 Berking M, Wupperman P, Reichardt A, et al. Emotion-regulation skills as a treatment target in psychotherapy. *Behav Res Ther* 2008;46:1230-7.
11 Cutuli D. Cognitive reappraisal and expressive suppression strategies role in the emotion regulation: an overview on their modulatory effects and neural correlates. *Front Syst Neurosci* 2014;8:175.
12 Garnefski N, Kraaij V. The cognitive emotion regulation questionnaire: Psychometric Features and Prospective Relationships with Depression and Anxiety in Adults. *Eur J Psychol Assess* 2007;23(3):141-9.
13 Joormann J, Gotlib IH. Emotion regulation in depression: relation to cognitive inhibition. *Cognition Emotion* 2010;24(2):281-98.
14 Schäfer JÖ, Naumann E, Holmes EA, et al. Emotion regulation strategies in depressive and anxiety symptoms in youth: A meta-analytic review. *J Youth Adolescence* 2017;46(2):261-76.
15 Dillon DG, Pizzagalli DA. Evidence of successful modulation of brain activation and subjective experience during reappraisal of negative emotion in unmedicated depression. *Psychiatry Res Neuroimaging* 2013;212(2):99-107.
16 Sheline YI, Barch DM, Price JL, et al. The default mode network and self-referential processes in depression. *P Natl Acad Sci* 2009;106(6):1942-7.
17 Greening SG, Osuch EA, Williamson PC, et al. The neural correlates of regulating positive and negative emotions in medication-free major depression. *SCAN* 2013;9(5):628-37.
18 Zilverstand A, Parvaz MA, Goldstein RZ. Neuroimaging cognitive reappraisal in clinical populations to define neural targets for enhancing emotion regulation. A systematic review. *Neuroimage* 2017;151:105-16.
19 Greimel E, Schulte-Ruether M, Fink GR, et al. Development of neural correlates of empathy from childhood to early adulthood: an fMRI study in boys and adult men. *J Neural Transm* 2010;117(6):781-91.
20 DeCicco JM, O'Toole LJ, Dennis TA. The late positive potential as a neural signature for cognitive reappraisal in children. *Dev Neuropsychol* 2014;39(7):497-515.
21 Moser JS, Krompinger JW, Dietz J, et al. Electrophysiological correlates of decreasing and increasing emotional responses to unpleasant pictures. *Psychophysiology* 2009;46:17-27.
22 Paul S, Simon D, Kniesche R, et al. Timing effects of antecedent-and response-focused emotion regulation strategies. *Biol Psychol* 2013;94(1):136-42.
23 Dennis TA, Hajcak G. The late positive potential: a neurophysiological marker for emotion regulation in children. *J Child Psychol Psyc* 2009;50(11):1373-83.

24 Wessing I, Rehbein MA, Romer G, et al. Cognitive emotion regulation in children: reappraisal of emotional faces modulates neural source activity in a frontoparietal network. *Dev Cogn Neurosci* 2015;13:1-10.
25 Bylsma LM. Emotional Reactivity and Regulation in Current and Remitted Depression: An Event Related Potential Study [Dissertation]: University of South Florida; 2012.
26 Kudinova AY, Owens M, Burkhouse KL, et al. Differences in emotion modulation using cognitive reappraisal in individuals with and without suicidal ideation: An ERP study. *Cognition Emotion* 2016;30(5):999-1007.
27 Bebko GM, Franconeri SL, Ochsner KN, et al. Attentional deployment is not necessary for successful emotion regulation via cognitive reappraisal or expressive suppression. *Emotion* 2014;14(3):504-12.
28 Manera V, Samson AC, Pehrs C, et al. The eyes have it: The role of attention in cognitive reappraisal of social stimuli. *Emotion* 2014;14(5):833-9.
29 Strauss GP, Ossenfort KL, Whearty KM. Reappraisal and distraction emotion regulation strategies are associated with distinct patterns of visual attention and differing levels of cognitive demand. *Plos One* 2016;11(11):e0162290.
30 Denny BT, Ochsner KN. Behavioral effects of longitudinal training in cognitive reappraisal. *Emotion* 2014;14(2):425-33.
31 De Witte NA, Sütterlin S, Braet C, et al. Psychophysiological correlates of emotion regulation training in adolescent anxiety: Evidence from the novel PIER task. *J Affect Disord* 2017;214:89-96.
32 World Health Organization. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines: Geneva: World Health Organization; 1992.
33 Schönfelder S, Kanske P, Heissler J, et al. Time course of emotion-related responding during distraction and reappraisal. *SCAN* 2014;9(9):1310-9.
34 Paul S, Simon D, Endrass T, et al. Altered emotion regulation in obsessive-compulsive disorder as evidenced by the late positive potential. *Psychol Med* 2016;46(1):137-47.
35 Sarlo M, Ubel S, Leutgeb V, et al. Cognitive reappraisal fails when attempting to reduce the appetitive value of food: an ERP study. *Biol Psychol* 2013;94(3):507-12.
36 Bradley MM, Lang PJ. Measuring emotion: the self-assessment manikin and the semantic differential. *J Behav Ther Exp Psy* 1994;25(1):49-59.
37 Suk H-J. Color and Emotion-a study on the affective judgment across media and in relation to visual stimuli [Dissertation]: Universität Mannheim; 2006.
38 Lang PJ. Behavioral treatment and bio-behavioral assessment: Computer applications. In: Sidowski JB, Johnson JH, Williams TA, editors. Technology in mental health care delivery systems. Norwood, NJ: Ablex; 1980. p. 119-37.
39 Patrick CJ, Lavoro SA. Ratings of emotional response to pictorial stimuli: Positive and negative affect dimensions. *Motiv Emotion* 1997;21(4):297-321.
40 Lang PJ, Bradley MM, Cuthbert BN. International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-8. Gainesville, FL: University of Florida; 2008.
41 Szymanska M, Monnin J, Noiret N, et al. The Besancon affective picture set-adolescents (the BAPS-Ado): development and validation. *Psychiatry Res* 2015;228(3):576-84.
42 Szymanska M, Comte A, Tio G, et al. The Besançon affective picture set-adult (BAPS-Adult): Development and validation. *Psychiatry Res* 2019;271:31-8.
43 Margraf J, Cwik JC, Pflug V, et al. Structured clinical interviews for mental disorders across the lifespan: Psychometric quality and further developments of the DIPS Open Access interviews. [Strukturierte klinische Interviews zur Erfassung psychischer Störungen über die Lebensspanne: Gütekriterien und Weiterentwicklungen der DIPS-Verfahren.]. *Z Klin Psychol Psychopathol Psychother* 2017;46(3):176-86.
44 Margraf J, Cwik JC, Suppiger A, et al. DIPS Open Access: Diagnostic Interview for Mental Disorders. [DIPS Open Access: Diagnostisches Interview bei psychischen Störungen.] Bochum: Mental Health Research and Treament Center; 2017.
45 Weiß RH. CFT 20-R, Grundintelligenztest Skala 2 - Revision (2. Auflage)2019.
46 Wechsler D. Wechsler Intelligence Scale for Children–Fifth Edition (WISC-V). Frankfurt/Main, Nürnberg, Leipzig: Pearson; 2017.

47 Kühner C, Huffziger S, Nolen-Hoeksema S. Response Styles Questionnaire-Deutsche Version: RSQ-D; Manual: Hogrefe; 2007.
48 Hautzinger M, Keller F, Kühner C. Das Beck Depressionsinventar II. Deutsche Bearbeitung und Handbuch zum BDI-II. Frankfurt am Main: Harcourt Test Services; 2006.
49 Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav* 1983;24(4):385-96.
50 Ebesutani C, Regan J, Smith A, et al. The 10-Item Positive and Negative Affect Schedule for Children, Child and Parent Shortened Versions: Application of Item Response Theory for More Efficient Assessment. *J Psychopathol Behav* 2012;34(2):191-203.
51 Stöber J. Die Soziale-Erwünschtheits-Skala-17 (SES-17): Entwicklung und erste Befunde zu Reliabilität und Validität. *Diagnostica* 1999;45(4):173-7.
52 Koster EH, De Lissnyder E, Derakshan N, et al. Understanding depressive rumination from a cognitive science perspective: The impaired disengagement hypothesis. *Clin Psychol Rev* 2011;31(1):138-45.
53 Sanchez-Lopez A, Everaert J, Van Put J, et al. Eye-gaze contingent attention training (ECAT): Examining the causal role of attention regulation in reappraisal and rumination. *Biol Psychol* 2019;142:116-25.
54 Cohen N, Ochsner KN. From surviving to thriving in the face of threats: the emerging science of emotion regulation training. *Curr Opin Behav Sci* 2018;24:143-55.
55 Miyake A, Friedman NP, Emerson MJ, et al. The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cognitive Psychol* 2000;41(1):49-100.
56 Friedman NP, Miyake A, Young SE, et al. Individual differences in executive functions are almost entirely genetic in origin. *J Exp Psychol Gen* 2008;137(2):201-25.
57 Zimmermann P, Fimm B. TAP Testbatterie zur Aufmerksamkeitsprüfung Version 2.3: Vera Fimm, Psychologische Testsysteme; 2012.
58 Grob A, Smolenski C. Fragebogen zur Erhebung der Emotionsregulation bei Kindern und Jugendlichen (FEEL-KJ). 2. Aktualisierte und ergänzte Auflage. Bern: Huber Verlag; 2009.
59 Axelson DA, Birmaher B. Relation between anxiety and depressive disorders in childhood and adolescence. *Depress Anxiety* 2001;14(2):67-78.
60 Laux L, Glanzmann P, Schaffner P, et al. Das State-Trait-Angstinventar Weinheim, Germany: Beltz; 1981.
61 Döpfner M, Achenbach TM, Plück J, et al. CBCL/6-18R-TRF/6-18R-YSR/11-18R: Deutsche Schulalter-Formen der Child Behavior Checklist von Thomas M. Achenbach: Elternfragebogen über das Verhalten von Kindern und Jugendlichen (CBCL/6-18R), Lehrerfragebogen über das Verhalten von Kindern und Jugendlichen (TRF/6-18R), Fragebogen für Jugendliche (YSR/11-18R). Göttingen: Hogrefe; 2014.
62 Moran TP, Jendrusina AA, Moser JS. The psychometric properties of the late positive potential during emotion processing and regulation. *Brain Res* 2013;1516:66-75.
63 Siegle GJ, Price RB, Jones NP, et al. You gotta work at it: Pupillary indices of task focus are prognostic for response to a neurocognitive intervention for rumination in depression. *Clin Psychol Sci* 2014;2(4):455-71.
64 Aldao A, Nolen-Hoeksema S, Schweizer S. Emotion-regulation strategies across psychopathology: A meta-analytic review. *Clin Psychol Rev* 2010;30(2):217-37.

Table 1. Overview over diagnostic measures and all variables of the study

Function	Measure	Instrument	Reliability	T0 Baseline/ Diagnostics	T1	T2	T3	T4	2-week Follow-up
Diagnostic	Diagnosis	Kinder-DIPS (A)	Retest-Reliability for depressive disorders=.95 (Kappa) for the predecessor version of the Kinder-Dips for DSM-IV diagnoses	X					
	Intelligence quotient (IQ)	CFT-20-R (A) (part 1)	Cronbach's α=.92 for the first part	X					
Primary Outcome	Depressive Symptoms	BDI-II (A)	Cronbach's α=.94 in adolescent population [72]	X				X	
	Negative and positive Affect	PANAS-C-SF (A)	Cronbach's α=.86 for positive affect scale and Cronbach's α=.82 for negative affect scale [53]		X	X	X	X	X
	Perceived Stress	PSS-10 (A)	Cronbach's α=.84		X	X	X	X	X
	Rumination	RSQ-D (A)	Cronbach's α=.77 for self-focused rumination scale and Cronbach's α=.88 for symptom-focused rumination in patients [56]	X				X	X
Secondary Outcome	Affective behavioral responses to pictures	SAM Rating Scale (A)			X	X	X	X	
	LPP (Late Positive Potential)	(A)			X	X	X	X	
	Gaze fixations in emotional areas of interest	(A)			X	X	X	X	
Confounding Variables	Social Desirability	SES-17 (A)	Cronbach's α=.72[57, 73]	X					
Mediators	State rumination during training	Questionnaire (A) applied in A Sanchez-Lopez, J			X	X	X	X	

		Everaert, J Van Put, R De Raedt and EHW Koster [59]							
	Habitual emotion regulation strategies	FEEL-KJ (A)	Cronbach's α=.93 for Adaptive emotion regulation scale and Cronbach's α=.82 for Maladaptive emotion regulation scale [64]	X					
	Executive Function abilities (Set shifting, Working Memory, Inhibition)	TAP 2.3 (A)	Odd–even– Reliability for reaction times in adolescents: .791 for working memory, .952 for flexibility, .911 for Go/nogo for trials applied in the current study	X					
Moderators	Trait and state anxiety	STAI (A)	Cronbach's α=.91 for STAI-S scale and Cronbach's α≥.89 for STAI-T scale in adolescents/young adults [66]	X					
	Psychopathology	CBCL 6-18R (P)	Cronbach's α=.93 for total behavior problem scale [67]	X					

Note. Applied to A=Adolescent P=Parent; Abbreviatons: Kinder-DIPS (Diagnostisches Interview bei psychischen Störungen im Kindes- und Jugendalter): Diagnostic interview for psychiatric disorders for children and adolescents; CFT-20-R (revidierte Grundintelligenztest Skala 2): Culture fair intelligence test; BDI-II: Beck depression inventory; PANAS-C-SF: Negative Affect Scale and Positive Affect Scale for Children Shortened Version for Children Shortened Version; PSS-10: Perceived Stress Scale 10; RSQ-D: German Version of the Response Styles Questionnaire; SAM: self-assessment manikin rating scale; SES-17: Social Desirability Scale; FEEL-KJ (Fragebogen zur Erhebung der Emotionsregulation bei Kindern und Jugendlichen): Questionnaire for the assessment of emotion regulation in children and adolescents; TAP (Testbatterie zur Aufmerksamkeitsprüfung): Test battery for executive functions; STAI: State-Trait-Anxiety Inventory; CBCL 6-18R: Child Behavior Checklist for the ages 6-18.

Figure Legends

Figure 1. Overview of the KONNI study design

Figure 2. Experimental time course. Exemplary illustration of a trial belonging to the CR training (negative-reappraise condition). The picture shown is exemplary and not part of the picture databases used in the study. Abbreviations: SAM: self-assessment manikin rating scale (as a portrait version; see Suk, 2006).

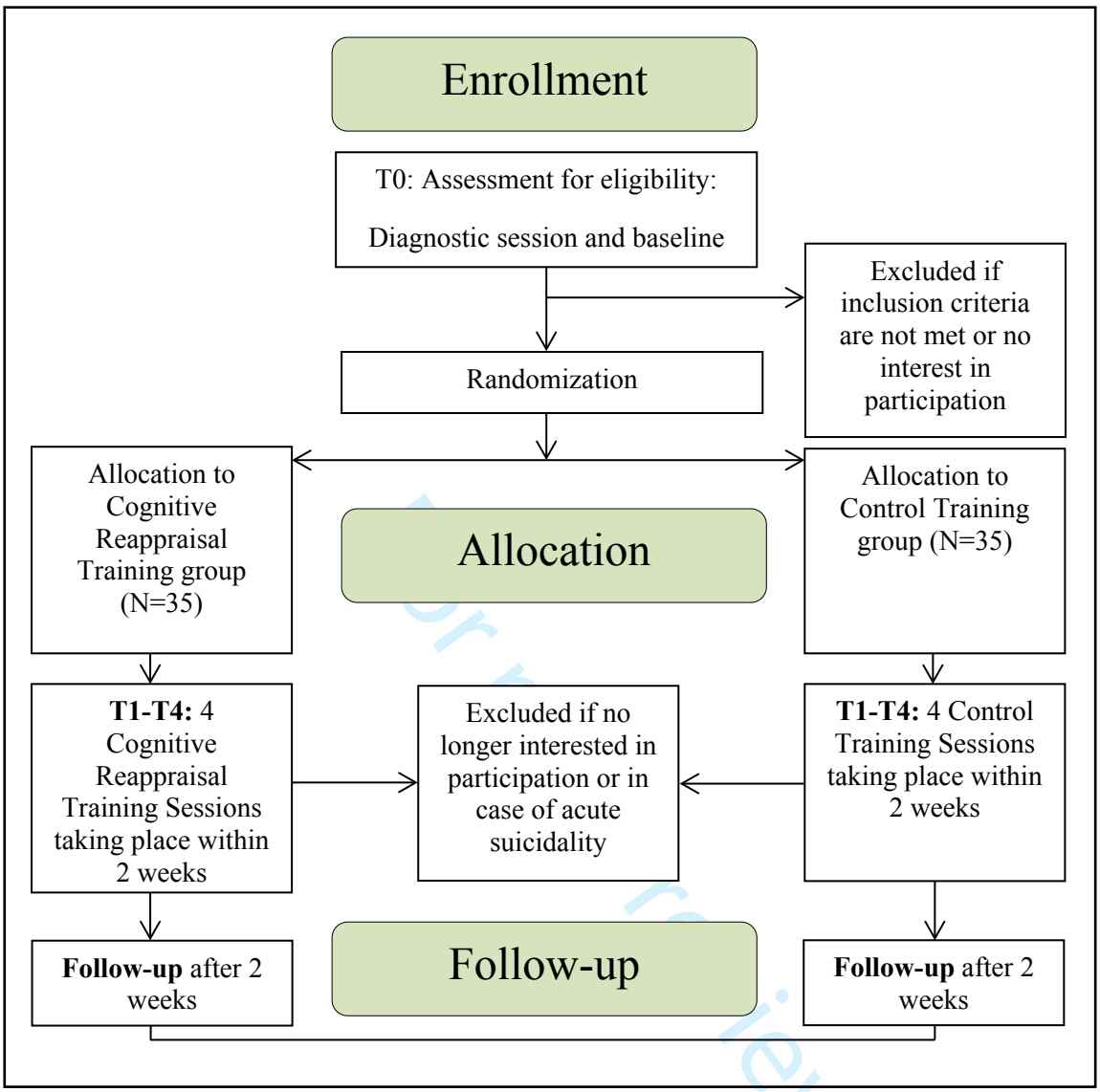

Figure 1. Overview of the KONNI study design

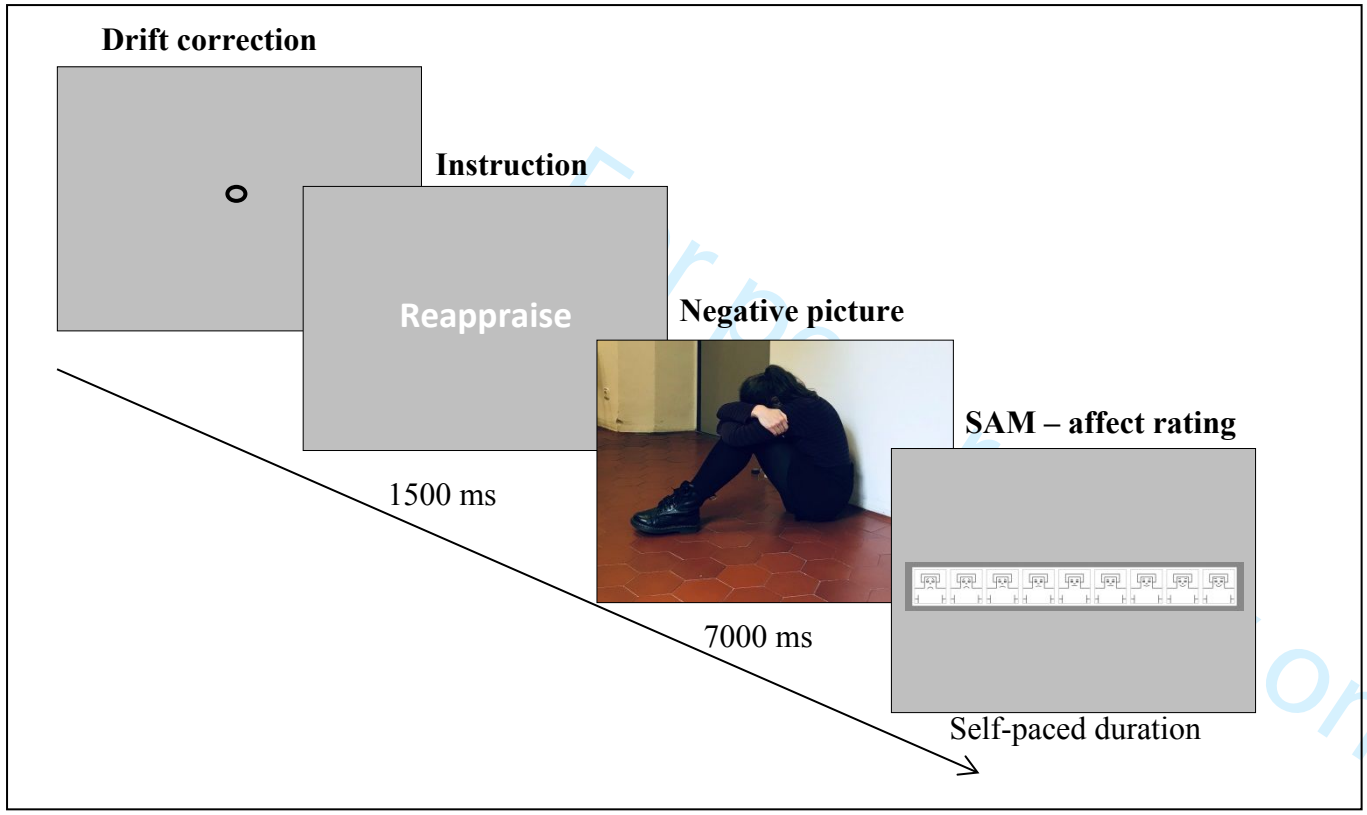

Fig. 2. Experimental time course. Exemplary illustration of a trial belonging to the CR training (negative-reappraise condition). The picture shown is exemplary and not part of the picture databases used in the study. Abbreviations: SAM: self-assessment manikin rating scale (as a portrait version; see Suk, 2006).

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **(p. 1 Title)**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **(p. 2 "Trial Registration")**
	2b	All items from the World Health Organization Trial Registration Data Set **(throughout the entire study protocol)**
Protocol version	3	Date and version identifier **(n.a., first version of the protocol)**
Funding	4	Sources and types of financial, material, and other support **(p. 16, section "funding")**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **(pp. 16-17, section "author's contributions")**
	5b	Name and contact information for the trial sponsor **(p. 17, section "trial sponsor")**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities **(p. 16, section "funding")**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) **(n.a.)**
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **(pp. 3-5; sections: "Introduction", "Cognitive reappraisal in depressed individuals", "Trainability of cognitive reappraisal", "Aim of the study")**

	6b	Explanation for choice of comparators **(pp. 8-9, section "Control training")**
Objectives	7	Specific objectives or hypotheses **(pp. 4-5, section "Aim of the study")**
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **(pp. 5-6, section "Design")**
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **(p. 6, section "Recruitment")**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **(pp. 6-7, sections "Participants", "Procedure")**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **(pp. 7-9, sections "Cognitive Reappraisal Training", "Control Training")**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **(p. 7, section "Procedure"; Fig. 1)**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **(p. 8, section "Cognitive Reappraisal Training")**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **(pp. 6-7, section "Procedure")**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **(pp. 9-10, sections "Primary outcomes", "Secondary outcomes")**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) **(Table 1; Fig. 1)**

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **(pp. 12-13, section "Calculation of sample size")**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **(p. 6, section "Recruitment")**
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **(pp. 6-7, section "Procedure")**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **(pp. 6-7, section "Procedure")**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **(pp. 6-7, section "Procedure")**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **(p. 6, section "Procedure")**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **(p. 7, section "Procedure")**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **(pp. 7-9, sections Cognitive Reappraisal Training", "Control training" "Diagnostic measures"; Table 1)**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **(p. 7, section "Procedure")**

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **(p. 12, section "Data management and confidentiality")**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **(pp. 13-14, section "Statistical analysis")**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **(p. 14, section "Statistical analysis")**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **(p. 13, section "Statistical analysis")**
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **(n.a. A data monitoring is not needed as the training (cognitive reappraisal training) and the control training are expected to carry no risks.)**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **(n.a., As the training (cognitive reappraisal training) and the control training are expected to carry no risks, there are no stopping guidelines and interims analyses planned.)**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **(p. 7, Section "Procedure")**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **(n.a.)**
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **(p. 16, section "Ethics approval")**

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **(p. 5, section "Methods and analysis")**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **(p. 6, section "Procedure")**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **(p. 6, section "Procedure")**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial **(p. 12, section "Data management and confidentiality")**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **(p. 16, section "Competing interests")**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators **(p. 12, section "Data management and confidentiality")**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **(n.a.)**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **(p. 2, section "Ethics and Dissemination")**
	31b	Authorship eligibility guidelines and any intended use of professional writers **(n.a., no intended use of professional writers; author's contribution are summerized in pp. 16-17)**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical **(p. 16, section "Availability of data and material")**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **(n.a., documents in German)**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **(n.a.)**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Study protocol for a randomized-controlled study on emotion regulation training for adolescents with major depression: the KONNI study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-036093.R1
Article Type:	Protocol
Date Submitted by the Author:	15-Apr-2020
Complete List of Authors:	Greimel, Ellen; University Hospital Munich, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy Feldmann, Lisa; University Hospital Munich, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy Piechaczek, Charlotte; University Hospital Munich, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy Oort, Frans; University of Amsterdam, Research Institute of Child Development and Education Bartling, Juergen; University Hospital Munich, Department of Child and Adolescent Psychiatry and Psychotherapy Schulte-Rüther, Martin; RWTH Aachen University, Translational Brain Medicine in Psychiatry and Neurology, Department of Child and Adolescent Psychiatry, Psychosomatics, and Psychotherapy; JARA-Brain Schulte-Körne, Gerd ; University Hospital Munich, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	Child & adolescent psychiatry < PSYCHIATRY, Depression & mood disorders < PSYCHIATRY, Clinical trials < THERAPEUTICS, NEUROPHYSIOLOGY

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Study protocol for a randomized-controlled study on emotion regulation training for adolescents with major depression: the KONNI study

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Word count - original submission: 4.221 (3.927 excluding the Discussion)

Word count – revision: 4.745 (4.315 excluding the Discussion)

Abstract

Introduction: Major depression (MD) often has its onset during adolescence and is associated with significant morbidity and mortality. One important factor for the development and maintenance of adolescent MD are disturbances in emotion regulation and the underlying neural processes. Cognitive reappraisal (CR) is a particular adaptive emotion regulation strategy. Previously, it has been shown in healthy adults that a task-based training in CR is efficient to reduce negative affect, and that these effects translate into everyday life.

The present randomized-controlled trial examines for the first time whether a task-based training in CR proves effective in MD adolescents. Specifically, we will investigate whether the CR training improves the ability to down-regulate negative affect in MD individuals as assessed by behavioral and neurobiological indices, and whether training effects generalize outside the laboratory.

Methods and analysis: Adolescents with MD will be randomly allocated to a group that either receives a task-based training in CR or control training. Both involve four training sessions over a time period of two weeks. In the CR training, participants will be instructed to down-regulate negative affective responses to negative pictures by means of CR, while the control training involves picture viewing. During the training sessions, the Late Positive Potential, gaze fixations on negative picture aspects and affective responses to pictures will be collected. Before and after the training programs, and at a two-week follow-up, overall negative and positive affect, rumination and perceived stress will be assessed as primary outcomes. ANOVAs will be conducted to test the effectiveness of the CR training with regard to both primary outcomes and task-based behavioral and neurobiological parameters.

Ethics and dissemination: The study was approved by the institutional review board of the local ethics committee. The results will be published in peer-reviewed journals and disseminated through conferences, social media and public events.

Trial Registration: Clinical Trials NCT03957850, registered Mai 21st 2019; URL: https://clinicaltrials.gov/ct2/show/NCT03957850.

Strengths and limitations of the study:

- This study is the first to examine the effectiveness of a targeted CR training in youths with major depression.
- A randomized-controlled design is employed including an active control group.
- In addition to behavioral and questionnaire data, objective neurobiological indices will be collected to assess the effectiveness of the CR training.
- If proven effective, the CR training can be a promising and cost-effective approach to complement and enhance the efficacy of established treatments for adolescent MD.
- As the follow-up is limited to two weeks, the long-term effectiveness needs to be explored in future studies.

Introduction

Major depression (MD) is among the most debilitating, costly and common psychiatric disorders worldwide.[1] The risk of suffering from a depressive episode sharply rises during adolescence, with point prevalence rates of up to 7%.[2] Adolescents with MD show deficient emotion regulation (ER),[3] i.e., they have difficulties to modulate emotional responses by initiating appropriate regulatory processes.[4] Disturbances in ER and the underlying neural processes have been suggested to be an important risk factor for the development and maintenance of MD.[3, 5] Thus, the development of training regimens that target deficient ER in MD is an important research avenue.

Cognitive-behavioral therapy (CBT) belongs to the gold standard treatments in juvenile MD. However, less than 50% of MD adolescents respond to CBT and only about one third enter remission after treatment.[6, 7] Given the debilitating consequences of adolescent MD,[8] there is an urgent need to enhance the efficacy of established intervention. Recent findings in adults with MD suggest that an additional training of ER might be a promising approach to improve treatment effects.[9, 10] To date, it remains unclear whether these findings can be transferred to juvenile MD. In this regard, the present study takes a first step and systematically investigates the effects of a focused ER training in adolescent MD.

Cognitive reappraisal in depressed individuals

Cognitive reappraisal (CR) is a frequently studied ER strategy and involves the reinterpretation of a situation such that the emotional response is changed. The habitual use of CR has been shown to relate to good interpersonal functioning and well-being.[11] Questionnaire studies have found that depressive symptoms are associated with less habitual use of CR and more use of maladaptive emotion regulation strategies such as rumination.[12-14] It has been proposed that this habitual pattern in depressed individuals might originate from deficits in the inhibition of negative material which is thought to enhance ruminative thoughts but hampering the effective reappraisal of negative information.[15] To experimentally investigate CR in MD, studies applied a well-established CR paradigm during which participants are instructed to reappraise negative pictures. This regulation condition is compared to an unregulated condition, during which participants are asked to simply attend to negative stimuli. Within

the framework of this paradigm, a number of studies in MD collected behavioral measures of self-reported affect to assess regulation success. Contrary to expectation, some studies found no group differences between depressive and healthy participants in this index of CR.[16, 17] However, these results might be biased due to social desirability which probably obscures group differences. Moreover, complex ER disturbances are unlikely to be captured using simple affect ratings,[18, 19] highlighting the importance of additionally assessing objective and more sensitive parameters when studying CR, including neurobiological indices.

A commonly studied neurobiological index of CR is the Late Positive Potential (LPP). Studies in healthy samples show that the LPP is reduced when individuals are instructed to reappraise unpleasant stimuli compared to attending to unpleasant pictures.[20-22] This decrease is thought to reflect a reduction of the emotional response following CR, which may result from a shift in stimulus meaning.[23, 24] Depressive psychopathology has been shown to be associated with a smaller reduction of the LPP during CR.[23, 25, 26] However, to date, no study has investigated whether this neurobiological disturbance can be normalized by a repeated training of CR.

Besides the LPP, a number of studies in healthy individuals have investigated gaze fixation patterns to gain insight into the mechanisms underlying CR.[27-29] They found that a greater regulation success is paralleled by less gaze fixations directed towards negative picture cues. This suggests that the regulatory effects of CR may partly be attributed to gaze deployment, highlighting the importance of also assessing gaze fixation when examining CR.

Trainability of cognitive reappraisal

Evidence from a randomized controlled trial (RCT) in adult MD suggests that systematically training ER skills in addition to standard CBT improves treatment efficacy.[9, 10] As the ER training of this RCT aimed at enhancing general ER skills and included CR among other ER strategies, the unique contribution of CR remains to be investigated. A recent investigation addressed this issue experimentally in healthy adults,[30] demonstrating that a task-based CR training resulted in less perceived stress in daily life. Beneficial effects of a task-based CR training have recently also been shown in healthy and anxious adolescents.[31] While these results are encouraging, it needs to be examined whether the

findings can be extended to MD samples and whether a CR training results in reductions in depressive symptomatology, including ruminative thoughts. In this context, it has been proposed that CR training improves cognitive control abilities, including the ability to inhibit negative material. As impairments in the ability to inhibit negative information are thought to play a causal role in rumination, training the ability to reappraise negative information should thus reduce ruminative thoughts.[15]

Aim of the study

The aim of the study is to assess whether in MD adolescents, a task-based CR training results in an improved downregulation of negative affective responses as assessed by behavioral and neurobiological indices. Moreover, the study aims to investigate whether the training effects generalize outside the laboratory, i.e., lead to affect-related changes and a reduction in perceived stress and rumination.

It is hypothesized that over the course of the CR training, MD adolescents show improvements in the downregulation of negative affective responses as assessed by task-based behavioral[30] and neurobiological indices. Based on prior research,[30, 31] it is further hypothesized that the CR training results in improvements in affect- and stress-related symptoms in daily life.

Methods and analysis

The study (Public and scientific Title: Cognitive Reappraisal in Adolescents with Major Depression: From Neurobiological Mechanisms to Intervention; German acronym: KONNI) was prospectively registered on ClinicalTrails.gov (NCT03957850) before recruitment start. The study protocol and the template informed consent/assent forms (including two amendments) were approved by the institutional review board of the local ethics committee (Ludwig-Maximilians-University Medical Division Ethics Committee, Munich, Germany; study ID: 63-16) on 30th January 2019 and are reported in line with the Standard Protocol Items: Recommendations for Interventional Trials Statement (SPIRIT 2013). Important modifications to the study protocol would require an additional amendment, which would have to be approved by the Ethics Committee before implementation. The trial registry (ClinicalTrials.gov) would then be updated.

Design

This interventional study is designed as a short-term randomized controlled, participant-blind clinical superiority trial including two parallel groups of MD adolescents. Participants will be randomly assigned to a group that receives task-based training in CR or to a control training. All participants will take part in one diagnostic assessment (T0), four training sessions (T1-4) over the course of two weeks, and a follow-up two weeks after T4. All questionnaires and test procedures are summarized in Table 1. During the training sessions, task-based indices of CR will be continuously assessed based on behavioral affect ratings and the LPP. Moreover, eye gaze will be recorded during the task-based training. The KONNI study design is depicted in Figure 1.

Participants

Participants aged 12-18 years with a current ICD-10 diagnosis of MD,[32] an IQ of ≥80 and sufficient German language skills will be included. The following exclusion criteria will be applied: acute suicidality, neurological disorders, schizophrenic disorder, pervasive developmental disorder, bipolar disorder, borderline personality disorder, substance dependence disorder and gender dysphoria. Participants with other psychiatric comorbidities are included if MD is the primary diagnosis.

Recruitment

MD adolescents will be primarily recruited from the Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital of the LMU Munich, Germany. Currently untreated MD patients from the waiting list, and in-and outpatients are enrolled in the study. The first participant was enrolled in May 27th, 2019. The planned completion of participant enrollment is in April 2021. Since the start of the study n=15 subjects were enrolled.

Procedure

Adolescents and one parent/legal custodian (for participants <18 years) will be contacted by an experienced study nurse certified in Good Clinical Practice (GCP) and will be informed about the study details, including the fact that the allocation to the training groups will be made based on a predefined

randomization list. All potential study participants and their parents/legal custodians will be approached by the study nurse unless it is known beforehand that the exclusion criteria are met (e.g., acute suicidality, gender dysphoria). If the clinicians of potential participants conclude that the capacity to provide informed consent/assent are not met (e.g., in case of insufficient German skills, cognitive disability or an acute crisis), participants and their parents/legal custodians will not be approached. In case of interest in participation, their written informed consent/assent will be collected. In the written informed consent/assent, participants and their parent/legal custodian are asked for their permission that the data can also be used for an ancillary case-control study on neurobiological underpinnings of ER in MD. The participants and the parent/legal custodian will be blinded regarding allocation to the CR/control training group until study completion and only unblinded prior to study completion if they terminate participation prematurely. At the first session (T0), a diagnostic interview and other baseline measures (see below) will be applied to the adolescent and will last ~2,5 hours. The diagnostic session will be conducted by psychologically trained staff.

If the participant is eligible for the study, the following session appointments will be scheduled and the participant will be randomly allocated to the CR or the control training group. To ensure allocation concealment, the random allocation to one of the groups is implemented after completion of baseline measurements; i.e., neither the recruiter nor the person conducting the baseline session know to which group the participant will be assigned after T0. Access to the allocation list is limited to the principal investigator (E.G.) and her deputy (L.F.), who will inform the experimenters about the allocation of the participant shortly before the first training session (after the diagnostic session and the decision to include the participant in the study). Randomization stratifying for age (<15 years vs. ≥15 years of age)[1] and sex will be performed by a statistician, who is neither involved in recruitment nor in testing of participants. The randomization will be performed with a 1:1 allocation. A follow-up session will take place two weeks after completion of the forth training session. After the follow-up, participants are unblinded regarding group allocation by one of the experimenters. As expense allowance for study participation (~10 hours including follow-up), the participants will receive 100€. Participation is

[1] Based on prior studies in MD adolescents conducted in our department, 15 is the expected approximate median age of MD participants.

voluntary and can be discontinued at any time for any reason. Participation is discontinued in case of acute suicidality during the study. No other criteria for discontinuation are defined. To assess the feasibility of conducting a large-scale multi-center RCT on the effects of a CR training in addition to standard treatment, the following data will be collected and reported: participation and non-participation rate, drop-outs and reasons for drop-outs, training attendance rates and spontaneously reported adverse effects.Treatment fidelity concerning the training is assured by standardized oral and written instructions and by comprehensive training of the experimenters. The experimenters will be either clinical psychologists or advanced and in-depth trained psychology students. The concomitant treatment as usual is permitted during the ongoing study and information on the type of treatment during the study will be assessed. Moreover, patient safety data will be assessed by recording any spontaneously reported adverse effects.

Cognitive Reappraisal Training

The CR training task is well-established and is adapted from previous studies,[22, 33-35] including a study from our group, in which we demonstrated that adolescents with MD understand and comply with task instructions, and are able to down-regulate negative affective responses to negative pictures via CR.[36] The training procedure was adapted from [30]. An exemplary illustration of an experimental trial is depicted in Figure 2. Participants will be presented emotional pictures which are preceded by a condition specific cue signaling the appropriate strategy (attend vs. reappraise) during picture presentation. Following each picture, participants are instructed to indicate their affective response to the image on the portrait version of the nine-point self-assessment manikin scale for valance [SAM; 37, for the portrait version see 38, 39], which has been frequently applied in youth samples.[40, 41] A higher score on this scale indicates a more positive valence rating. The task involves four conditions: 1) **Negative-reappraise:** participants are asked to view negative pictures and to decrease their affective response by reappraising the negative event. Participants are explicitly instructed to use the reinterpretation tactic during CR, which involves "mentally changing the meaning of the actions, context and/or outcome depicted in a stimulus".[30] 2) **Negative-attend,** 3) **Neutral-attend and** 4) **Positive-attend:** participants are asked to view the pictures and to respond naturally to them without trying to

alter their affective response. Comparison of the negative-reappraise and the negative-attend conditions allows assessing behavioral and neural indices of reappraisal success. The neutral-attend and the positive-attend conditions are included to avoid slight changes in negative affect due to the exclusive presentation of unpleasant pictures.[42]

The training task will be repeated over four training sessions. Before the first session, participants will complete a comprehensive practice training, during which a trained experimenter will provide standardized oral instructions regarding the task and the two strategies (attend, reappraise).[30, 36] Thereafter, walk-through images are presented to confirm the appropriate use of the strategies. Task instructions will be briefly summarized before each training session.

In each training session, 144 pictures will be presented in 3 blocks, each containing 12 positive-attend, 12 neutral-attend, 12 negative-attend, and 12 negative-reappraise trials. Developmentally appropriate pictures (e.g., excluding pictures of dead persons or pornographic images) are taken from the International Affective Picture System,[IAPS; 43] Besançon Affective Picture Set-Adolescents,[BAPS-Ado; 44] and Besançon Affective Picture Set-Adults,[BAPS-Adult; 45] with the latter two sets being derived from the Besançon Attachment Pictures Set. Each picture will be presented twice over the course of the training.[30] To ensure adherence to task instructions, participants will fill in a questionnaire after each training session to indicate which strategies they used during the task.

Control training

The control training is implemented to account for unspecific effects and the task employed is similar to the CR task except that it involves no "negative-reappraise" condition. Instead, the control task only involves attend conditions (negative-attend, neutral-attend, positive-attend). To keep the total number of trials involving negative pictures constant across the two groups, the control task involves twice as many negative-attend trials as the CR training group. Mirroring the CR training procedure, the control training is repeated over four sessions and preceded by standardized oral instructions and a practice session. Participants of the control training group will also fill in a questionnaire on how they resolved the task after each training session.

Measures

Information about psychometric properties of all measures described in the following paragraph are summarized in Table 1 along with the respective assessments points.

Diagnostic measures

A diagnosis of MD and potential comorbidities will be assessed using a well-established German standardized semi-structured diagnostic interview (Kinder-DIPS).[46, 47] The interview will be administered by experienced, psychologically trained experimenters. To assess inter-rater reliability based on Cohen´s kappa (k), 10% of the Kinder-DIPS interviews will be rated by two experimenters. IQ will be estimated based on the first part of the CFT-20-R.[48] For some patients, results from other established IQ tests [e.g. WISC-V; 49] will be available from routine care, which will be used instead.

Outcome measures

Primary outcomes

The primary outcomes of the study are (1) change in rumination from baseline (T0) to post-training (directly after T4) and follow-up [assessed by the scales "self-focused rumination" and "symptom-focused rumination" of the German short version of the Response Styles Questionnaire; RSQ-D; 50]; (2) change in depressive symptoms [assessed by the German version of the Beck Depression Inventory – Second Edition; BDI-II; 51] from baseline (T0) to post-training (directly after T4); (3) change in perceived stress over the course of the four training sessions and at follow-up [assessed by the German translation of the Perceived Stress Scale 10; PSS-10; by Prof. Dr. Arndt Büssing; 52][2]; (4) changes in negative and positive affect [assessed by the Negative Affect Scale and Positive Affect Scale for Children Shortened Version; PANAS-C-SF; 53] over the course of the four training sessions and at follow-up.

Secondary outcomes

[2]In the PSS-10, items were reworded to “in the past few days” instead of “in general” to better allow assessing changes of the course of the training.

One secondary outcome is the change in the downregulation of affective behavioral responses to negative pictures by means of CR. Affective behavioral responses to negative pictures will be continuously assessed during each of the four training sessions using the SAM rating scale.[37, with the portrait version from 38, 39]

Another secondary outcome is the change in the downregulation of the early and late LPP amplitude to negative pictures by means of CR. The LPP elicited to pictures in the negative-attend and the negative-reappraise condition will be continuously assessed during each of the four training sessions. Additionally, changes in the percent duration of gaze fixations within a-priori defined emotional interest areas of negative pictures[3] will be assessed during both the negative-attend and negative-reappraise condition over the course of the four training sessions.

All secondary outcome measures will only be assessed in the CR training group, as participants in the control training group are not instructed to apply CR. However, these measures will also be assessed in the control training group during the negative-attend condition to allow additional exploratory analyses.

Confounding variable

Participants will complete the Social Desirability Scale.[SES-17; 54] The rationale for assessing this confounding variable is that behavioral ratings of affective responses to pictures will be assessed, which are prone to response biases.[18]

Mediators

State rumination during the training will be treated as a potential mediator as ruminative thoughts might hamper beneficial training effects.[55] After completion of each training session, participants in the CR and control training group rate state rumination during the task on a scale from 0 “not at all” to 10 “exactly” based on a 5-item questionnaire applied in a previous study.[56]

We will also assess a potential mediating role of executive function abilities, which are thought to be critically involved in ER.[57] Individual baseline differences in executive function abilities might thus prove important mediators of training outcome. Therefore, set-shifting, working memory and inhibition

[3]Emotional areas of interest of negative pictures will be defined based on a separate validation study.

[58, 59] as the three core components of executive functions will be assessed based on the TAP 2.3.[Testbatterie zur Aufmerksamkeitspruefung; 60]

Moreover, we will treat habitual ER as a potential mediator, which will be assessed based on the FEEL-KJ [61]. The FEEL-KJ is a self-report questionnaire assessing habitual adaptive and maladaptive ER strategies.

Moderators

As anxiety disorders/symptoms frequently co-occur with MD,[62] state and trait anxiety will be assessed based on the State-Trait-Anxiety Inventory (STAI).[63] Moreover, symptoms of psychopathology will be screened using the Child Behavior Checklist (CBCL 6-18R).[64] Both variables will be treated as potential moderators.

Eye-tracking apparatus

During the four training sessions, eye-movements will be continuously recorded using the Eyelink 1000 Plus SR Research eye-tracker. At the beginning of the training, participants are seated at the viewing distance of approx. 55 cm from the monitor and a 9-point calibration is performed. Prior to each experimental trial, a drift correction is conducted.

Electroencephalogram recording and preprocessing

The electroencephalogram data is recorded using the Electrical Geodesic Inc. 128-channel system with 500 Hz sampling rate and Cz as reference electrode. Impedance is kept below 50 kΩ during recording. The further preprocessing and analyses steps will be performed with Brainvision Analyzer 2.1 (Brain Products GmbH, Germany). After filtering, removal of electro-oculographic artefacts based on Independent Component Analysis and exclusion of other artefacts, the signal will be re-referenced. Data will be segmented into epochs, baseline-corrected and averaged separately for each participant and condition. The LPP will be measured as the mean amplitude at a centro-parietal region-of-interest within early (<300ms) and late time windows (≥300 ms) following picture onset.[33, 65]

Data management and confidentiality

All data will be entered electronically in IBM SPSS statistics by a scientific assistant. Plausibility and completeness checks will be regularly performed by E.G., L.F., C.P. to promote and monitor data quality. Original documents will be maintained for 15 years in the department. All original and electronic data is stored on the hospitals server under a pseudorandomized coded ID, which does not contain names or birth dates of the participants. Only the project leader and her deputies have access to the participants' names and the corresponding allocation to the encryption code and the original documents, which are kept in locked cabinets. The records containing names and other personal identifiers (e.g., informed consent/assent forms) will be stored in locked cabinets separately from the study records which are identified by the coded ID. The participants' study information will not be released outside the study, except in case of threat to self or threat to others. The final cleaned data sets will be provided to all investigators of the study. To adhere to principles of open science and to facilitate further use of aggregated data in meta-analytic approaches, we will consider making raw data available to other researchers if this can be achieved along with protecting sensitive patient information, such as sociodemographic information. Since patients could possibly be identified by making our raw data publicly available, ethical principles of protecting patient confidentiality would be breached. Aggregated group data can be made available upon request.

Calculation of sample size

A rough approximation of the requested sample size targeted at rumination as one of the primary outcomes can be achieved by referring to a previous study.[66] This study investigated the effects of a task-based cognitive control training compared to treatment as usual in adult MD. The training aimed at improving ER skills indirectly by targeting mechanisms thought to underlie ER. This study reported a large effect size in the training group from pre to post (Cohen's d=1.42) on a measure related to negative affect (rumination). Based on a conservative assumption, a large effect size of d=0.85 is expected with regard to changes in rumination for the CR training from pre to post. For the control training, a small effect size (d=0.2) is expected from pre to post due to unspecific "positive" effects of the control

intervention. This effect size is based on prior evidence[4] on the effects of a similar control training in young adults.[30]

Based on these assumptions, calculation of the required sample size to detect a significant 2(group) x 2(time: T0=pre, T4=post) interaction for rumination using a repeated measures ANOVA with a 5% level of significance (alpha=0.05) and 80% statistical power (1–beta=0.80) revealed an N=47 for the total group (assuming a 0.7 pre-post correlation). The drop-out rate for the study is estimated at approx. 33%. Thus, n=35 adolescents will be enrolled in each group. The necessary sample size was calculated with G*power 3.1. Statistical power of analyses that involve more measurements, such as the analysis of affect, will have more than 80% statistical power if effect sizes are similar.

Statistical analysis

To test the hypotheses that the CR training results in a stronger decrease in depressive symptoms/rumination from baseline to post-training assessment compared to a control training, a mixed-model ANOVA with the factors group (CR vs. control training) and time (T0, T4) will be conducted for the BDI-II and the two RSQ-D scales "self-focused rumination", "symptom-focused rumination". To account for the fact that the RSQ-D will be reassessed at follow-up, a mixed-model ANOVA with the factors group (CR vs. control training) and time (T0, T4, follow-up) will additionally be conducted for the two rumination scales. Mixed modeling (also known as multilevel analysis, with observations "nested" within participants) has the advantage over regular repeated measures ANOVA that all available data can be used, including data from incomplete cases, without using imputation techniques for missing data.[67] To test the hypotheses that the CR training results in a a) stronger decrease in negative and b) stronger increase in positive affect from pre- to post-training and follow-up assessment compared to the control training, mixed-model ANOVAs with the factors group (CR vs. control training) and time (T1, T2, T3, T4, follow-up) will be conducted for the Negative Affect/ Positive Affect scale of the PANAS-C-SF. The same statistical model procedure will be applied for perceived stress (PSS-10).

[4] Detailed statistical information was derived from personal communication with corresponding author of this study; B. Denny, April 26th, 2017.

To test the hypothesis that over the course of the CR training, MD adolescents show an increased downregulation of the early and late LPP amplitude via CR, a mixed-model ANOVA with the factors 2(condition: negative-reappraise, negative-attend) x 4(training session: T1, T2, T3, T4) will be conducted separately for early and late LPP time windows. The same statistical procedure will be conducted for the affective ratings of negative pictures and the percent of gaze fixation duration in emotional areas of negative pictures. Correlation analyses will be performed between the percent of gaze fixation duration in emotional areas of negative pictures and ER success (downregulation of the LPP and affective ratings of negative pictures via CR).

To examine changes of the LPP, affective ratings of negative pictures and gaze fixations for the negative-attend condition in the control training group over the course of the training, additional exploratory ANOVAs will be conducted. Likewise, for the control training group, exploratory correlation analyses will be calculated to examine relationships between these measures and gaze fixation duration in emotional areas of negative pictures. Finally, moderation and mediation analyses will be applied to examine the role of mediating and moderating variables.

Patient and public involvement

Participants or their parents were not involved in designing the study. However, we will present the results of the study to parent and participant representatives to include their suggestions in the dissemination plan. Moreover, parallel to publication of the results, all participants and their families will receive a letter summarizing the main findings and conclusions in comprehensible language.

Discussion

This study will for the first time elucidate whether in adolescents with MD, a CR training shows beneficial effects both in and outside the laboratory. If the training proves effective, this approach might be a promising resource-effective intervention for adolescents with MD. Such an intervention could, e.g., be applied to bridge the often long waiting times for treatment of MD or as an adjunction to a treatment as usual. Moreover, after psychoeducation on CR and guided practice of this strategy in psychotherapy, the training could also be (online) applied as an adjunct to treatment as usual. In such a

context, the psychotherapist could monitor difficulties and progress in the use of CR, and promote the transfer of strategy into everyday life of the patient.

Building on the results from the present RCT, future investigations could additionally consider transfer effects to CR tasks other than the training tasks or to CR abilities in daily life e.g., based on ecological momentary assessment. Moreover, as a next step, it would be worthwhile to assess whether this training might prove effective in patients with other psychiatric disorders which are also characterized by deficient ER abilities, such as anxiety disorders and eating disorders.[68]

A limiting factor of the study is the short follow-up interval of two weeks. Thus, future studies should include a longer follow-up interval to also examine whether the effects of the training are long-lasting. Another limitation is that the study is single-blinded (participant-blinded) concerning the allocation to the CR training vs. control training. This single-blinding procedure entails the risk that the experimenters will transfer their expectations to the participants. However, as the participants will perform a comprehensive practice training that is guided by the experimenter, double-blinding would not be feasible. Finally, it should be stated the present study does not include the ecological momentary assessment of outcome measures. Expanding upon the present study, it would be important to also apply experience sampling methods in future work to be able to draw comprehensive conclusions regarding transfer effects of the CR training to daily live. Despite these caveats, the results of our study will be an important step towards larger scale, multi-center RCTs in MD adolescents to investigate whether a CR training increases the efficacy of standard treatments. Furthermore, the study will elucidate neurobiological changes that occur during training and whether these are linked to changes in training outcome. To this end, our protocol may also aid to identify potential biomarkers for monitoring and predicting treatment success and thereby spark further research into the direction of individualized treatment adaptation based on neurobiological parameters.

Ethics approval

Written informed consent/assent will be taken by the participating adolescents and their parents/legal custodians. The study protocol and the template informed consent/assent forms were approved (including two amendments) by the institutional review board of the local ethics committee (Ludwig-Maximilians-University Medical Division Ethics Committee, Munich, Germany; study ID: 63-16) on 30th January 2019.

Dissemination

Study results will be presented at national and international confernces and published in peer-reviewed publications. Moreover, the particiants and their parents will receive a summary of the study results in layman's language.

Abbreviations

BAPS-Ado: Besançon Affective Picture Set-Adolescents; BAPS-Adult: Besançon Affective Picture Set-Adults; BDI-II: Beck depression inventory; CBCL 6-18R: Child Behavior Checklist for the ages 6-18; CFT-20-R (revidierte Grundintelligenztest Skala 2): Culture fair intelligence test; CBT: Cognitive-behavioral therapy; CR: Cognitive reappraisal; DFG (Deutsche Forschungsgemeinschaft): German Research Foundation; FEEL-KJ (Fragebogen zur Erhebung der Emotionsregulation bei Kindern und Jugendlichen): Questionnaire for the assessment of emotion regulation in children and adolescents; IAPS: International Affective Picture System; ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision; IQ: Intelligence Quotient; Kinder-DIPS (Diagnostisches Interview bei psychischen Störungen im Kindes- und Jugendalter): Diagnostic interview for psychiatric disorders for children and adolescents; LMU: Ludwig-Maximilians University; LPP: Late Positive Potential; MD: Major depression; PANAS-C-SF: Negative Affect Scale and Positive Affect Scale for Children Shortened Version for Children Shortened Version; PSS-10: Perceived Stress Scale 10; RSQ-D: German Version of the Response Styles Questionnaire; SAM: self-assessment manikin rating scale; SES-17: Social Desirability Scale; SPIRIT: Standard protocol items: recommendations for interventional trials; STAI: State-Trait-Anxiety Inventory; TAP (Testbatterie zur Aufmerksamkeitsprüfung): Test battery for executive functions; WISC-V: Wechsler Intelligence Scale for Children - Fifth Edition.

Declarations

Consent for publication

This manuscript does not contain any form of individual person's data, all data will be reported based on aggregated group data.

Availability of data and material

The datasets generated and/or analyzed during the current study are not publicly available due to sensitive patient information, such as sociodemographic information, birth date and comorbidities, but aggregated group data can be made available upon request.

Competing interests statement

The authors declare that they have no competing financial or non-financial interests.

Funding

This work was supported by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Grant GR4753/2-1 to E.G. The funding body played no role in the design of the study or writing of the manuscript or the decision to submit the report for publication.

Authors' contributions

EG, LF, GSK and CP contributed to the study design. Data management will be conducted by LF and EG and data analysis and interpretation will be performed by LF, EG, FO, GSK, JB, MSR and CP. EG and LF wrote the study protocol. All authors read and critically revised the draft of the paper and approved the final version of this manuscript.

Acknowledgements

We are grateful to Carolin Zsigo for the assistance during the implementation of the experiment. We wish to thank Petra Wagenbüchler for her assistance in data collection. We further would like to thank Dr. Lauriane Vulliez and Dr. Monika Szymanska for providing BAPS-Ado and BAPS-Adult picture sets.

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References

1. Kessler RC, Bromet EJ. The epidemiology of depression across cultures. Annu Rev Publ Health. 2013;34:119-38.
2. Avenevoli S, Knight E, Kessler RC, Merikangas KR. Epidemiology of depression in children and adolescents. In: Abela JRZ, Hankin BL, editors. Handbook of depression in children and adolescents. New York: Guilford; 2008. p. 6-32.
3. Kovacs M, Yaroslavsky I. Practitioner review: Dysphoria and its regulation in child and adolescent depression. J Child Psychol Psychiatry. 2014;55(7):741-57.
4. Ochsner KN, Gross JJ. The cognitive control of emotion. Trends Cogn Sci. 2005;9(5):242-9.
5. Ahmed SP, Bittencourt-Hewitt A, Sebastian CL. Neurocognitive bases of emotion regulation development in adolescence. Dev Cogn Neurosci. 2015;15:11-25.
6. Compton SN, March JS, Brent D, Albano AM, Weersing VR, Curry J. Cognitive-behavioral psychotherapy for anxiety and depressive disorders in children and adolescents: an evidence-based medicine review. J Am Acad Child Psy. 2004;43(8):930-59.
7. Curry J, Rohde P, Simons A, Silva S, Vitiello B, Kratochvil C, et al. Predictors and moderators of acute outcome in the Treatment for Adolescents with Depression Study (TADS). J Am Acad Child Psy. 2006;45(12):1427-39.
8. Thapar A, Collishaw S, Pine DS, Thapar AK. Depression in adolescence. Lancet. 2012;379(9820):1056-67.
9. Berking M, Ebert D, Cuijpers P, Hofmann SG. Emotion regulation skills training enhances the efficacy of inpatient cognitive behavioral therapy for major depressive disorder: a randomized controlled trial. Psychother Psychosom. 2013;82:234-45.
10. Berking M, Wupperman P, Reichardt A, Pejic T, Dippel A, Znoj H. Emotion-regulation skills as a treatment target in psychotherapy. Behav Res Ther. 2008;46:1230-7.
11. Cutuli D. Cognitive reappraisal and expressive suppression strategies role in the emotion regulation: an overview on their modulatory effects and neural correlates. Front Syst Neurosci. 2014;8:175.
12. Garnefski N, Kraaij V. The cognitive emotion regulation questionnaire: Psychometric Features and Prospective Relationships with Depression and Anxiety in Adults. Eur J Psychol Assess. 2007;23(3):141-9.
13. Joormann J, Gotlib IH. Emotion regulation in depression: relation to cognitive inhibition. Cognition Emotion. 2010;24(2):281-98.
14. Schäfer JÖ, Naumann E, Holmes EA, Tuschen-Caffier B, Samson AC. Emotion regulation strategies in depressive and anxiety symptoms in youth: A meta-analytic review. J Youth Adolescence. 2017;46(2):261-76.
15. Cohen N, Daches S, Mor N, Henik A. Inhibition of negative content - a shared process in rumination and reappraisal. Front Psychol. 2014; 5: 622.
16. Dillon DG, Pizzagalli DA. Evidence of successful modulation of brain activation and subjective experience during reappraisal of negative emotion in unmedicated depression. Psychiatry Res Neuroimaging. 2013;212(2):99-107.
17. Sheline YI, Barch DM, Price JL, Rundle MM, Vaishnavi SN, Snyder AZ, et al. The default mode network and self-referential processes in depression. P Natl Acad Sci. 2009;106(6):1942-7.
18. Zilverstand A, Parvaz MA, Goldstein RZ. Neuroimaging cognitive reappraisal in clinical populations to define neural targets for enhancing emotion regulation. A systematic review. Neuroimage. 2017;151:105-16.
19. Greimel E, Schulte-Ruether M, Fink GR, Piefke M, Herpertz-Dahlmann B, Konrad K. Development of neural correlates of empathy from childhood to early adulthood: an fMRI study in boys and adult men. J Neural Transm. 2010;117(6):781-91.
20. DeCicco JM, O'Toole LJ, Dennis TA. The late positive potential as a neural signature for cognitive reappraisal in children. Dev Neuropsychol. 2014;39(7):497-515.

21. Moser JS, Krompinger JW, Dietz J, Simons RF. Electrophysiological correlates of decreasing and increasing emotional responses to unpleasant pictures. Psychophysiology. 2009;46:17-27.
22. Paul S, Simon D, Kniesche R, Kathmann N, Endrass T. Timing effects of antecedent-and response-focused emotion regulation strategies. Biol Psychol. 2013;94(1):136-42.
23. Dennis TA, Hajcak G. The late positive potential: a neurophysiological marker for emotion regulation in children. J Child Psychol Psyc. 2009;50(11):1373-83.
24. Wessing I, Rehbein MA, Romer G, Achtergarde S, Dobel C, Zwitserlood P, et al. Cognitive emotion regulation in children: reappraisal of emotional faces modulates neural source activity in a frontoparietal network. Dev Cogn Neurosci. 2015;13:1-10.
25. Bylsma LM. Emotional Reactivity and Regulation in Current and Remitted Depression: An Event Related Potential Study [Dissertation]: University of South Florida; 2012.
26. Kudinova AY, Owens M, Burkhouse KL, Barretto KM, Bonanno GA, Gibb BE. Differences in emotion modulation using cognitive reappraisal in individuals with and without suicidal ideation: An ERP study. Cognition Emotion. 2016;30(5):999-1007.
27. Bebko GM, Franconeri SL, Ochsner KN, Chiao JY. Attentional deployment is not necessary for successful emotion regulation via cognitive reappraisal or expressive suppression. Emotion. 2014;14(3):504-12.
28. Manera V, Samson AC, Pehrs C, Lee IA, Gross JJ. The eyes have it: The role of attention in cognitive reappraisal of social stimuli. Emotion. 2014;14(5):833-9.
29. Strauss GP, Ossenfort KL, Whearty KM. Reappraisal and distraction emotion regulation strategies are associated with distinct patterns of visual attention and differing levels of cognitive demand. Plos One. 2016;11(11):e0162290.
30. Denny BT, Ochsner KN. Behavioral effects of longitudinal training in cognitive reappraisal. Emotion. 2014;14(2):425-33.
31. De Witte NA, Sütterlin S, Braet C, Mueller SC. Psychophysiological correlates of emotion regulation training in adolescent anxiety: Evidence from the novel PIER task. J Affect Disord. 2017;214:89-96.
32. World Health Organization. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines: Geneva: World Health Organization; 1992.
33. Schönfelder S, Kanske P, Heissler J, Wessa M. Time course of emotion-related responding during distraction and reappraisal. SCAN. 2014;9(9):1310-9.
34. Paul S, Simon D, Endrass T, Kathmann N. Altered emotion regulation in obsessive-compulsive disorder as evidenced by the late positive potential. Psychol Med. 2016;46(1):137-47.
35. Sarlo M, Ubel S, Leutgeb V, Schienle A. Cognitive reappraisal fails when attempting to reduce the appetitive value of food: an ERP study. Biol Psychol. 2013;94(3):507-12.
36. Greimel E, Piechaczek C, Schulte-Rüther M, Feldmann L, Schulte-Körne G. The role of attentional deployment during distancing in adolescents with major depression. BRAT. 2020;126:103554.
37. Bradley MM, Lang PJ. Measuring emotion: the self-assessment manikin and the semantic differential. J Behav Ther Exp Psy. 1994;25(1):49-59.
38. Suk H-J. Color and Emotion-a study on the affective judgment across media and in relation to visual stimuli [Dissertation]: Universität Mannheim; 2006.
39. Lang PJ. Behavioral treatment and bio-behavioral assessment: Computer applications. In: Sidowski JB, Johnson JH, Williams TA, editors. Technology in mental health care delivery systems. Norwood, NJ: Ablex; 1980. p. 119-37.
40. Musser ED, Galloway-Long HS, Frick PJ, Nigg JT. Emotion regulation and heterogeneity in attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2013;52(2):163-71.e2.
41. Reichel VA, Schneider N, Grünewald B, Kienast T, Pfeiffer E, Lehmkuhl U, et al. “Glass fairies” and “bone children”: Adolescents and young adults with anorexia nervosa show positive reactions towards extremely emaciated body pictures measured by the startle reflex paradigm. Psychophysiology. 2014;51(2):168-77.

42. Patrick CJ, Lavoro SA. Ratings of emotional response to pictorial stimuli: Positive and negative affect dimensions. Motiv Emotion. 1997;21(4):297-321.
43. Lang PJ, Bradley MM, Cuthbert BN. International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-8. Gainesville, FL: University of Florida; 2008.
44. Szymanska M, Monnin J, Noiret N, Tio G, Galdon L, Laurent E, et al. The Besancon affective picture set-adolescents (the BAPS-Ado): development and validation. Psychiatry Res. 2015;228(3):576-84.
45. Szymanska M, Comte A, Tio G, Vidal C, Monnin J, Smith CC, et al. The Besançon affective picture set-adult (BAPS-Adult): Development and validation. Psychiatry Res. 2019;271:31-8.
46. Margraf J, Cwik JC, Pflug V, Schneider S. Structured clinical interviews for mental disorders across the lifespan: Psychometric quality and further developments of the DIPS Open Access interviews. [Strukturierte klinische Interviews zur Erfassung psychischer Störungen über die Lebensspanne: Gütekriterien und Weiterentwicklungen der DIPS-Verfahren.]. Z Klin Psychol Psychopathol Psychother. 2017;46(3):176-86.
47. Margraf J, Cwik JC, Suppiger A, Schneider S. DIPS Open Access: Diagnostic Interview for Mental Disorders. [DIPS Open Access: Diagnostisches Interview bei psychischen Störungen.] Bochum: Mental Health Research and Treament Center; 2017.
48. Weiß RH. CFT 20-R, Grundintelligenztest Skala 2 - Revision (2. Auflage)2019.
49. Wechsler D. Wechsler Intelligence Scale for Children–Fifth Edition (WISC-V). Frankfurt/Main, Nürnberg, Leipzig: Pearson; 2017.
50. Kühner C, Huffziger S, Nolen-Hoeksema S. Response Styles Questionnaire-Deutsche Version: RSQ-D; Manual: Hogrefe; 2007.
51. Hautzinger M, Keller F, Kühner C. Das Beck Depressionsinventar II. Deutsche Bearbeitung und Handbuch zum BDI-II. Frankfurt am Main: Harcourt Test Services; 2006.
52. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24(4):385-96.
53. Ebesutani C, Regan J, Smith A, Reise S, Higa-McMillan C, Chorpita BF. The 10-Item Positive and Negative Affect Schedule for Children, Child and Parent Shortened Versions: Application of Item Response Theory for More Efficient Assessment. J Psychopathol Behav. 2012;34(2):191-203.
54. Stöber J. Die Soziale-Erwünschtheits-Skala-17 (SES-17): Entwicklung und erste Befunde zu Reliabilität und Validität. Diagnostica. 1999;45(4):173-7.
55. Koster EH, De Lissnyder E, Derakshan N, De Raedt R. Understanding depressive rumination from a cognitive science perspective: The impaired disengagement hypothesis. Clin Psychol Rev. 2011;31(1):138-45.
56. Sanchez-Lopez A, Everaert J, Van Put J, De Raedt R, Koster EHW. Eye-gaze contingent attention training (ECAT): Examining the causal role of attention regulation in reappraisal and rumination. Biol Psychol. 2019;142:116-25.
57. Cohen N, Ochsner KN. From surviving to thriving in the face of threats: the emerging science of emotion regulation training. Curr Opin Behav Sci. 2018;24:143-55.
58. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex “frontal lobe” tasks: A latent variable analysis. Cognitive Psychol. 2000;41(1):49-100.
59. Friedman NP, Miyake A, Young SE, DeFries JC, Corley RP, Hewitt JK. Individual differences in executive functions are almost entirely genetic in origin. J Exp Psychol Gen. 2008;137(2):201-25.
60. Zimmermann P, Fimm B. TAP Testbatterie zur Aufmerksamkeitsprüfung Version 2.3: Vera Fimm, Psychologische Testsysteme; 2012.
61. Grob A, Smolenski C. Fragebogen zur Erhebung der Emotionsregulation bei Kindern und Jugendlichen (FEEL-KJ). 2. Aktualisierte und ergänzte Auflage. Bern: Huber Verlag; 2009.
62. Axelson DA, Birmaher B. Relation between anxiety and depressive disorders in childhood and adolescence. Depress Anxiety. 2001;14(2):67-78.

63. Laux L, Glanzmann P, Schaffner P, Spielberger C. Das State-Trait-Angstinventar Weinheim, Germany: Beltz; 1981.
64. Döpfner M, Achenbach TM, Plück J, Kinnen C, Plück J. CBCL/6-18R-TRF/6-18R-YSR/11-18R: Deutsche Schulalter-Formen der Child Behavior Checklist von Thomas M. Achenbach: Elternfragebogen über das Verhalten von Kindern und Jugendlichen (CBCL/6-18R), Lehrerfragebogen über das Verhalten von Kindern und Jugendlichen (TRF/6-18R), Fragebogen für Jugendliche (YSR/11-18R). Göttingen: Hogrefe; 2014.
65. Moran TP, Jendrusina AA, Moser JS. The psychometric properties of the late positive potential during emotion processing and regulation. Brain Res. 2013;1516:66-75.
66. Siegle GJ, Price RB, Jones NP, Ghinassi F, Painter T, Thase ME. You gotta work at it: Pupillary indices of task focus are prognostic for response to a neurocognitive intervention for rumination in depression. Clin Psychol Sci. 2014;2(4):455-71.
67. Murrar S, Brauer M. Mixed model analysis of variance. In: Frey BB, editor. The SAGE encyclopedia of educational research, measurement, and evaluation. Thousand Oaks: SAGE Publications, Inc.; 2018. p. 1075-8.
68. Aldao A, Nolen-Hoeksema S, Schweizer S. Emotion-regulation strategies across psychopathology: A meta-analytic review. Clin Psychol Rev. 2010;30(2):217-37.
69. Adornetto C, In-Albon T, Schneider S. Diagnostik im Kindes-und Jugendalter anhand strukturierter Interviews: Anwendung und Durchführung des Kinder-DIPS. Klin Diagnostik u Evaluation. 2008;1(4):363-77.
70. Dolle K, Schulte-Körne G, O'Leary AM, von Hofacker N, Izat Y, Allgaier A-K. The Beck Depression Inventory-II in adolescent mental health patients: Cut-off scores for detecting depression and rating severity. Psychiat Research. 2012;200(2-3):843-8.
71. Stockings E, Degenhardt L, Lee YY, Mihalopoulos C, Liu A, Hobbs M, et al. Symptom screening scales for detecting major depressive disorder in children and adolescents: a systematic review and meta-analysis of reliability, validity and diagnostic utility. J Affect Disorders. 2015;174:447-63.
72. Löwe B, Kroenke K, Gräfe K. Detecting and monitoring depression with a two-item questionnaire (PHQ-2). J Psychosom Res. 2005;58(2):163-71.
73. Klein EM, Brähler E, Dreier M, Reinecke L, Müller KW, Schmutzer G, et al. The German version of the Perceived Stress Scale–psychometric characteristics in a representative German community sample. BMC Psychiatry. 2016;16:159.
74. Conway M, Csank PA, Holm SL, Blake CK. On assessing individual differences in rumination on sadness. J Pers Assess. 2000;75(3):404-25.
75. Stöber J. The Social Desirability Scale-17 (SDS-17): Convergent validity, discriminant validity, and relationship with age. Eur J Psychol Assess. 2001;17(3):222-32.

Table 1. Overview over diagnostic measures and all variables of the study

Function	Measure	Instrument	Reliability/Validity	T0 Baseline/ Diagnostics	T1	T2	T3	T4	2-week Follow-up
Diagnostic	Diagnosis	Kinder-DIPS (A)	Retest-Reliability for depressive disorders=.95 (Kappa) for the predecessor version of the Kinder-Dips for DSM-IV diagnoses in children and adolescents[69]	X					
	Intelligence quotient (IQ)	CFT-20-R (A) (part 1)	Cronbach's α=.92 for the first part in children, adolescents and adults[48]	X					
Primary Outcome	Depressive Symptoms	BDI-II (A)	Cronbach's α=.94 in an adolescent population[70]; pooled estimate for internal reliability: .86; discriminative validity - pooled estimate for sensitivity and specifity: .81; based on meta-analytic data in non-clinical and clincal child and adolescent populations[71]	X				X	
	Negative and positive Affect	PANAS-C-SF (A)	Cronbach's α=.86 for positive affect scale and Cronbach's α=.82 for negative affect scale; divergent validity - correlation between positive and negative affect scales: -.13; based on data in an adolescent population[53]		X	X	X	X	X
	Perceived Stress	PSS-10 (A)	Cronbach's α=.84; construct validity of .59 with the PHQ-2 [Patient Health Questionnaire; 72]; based on a sample of adolescents and adults for the original version of the PSS-10[73]		X	X	X	X	X
	Rumination	RSQ-D (A)	Cronbach's α=.77 for self-focused rumination scale and Cronbach's	X				X	X

			α=.88 for symptom-focused rumination; convergent validity of .52 for symptom-focused rumination and .72 for self-focused rumination with the RSS [Rumination on Sadness Scale; 74]; based on depressed adult patients[50]						
Secondary Outcome	Affective behavioral responses to pictures	SAM Rating Scale (A) of valence	Cronbach´s α for SAM ratings of the stimuli applied in the current study will be calculated based on the present sample		X	X	X	X	
	LPP (Late Positive Potential)	(A)	n.a.		X	X	X	X	
	Gaze fixations in emotional areas of interest	(A)	n.a.		X	X	X	X	
Confounding Variables	Social Desirability	SES-17 (A)	Cronbach's α=.78 in a young adult population[54, 75]	X					
Mediators	State rumination during training	Questionnaire (A) applied in A Sanchez-Lopez, J Everaert, J Van Put, R De Raedt and EHW Koster [56]	Cronbach´s α=.72 to .73; based on data in a young adult population[56]		X	X	X	X	
	Habitual emotion regulation strategies	FEEL-KJ (A)	Cronbach's α=.93 for Adaptive emotion regulation scale and Cronbach's α=.82 for Maladaptive emotion regulation scale in children and adolescents[61]	X					
	Executive Function abilities (Set shifting, Working Memory, Inhibition)	TAP 2.3 (A)	Odd–even– Reliability for reaction times in adolescents: .791 for working memory, .952 for flexibility, .911 for Go/nogo for trials applied in the current study[60]	X					

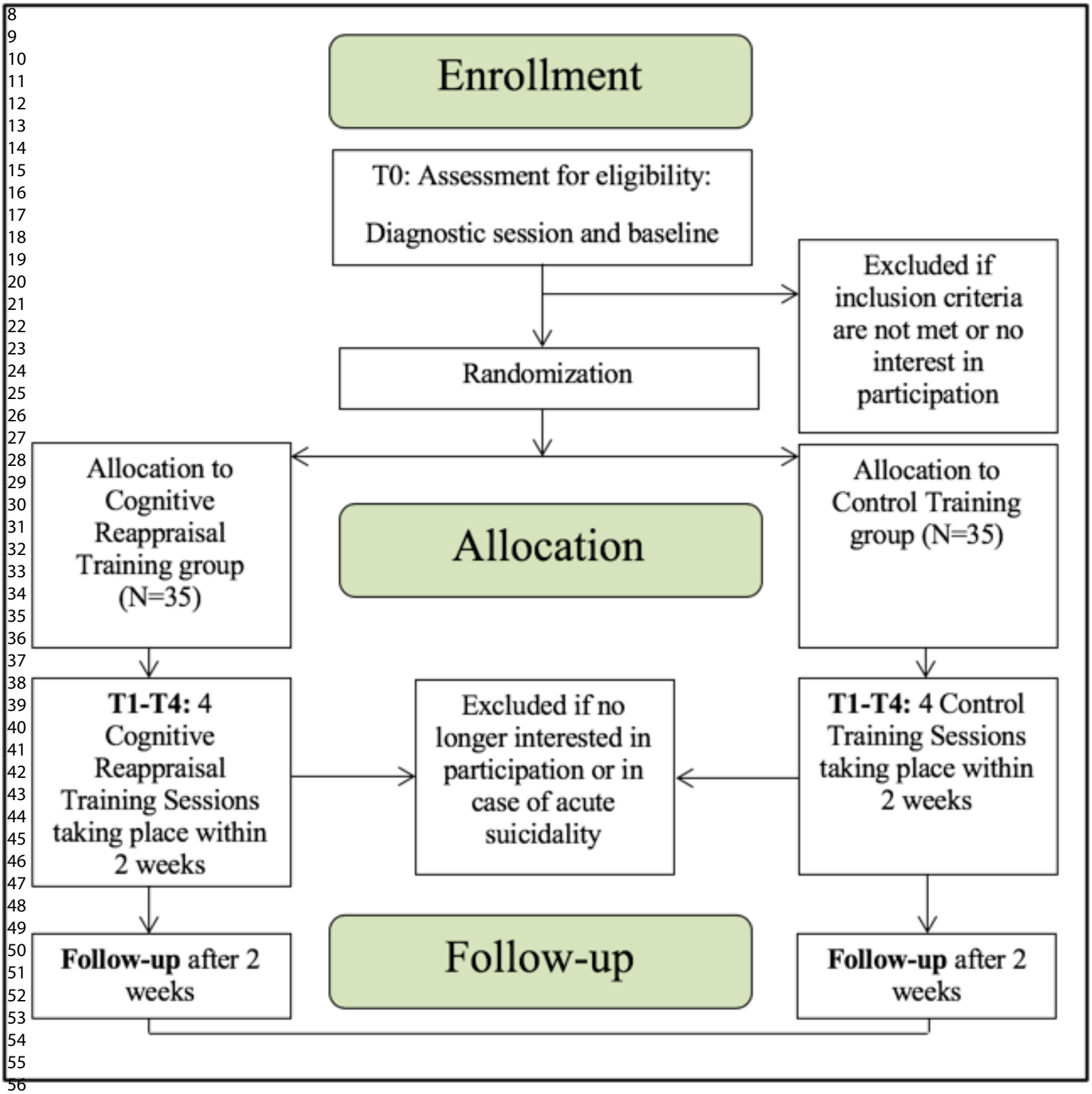
Moderators	Trait and state anxiety	STAI (A)	Cronbach's α=.91 for STAI-S scale and Cronbach's α≥.89 for STAI-T scale in adolescents/young adults[63]	X					
	Psychopathology	CBCL 6-18R (P)	Cronbach's α=.93 for total behavior problem scale based on a sample of children and adolescents[64]	X					

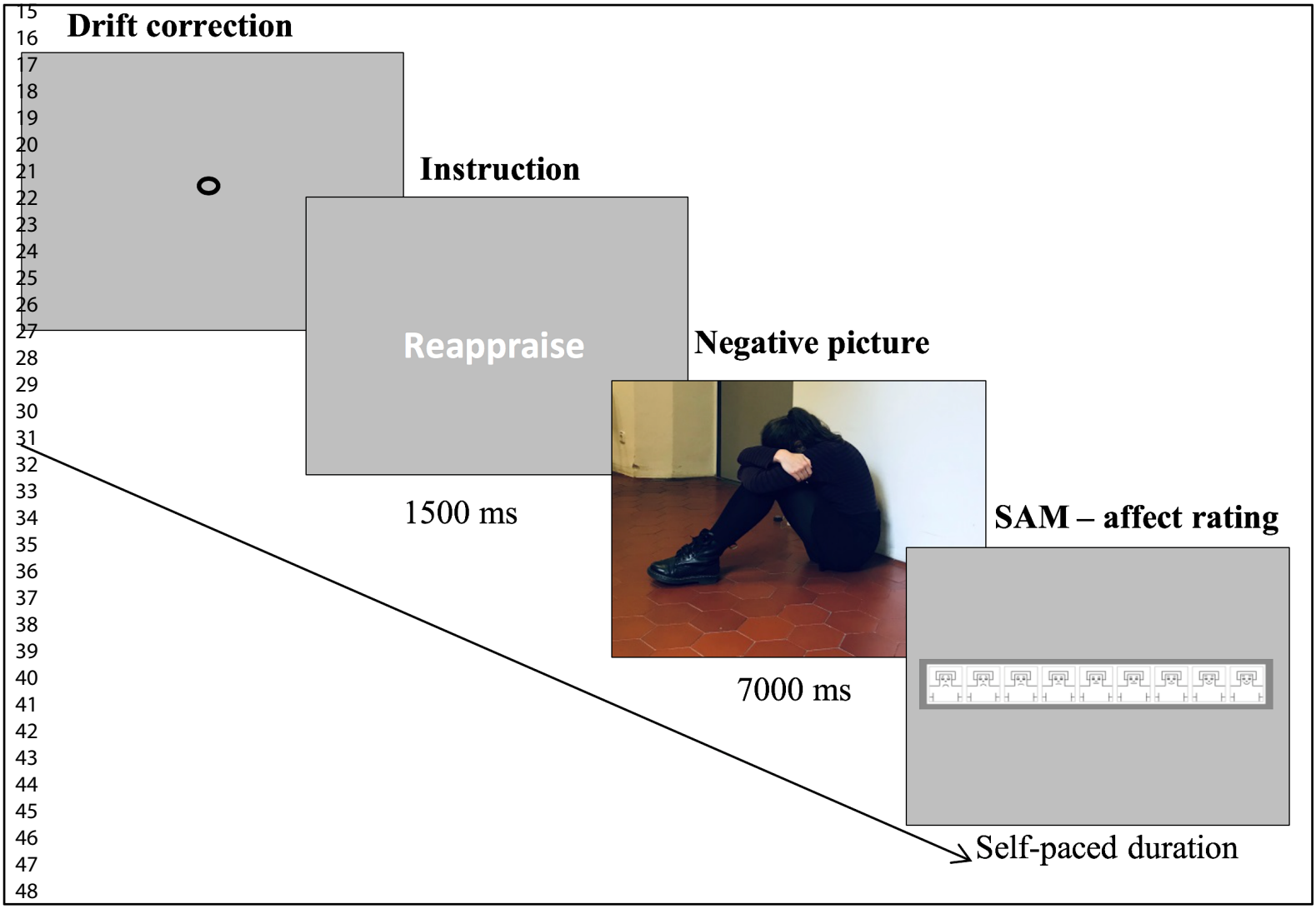
Note. Applied to A=Adolescent P=Parent; Abbreviatons: Kinder-DIPS (Diagnostisches Interview bei psychischen Störungen im Kindes- und Jugendalter): Diagnostic interview for psychiatric disorders for children and adolescents; CFT-20-R (revidierte Grundintelligenztest Skala 2): Culture fair intelligence test; BDI-II: Beck depression inventory; PANAS-C-SF: Negative Affect Scale and Positive Affect Scale for Children Shortened Version for Children Shortened Version; PSS-10: Perceived Stress Scale 10; RSQ-D: German Version of the Response Styles Questionnaire; SAM: self-assessment manikin rating scale; n.a.: not applicable; SES-17: Social Desirability Scale; FEEL-KJ (Fragebogen zur Erhebung der Emotionsregulation bei Kindern und Jugendlichen): Questionnaire for the assessment of emotion regulation in children and adolescents; TAP (Testbatterie zur Aufmerksamkeitsprüfung): Test battery for executive functions; STAI: State-Trait-Anxiety Inventory; CBCL 6-18R: Child Behavior Checklist for the ages 6-18.

Figure Legends

Figure 1. Overview of the KONNI study design

Figure 2. Experimental time course. Exemplary illustration of a trial belonging to the CR training (negative-reappraise condition). The picture shown is exemplary and not part of the picture databases used in the study. Abbreviations: SAM: self-assessment manikin rating scale (as a portrait version).


Enrollment
T0: Assessment for eligibility:
Diagnostic session and baseline
Excluded if inclusion criteria are not met or no interest in participation
Randomization
Allocation to Cognitive Reappraisal Training group (N=35)
Allocation
Allocation to Control Training group (N=35)
T1-T4: 4 Cognitive Reappraisal Training Sessions taking place within 2 weeks
Excluded if no longer interested in participation or in case of acute suicidality
T1-T4: 4 Control Training Sessions taking place within 2 weeks
Follow-up after 2 weeks
Follow-up
Follow-up after 2 weeks


Drift correction
Instruction
Reappraise
1500 ms
Negative picture
7000 ms
SAM – affect rating
Self-paced duration

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **(p. 1 Title)**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **(p. 2 "Trial Registration")**
	2b	All items from the World Health Organization Trial Registration Data Set **(throughout the entire study protocol)**
Protocol version	3	Date and version identifier **(n.a., first version of the protocol)**
Funding	4	Sources and types of financial, material, and other support **(p. 18, section "funding")**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **(p. 18, section "author's contributions")**
	5b	Name and contact information for the trial sponsor **(p. 18, section "trial sponsor")**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities **(p. 18, section "funding")**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) **(n.a.)**
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **(pp. 3-5; sections: "Introduction", "Cognitive reappraisal in depressed individuals", "Trainability of cognitive reappraisal", "Aim of the study")**

	6b	Explanation for choice of comparators **(p. 9, section "Control training")**
Objectives	7	Specific objectives or hypotheses **(p. 5, section "Aim of the study")**
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **(p. 6, section "Design")**
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **(p. 6, section "Recruitment")**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **(pp. 6-7, sections "Participants", "Procedure")**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **(pp. 8-9, sections "Cognitive Reappraisal Training", "Control Training")**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **(pp. 7-8, section "Procedure"; Fig. 1)**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **(p. 9, section "Cognitive Reappraisal Training")**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **(p. 8, section "Procedure")**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **(p. 10, sections "Primary outcomes", "Secondary outcomes")**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) **(Table 1; Fig. 1)**

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **(pp. 12-13, section "Calculation of sample size")**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **(p. 6, section "Recruitment")**

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **(pp. 6-7, section "Procedure")**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **(pp. 6-7, section "Procedure")**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **(pp. 6-7, section "Procedure")**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **(p. 7, section "Procedure")**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **(p. 7, section "Procedure")**

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **(pp. 8-10, sections Cognitive Reappraisal Training", "Control training" "Diagnostic measures"; Table 1)**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **(p. 7-8, section "Procedure")**

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **(p. 13, section "Data management and confidentiality")**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **(pp. 14-15, section "Statistical analysis")**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **(p. 15, section "Statistical analysis")**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **(p. 14, section "Statistical analysis")**
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **(n.a. A data monitoring is not needed as the training (cognitive reappraisal training) and the control training are expected to carry no risks.)**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **(n.a., As the training (cognitive reappraisal training) and the control training are expected to carry no risks, there are no stopping guidelines and interims analyses planned.)**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **(p. 8, Section "Procedure")**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **(n.a.)**
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **(p. 17, section "Ethics approval")**

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **(p. 5, section "Methods and analysis")**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **(p. 6, section "Procedure")**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **(pp. 6-7, section "Procedure")**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial **(p. 13, section "Data management and confidentiality")**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **(p. 18, section "Competing interests")**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators **(p. 13, section "Data management and confidentiality")**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **(n.a.)**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **(p. 2, section "Ethics and Dissemination")**
	31b	Authorship eligibility guidelines and any intended use of professional writers **(n.a., no intended use of professional writers; author's contribution are summerized on p. 18)**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical **(p. 18, section "Availability of data and material")**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **(n.a., documents in German)**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **(n.a.)**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Study protocol for a randomized-controlled study on emotion regulation training for adolescents with major depression: the KONNI study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-036093.R2
Article Type:	Protocol
Date Submitted by the Author:	17-Jun-2020
Complete List of Authors:	Greimel, Ellen; University Hospital Munich, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy Feldmann, Lisa; University Hospital Munich, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy Piechaczek, Charlotte; University Hospital Munich, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy Oort, Frans; University of Amsterdam, Research Institute of Child Development and Education Bartling, Juergen; University Hospital Munich, Department of Child and Adolescent Psychiatry and Psychotherapy Schulte-Rüther, Martin; RWTH Aachen University, Translational Brain Medicine in Psychiatry and Neurology, Department of Child and Adolescent Psychiatry, Psychosomatics, and Psychotherapy; JARA-Brain Schulte-Körne, Gerd ; University Hospital Munich, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	Child & adolescent psychiatry < PSYCHIATRY, Depression & mood disorders < PSYCHIATRY, Clinical trials < THERAPEUTICS, NEUROPHYSIOLOGY

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Study protocol for a randomized-controlled study on emotion regulation training for adolescents with major depression: the KONNI study

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Word count after revisions: 4.745 (4.315 excluding the Discussion)

Abstract

Introduction: Major depression (MD) often has its onset during adolescence and is associated with significant morbidity and mortality. One important factor for the development and maintenance of adolescent MD are disturbances in emotion regulation and the underlying neural processes. Cognitive reappraisal (CR) is a particular adaptive emotion regulation strategy. Previously, it has been shown in healthy adults that a task-based training in CR is efficient to reduce negative affect, and that these effects translate into everyday life.

This randomized-controlled trial examines for the first time whether a task-based training in CR proves effective in MD adolescents. Specifically, we will investigate whether the CR training improves the ability to down-regulate negative affect in MD individuals as assessed by behavioral and neurobiological indices, and whether training effects generalize outside the laboratory.

Methods and analysis: Adolescents with MD will be randomly allocated to a group that either receives a task-based training in CR or control training. Both involve four training sessions over a time period of two weeks. In the CR training, participants will be instructed to down-regulate negative affective responses to negative pictures via CR, while the control training involves picture viewing. During the training sessions, the Late Positive Potential, gaze fixations on negative picture aspects and affective responses to pictures will be collected. Before and after the training programs, and at a two-week follow-up, overall negative and positive affect, rumination and perceived stress will be assessed as primary outcomes. ANOVAs will be conducted to test the effectiveness of the CR training with regard to both primary outcomes and task-based behavioral and neurobiological parameters.

Ethics and dissemination: The study was approved by the Ethics Committee of the Medical Faculty of the LMU Munich, Germany. The results will be published in peer-reviewed journals and disseminated through conferences, social media and public events.

Trial Registration: Clinical Trials NCT03957850, registered Mai 21st 2019; URL: https://clinicaltrials.gov/ct2/show/NCT03957850.

Strengths and limitations of the study:

- This study is the first to examine the effectiveness of a targeted CR training in youths with major depression.
- A randomized-controlled design is employed including an active control group.
- In addition to behavioral and questionnaire data, objective neurobiological indices will be collected to assess the effectiveness of the CR training.
- If proven effective, the CR training can be a promising and cost-effective approach to complement and enhance the efficacy of established treatments for adolescent MD.
- As the follow-up is limited to two weeks, the long-term effectiveness needs to be explored in future studies.

Introduction

Major depression (MD) is among the most debilitating, costly and common psychiatric disorders worldwide.[1] The risk of suffering from a depressive episode sharply rises during adolescence, with point prevalence rates of up to 7%.[2] Adolescents with MD show deficient emotion regulation (ER),[3] i.e., they have difficulties to modulate emotional responses by initiating appropriate regulatory processes.[4] Disturbances in ER and the underlying neural processes have been suggested to be an important risk factor for the development and maintenance of MD.[3, 5] Thus, the development of training regimens that target deficient ER in MD is an important research avenue.

Cognitive-behavioral therapy (CBT) belongs to the gold standard treatments in juvenile MD. However, less than 50% of MD adolescents respond to CBT and only about one third enter remission after treatment.[6, 7] Given the debilitating consequences of adolescent MD,[8] there is an urgent need to enhance the efficacy of established intervention. Recent findings in adults with MD suggest that an additional training of ER might be a promising approach to improve treatment effects.[9, 10] To date, it remains unclear whether these findings can be transferred to juvenile MD. In this regard, the present study takes a first step and systematically investigates the effects of a focused ER training in adolescent MD.

Cognitive reappraisal in depressed individuals

Cognitive reappraisal (CR) is a frequently studied ER strategy and involves the reinterpretation of a situation such that the emotional response is changed. The habitual use of CR has been shown to relate to good interpersonal functioning and well-being.[11] Questionnaire studies have found that depressive symptoms are associated with less habitual use of CR and more use of maladaptive emotion regulation strategies such as rumination.[12-14] It has been proposed that this habitual pattern in depressed individuals might originate from deficits in the inhibition of negative material which is thought to enhance ruminative thoughts but hampering the effective reappraisal of negative information.[15] To experimentally investigate CR in MD, studies applied a well-established CR paradigm during which participants are instructed to reappraise negative pictures. This regulation condition is compared to an unregulated condition, during which participants are asked to simply attend to negative stimuli. Within

the framework of this paradigm, a number of studies in MD collected behavioral measures of self-reported affect to assess regulation success. Contrary to expectation, some studies found no group differences between depressive and healthy participants in this index of CR.[16, 17] However, these results might be biased due to social desirability which probably obscures group differences. Moreover, complex ER disturbances are unlikely to be captured using simple affect ratings,[18, 19] highlighting the importance of additionally assessing objective and more sensitive parameters when studying CR, including neurobiological indices.

A commonly studied neurobiological index of CR is the Late Positive Potential (LPP). Studies in healthy samples show that the LPP is reduced when individuals are instructed to reappraise unpleasant stimuli compared to attending to unpleasant pictures.[20-22] This decrease is thought to reflect a reduction of the emotional response following CR, which may result from a shift in stimulus meaning.[23, 24] Depressive psychopathology has been shown to be associated with a smaller reduction of the LPP during CR.[23, 25, 26] However, to date, no study has investigated whether this neurobiological disturbance can be normalized by a repeated training of CR.

Besides the LPP, a number of studies in healthy individuals have investigated gaze fixation patterns to gain insight into the mechanisms underlying CR.[27-29] They found that a greater regulation success is paralleled by less gaze fixations directed towards negative picture cues. This suggests that the regulatory effects of CR may partly be attributed to gaze deployment, highlighting the importance of also assessing gaze fixation when examining CR.

Trainability of cognitive reappraisal

Evidence from a randomized controlled trial (RCT) in adult MD suggests that systematically training ER skills in addition to standard CBT improves treatment efficacy.[9, 10] As the ER training of this RCT aimed at enhancing general ER skills and included CR among other ER strategies, the unique contribution of CR remains to be investigated. A recent investigation addressed this issue experimentally in healthy adults,[30] demonstrating that a task-based CR training resulted in less perceived stress in daily life. Beneficial effects of a task-based CR training have recently also been shown in healthy and anxious adolescents.[31] While these results are encouraging, it needs to be examined whether the

findings can be extended to MD samples and whether a CR training results in reductions in depressive symptomatology, including ruminative thoughts. In this context, it has been proposed that CR training improves cognitive control abilities, including the ability to inhibit negative material. As impairments in the ability to inhibit negative information are thought to play a causal role in rumination, training the ability to reappraise negative information should thus reduce ruminative thoughts.[15]

Aim of the study

The aim of the study is to assess whether in MD adolescents, a task-based CR training results in an improved downregulation of negative affective responses as assessed by behavioral and neurobiological indices. Moreover, the study aims to investigate whether the training effects generalize outside the laboratory, i.e., lead to affect-related changes and a reduction in perceived stress and rumination.

It is hypothesized that over the course of the CR training, MD adolescents show improvements in the downregulation of negative affective responses as assessed by task-based behavioral[30] and neurobiological indices. Based on prior research,[30, 31] it is further hypothesized that the CR training results in improvements in affect- and stress-related symptoms in daily life.

Methods and analysis

The study (Public and scientific Title: Cognitive Reappraisal in Adolescents with Major Depression: From Neurobiological Mechanisms to Intervention; German acronym: KONNI) was prospectively registered on ClinicalTrails.gov (NCT03957850) before recruitment start. The study protocol and the template informed consent/assent forms (including two amendments) were approved by the institutional review board of the local ethics committee (Ethics Committee of the Medical Faculty of the LMU Munich, Germany; study ID: 63-16) on 30th January 2019 and are reported in line with the Standard Protocol Items: Recommendations for Interventional Trials Statement (SPIRIT 2013). Important modifications to the study protocol would require an additional amendment, which would have to be approved by the Ethics Committee before implementation. The trial registry (ClinicalTrials.gov) would then be updated.

Design

This interventional study is designed as a short-term randomized controlled, participant-blind clinical superiority trial including two parallel groups of MD adolescents. Participants will be randomly assigned to a group that receives task-based training in CR or to a control training. All participants will take part in one diagnostic assessment (T0), four training sessions (T1-4) over the course of two weeks, and a follow-up two weeks after T4. All questionnaires and test procedures are summarized in Table 1. During the training sessions, task-based indices of CR will be continuously assessed based on behavioral affect ratings and the LPP. Moreover, eye gaze will be recorded during the task-based training. The KONNI study design is depicted in Figure 1.

Participants

Participants aged 12-18 years with a current ICD-10 diagnosis of MD,[32] an IQ of ≥80 and sufficient German language skills will be included. The following exclusion criteria will be applied: acute suicidality, neurological disorders, schizophrenic disorder, pervasive developmental disorder, bipolar disorder, borderline personality disorder, substance dependence disorder and gender dysphoria. Participants with other psychiatric comorbidities are included if MD is the primary diagnosis.

Recruitment

MD adolescents will be primarily recruited from the Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital of the LMU Munich, Germany. Currently untreated MD patients from the waiting list, and in-and outpatients are enrolled in the study. The first participant was enrolled in May 27th, 2019. The planned completion of participant enrollment is in April 2021. Since the start of the study n=15 subjects were enrolled.

Procedure

Adolescents and one parent/legal custodian (for participants <18 years) will be contacted by an experienced study nurse certified in Good Clinical Practice (GCP) and will be informed about the study details, including the fact that the allocation to the training groups will be made based on a predefined

randomization list. All potential study participants and their parents/legal custodians will be approached by the study nurse unless it is known beforehand that the exclusion criteria are met (e.g., acute suicidality, gender dysphoria). If the clinicians of potential participants conclude that the capacity to provide informed consent/assent are not met (e.g., in case of insufficient German skills, cognitive disability or an acute crisis), participants and their parents/legal custodians will not be approached. In case of interest in participation, their written informed consent/assent will be collected. In the written informed consent/assent, participants and their parent/legal custodian are asked for their permission that the data can also be used for an ancillary case-control study on neurobiological underpinnings of ER in MD. The participants and the parent/legal custodian will be blinded regarding allocation to the CR/control training group until study completion and only unblinded prior to study completion if they terminate participation prematurely. At the first session (T0), a diagnostic interview and other baseline measures (see below) will be applied to the adolescent and will last ~2,5 hours. The diagnostic session will be conducted by psychologically trained staff.

If the participant is eligible for the study, the following session appointments will be scheduled and the participant will be randomly allocated to the CR or the control training group. To ensure allocation concealment, the random allocation to one of the groups is implemented after completion of baseline measurements; i.e., neither the recruiter nor the person conducting the baseline session know to which group the participant will be assigned after T0. Access to the allocation list is limited to the principal investigator (E.G.) and her deputy (L.F.), who will inform the experimenters about the allocation of the participant shortly before the first training session (after the diagnostic session and the decision to include the participant in the study). Randomization stratifying for age (<15 years vs. ≥15 years of age)[1] and sex will be performed by a statistician, who is neither involved in recruitment nor in testing of participants. The randomization will be performed with a 1:1 allocation. A follow-up session will take place two weeks after completion of the forth training session. After the follow-up, participants are unblinded regarding group allocation by one of the experimenters. As expense allowance for study participation (~10 hours including follow-up), the participants will receive 100€. Participation is

[1] Based on prior studies in MD adolescents conducted in our department, 15 is the expected approximate median age of MD participants.

voluntary and can be discontinued at any time for any reason. Participation is discontinued in case of acute suicidality during the study. No other criteria for discontinuation are defined. To assess the feasibility of conducting a large-scale multi-center RCT on the effects of a CR training in addition to standard treatment, the following data will be collected and reported: participation and non-participation rate, drop-outs and reasons for drop-outs, training attendance rates and spontaneously reported adverse effects.Treatment fidelity concerning the training is assured by standardized oral and written instructions and by comprehensive training of the experimenters. The experimenters will be either clinical psychologists or advanced and in-depth trained psychology students. The concomitant treatment as usual is permitted during the ongoing study and information on the type of treatment during the study will be assessed. Moreover, patient safety data will be assessed by recording any spontaneously reported adverse effects.

Cognitive Reappraisal Training

The CR training task is well-established and is adapted from previous studies,[22, 33-35] including a study from our group, in which we demonstrated that adolescents with MD understand and comply with task instructions, and are able to down-regulate negative affective responses to negative pictures via CR.[36] The training procedure was adapted from [30]. An exemplary illustration of an experimental trial is depicted in Figure 2. Participants will be presented emotional pictures which are preceded by a condition specific cue signaling the appropriate strategy (attend vs. reappraise) during picture presentation. Following each picture, participants are instructed to indicate their affective response to the image on the portrait version of the nine-point self-assessment manikin scale for valance [SAM; 37, for the portrait version see 38, 39], which has been frequently applied in youth samples.[40, 41] A higher score on this scale indicates a more positive valence rating. The task involves four conditions: 1) **Negative-reappraise:** participants are asked to view negative pictures and to decrease their affective response by reappraising the negative event. Participants are explicitly instructed to use the reinterpretation tactic during CR, which involves "mentally changing the meaning of the actions, context and/or outcome depicted in a stimulus".[30] 2) **Negative-attend,** 3) **Neutral-attend and** 4) **Positive-attend:** participants are asked to view the pictures and to respond naturally to them without trying to

alter their affective response. Comparison of the negative-reappraise and the negative-attend conditions allows assessing behavioral and neural indices of reappraisal success. The neutral-attend and the positive-attend conditions are included to avoid slight changes in negative affect due to the exclusive presentation of unpleasant pictures.[42]

The training task will be repeated over four training sessions. Before the first session, participants will complete a comprehensive practice training, during which a trained experimenter will provide standardized oral instructions regarding the task and the two strategies (attend, reappraise).[30, 36] Thereafter, walk-through images are presented to confirm the appropriate use of the strategies. Task instructions will be briefly summarized before each training session.

In each training session, 144 pictures will be presented in 3 blocks, each containing 12 positive-attend, 12 neutral-attend, 12 negative-attend, and 12 negative-reappraise trials. Developmentally appropriate pictures (e.g., excluding pictures of dead persons or pornographic images) are taken from the International Affective Picture System,[IAPS; 43] Besançon Affective Picture Set-Adolescents,[BAPS-Ado; 44] and Besançon Affective Picture Set-Adults,[BAPS-Adult; 45] with the latter two sets being derived from the Besançon Attachment Pictures Set. Each picture will be presented twice over the course of the training.[30] To ensure adherence to task instructions, participants will fill in a questionnaire after each training session to indicate which strategies they used during the task.

Control training

The control training is implemented to account for unspecific effects and the task employed is similar to the CR task except that it involves no "negative-reappraise" condition. Instead, the control task only involves attend conditions (negative-attend, neutral-attend, positive-attend). To keep the total number of trials involving negative pictures constant across the two groups, the control task involves twice as many negative-attend trials as the CR training group. Mirroring the CR training procedure, the control training is repeated over four sessions and preceded by standardized oral instructions and a practice session. Participants of the control training group will also fill in a questionnaire on how they resolved the task after each training session.

Measures

Information about psychometric properties of all measures described in the following paragraph are summarized in Table 1 along with the respective assessments points.

Diagnostic measures

A diagnosis of MD and potential comorbidities will be assessed using a well-established German standardized semi-structured diagnostic interview (Kinder-DIPS).[46, 47] The interview will be administered by experienced, psychologically trained experimenters. To assess inter-rater reliability based on Cohen´s kappa (k), 10% of the Kinder-DIPS interviews will be rated by two experimenters. IQ will be estimated based on the first part of the CFT-20-R.[48] For some patients, results from other established IQ tests [e.g. WISC-V; 49] will be available from routine care, which will be used instead.

Outcome measures

Primary outcomes

The primary outcomes of the study are (1) change in rumination from baseline (T0) to post-training (directly after T4) and follow-up [assessed by the scales "self-focused rumination" and "symptom-focused rumination" of the German short version of the Response Styles Questionnaire; RSQ-D; 50]; (2) change in depressive symptoms [assessed by the German version of the Beck Depression Inventory – Second Edition; BDI-II; 51] from baseline (T0) to post-training (directly after T4); (3) change in perceived stress over the course of the four training sessions and at follow-up [assessed by the German translation of the Perceived Stress Scale 10; PSS-10; by Prof. Dr. Arndt Büssing; 52][2]; (4) changes in negative and positive affect [assessed by the Negative Affect Scale and Positive Affect Scale for Children Shortened Version; PANAS-C-SF; 53] over the course of the four training sessions and at follow-up.

Secondary outcomes

[2]In the PSS-10, items were reworded to “in the past few days” instead of “in general” to better allow assessing changes of the course of the training.

One secondary outcome is the change in the downregulation of affective behavioral responses to negative pictures by means of CR. Affective behavioral responses to negative pictures will be continuously assessed during each of the four training sessions using the SAM rating scale.[37, with the portrait version from 38, 39]

Another secondary outcome is the change in the downregulation of the early and late LPP amplitude to negative pictures by means of CR. The LPP elicited to pictures in the negative-attend and the negative-reappraise condition will be continuously assessed during each of the four training sessions. Additionally, changes in the percent duration of gaze fixations within a-priori defined emotional interest areas of negative pictures[3] will be assessed during both the negative-attend and negative-reappraise condition over the course of the four training sessions.

All secondary outcome measures will only be assessed in the CR training group, as participants in the control training group are not instructed to apply CR. However, these measures will also be assessed in the control training group during the negative-attend condition to allow additional exploratory analyses.

Confounding variable

Participants will complete the Social Desirability Scale.[SES-17; 54] The rationale for assessing this confounding variable is that behavioral ratings of affective responses to pictures will be assessed, which are prone to response biases.[18]

Mediators

State rumination during the training will be treated as a potential mediator as ruminative thoughts might hamper beneficial training effects.[55] After completion of each training session, participants in the CR and control training group rate state rumination during the task on a scale from 0 “not at all” to 10 “exactly” based on a 5-item questionnaire applied in a previous study.[56]

We will also assess a potential mediating role of executive function abilities, which are thought to be critically involved in ER.[57] Individual baseline differences in executive function abilities might thus

[3]Emotional areas of interest of negative pictures will be defined based on a separate validation study.

prove important mediators of training outcome. Therefore, set-shifting, working memory and inhibition [58, 59] as the three core components of executive functions will be assessed based on the TAP 2.3.[Testbatterie zur Aufmerksamkeitspruefung; 60]

Moreover, we will treat habitual ER as a potential mediator, which will be assessed based on the FEEL-KJ [61]. The FEEL-KJ is a self-report questionnaire assessing habitual adaptive and maladaptive ER strategies.

Moderators

As anxiety disorders/symptoms frequently co-occur with MD,[62] state and trait anxiety will be assessed based on the State-Trait-Anxiety Inventory (STAI).[63] Moreover, symptoms of psychopathology will be screened using the Child Behavior Checklist (CBCL 6-18R).[64] Both variables will be treated as potential moderators.

Eye-tracking apparatus

During the four training sessions, eye-movements will be continuously recorded using the Eyelink 1000 Plus SR Research eye-tracker. At the beginning of the training, participants are seated at the viewing distance of approx. 55 cm from the monitor and a 9-point calibration is performed. Prior to each experimental trial, a drift correction is conducted.

Electroencephalogram recording and preprocessing

The electroencephalogram data is recorded using the Electrical Geodesic Inc. 128-channel system with 500 Hz sampling rate and Cz as reference electrode. Impedance is kept below 50 kΩ during recording. The further preprocessing and analyses steps will be performed with Brainvision Analyzer 2.1 (Brain Products GmbH, Germany). After filtering, removal of electro-oculographic artefacts based on Independent Component Analysis and exclusion of other artefacts, the signal will be re-referenced. Data will be segmented into epochs, baseline-corrected and averaged separately for each participant and condition. The LPP will be measured as the mean amplitude at a centro-parietal region-of-interest within early (<300ms) and late time windows (≥300 ms) following picture onset.[33, 65]

Data management and confidentiality

All data will be entered electronically in IBM SPSS statistics by a scientific assistant. Plausibility and completeness checks will be regularly performed by E.G., L.F., C.P. to promote and monitor data quality. Original documents will be maintained for 15 years in the department. All original and electronic data is stored on the hospitals server under a pseudorandomized coded ID, which does not contain names or birth dates of the participants. Only the project leader and her deputies have access to the participants' names and the corresponding allocation to the encryption code and the original documents, which are kept in locked cabinets. The records containing names and other personal identifiers (e.g., informed consent/assent forms) will be stored in locked cabinets separately from the study records which are identified by the coded ID. The participants' study information will not be released outside the study, except in case of threat to self or threat to others. The final cleaned data sets will be provided to all investigators of the study. To adhere to principles of open science and to facilitate further use of aggregated data in meta-analytic approaches, we will consider making raw data available to other researchers if this can be achieved along with protecting sensitive patient information, such as sociodemographic information. Since patients could possibly be identified by making our raw data publicly available, ethical principles of protecting patient confidentiality would be breached. Aggregated group data can be made available upon request.

Calculation of sample size

A rough approximation of the requested sample size targeted at rumination as one of the primary outcomes can be achieved by referring to a previous study.[66] This study investigated the effects of a task-based cognitive control training compared to treatment as usual in adult MD. The training aimed at improving ER skills indirectly by targeting mechanisms thought to underlie ER. This study reported a large effect size in the training group from pre to post (Cohen's d=1.42) on a measure related to negative affect (rumination). Based on a conservative assumption, a large effect size of d=0.85 is expected with regard to changes in rumination for the CR training from pre to post. For the control training, a small effect size (d=0.2) is expected from pre to post due to unspecific "positive" effects of the control

intervention. This effect size is based on prior evidence[4] on the effects of a similar control training in young adults.[30]

Based on these assumptions, calculation of the required sample size to detect a significant 2(group) x 2(time: T0=pre, T4=post) interaction for rumination using a repeated measures ANOVA with a 5% level of significance (alpha=0.05) and 80% statistical power (1–beta=0.80) revealed an N=47 for the total group (assuming a 0.7 pre-post correlation). The drop-out rate for the study is estimated at approx. 33%. Thus, n=35 adolescents will be enrolled in each group. The necessary sample size was calculated with G*power 3.1. Statistical power of analyses that involve more measurements, such as the analysis of affect, will have more than 80% statistical power if effect sizes are similar.

Statistical analysis

To test the hypotheses that the CR training results in a stronger decrease in depressive symptoms/rumination from baseline to post-training assessment compared to a control training, a mixed-model ANOVA with the factors group (CR vs. control training) and time (T0, T4) will be conducted for the BDI-II and the two RSQ-D scales "self-focused rumination", "symptom-focused rumination". To account for the fact that the RSQ-D will be reassessed at follow-up, a mixed-model ANOVA with the factors group (CR vs. control training) and time (T0, T4, follow-up) will additionally be conducted for the two rumination scales. Mixed modeling (also known as multilevel analysis, with observations "nested" within participants) has the advantage over regular repeated measures ANOVA that all available data can be used, including data from incomplete cases, without using imputation techniques for missing data.[67] To test the hypotheses that the CR training results in a a) stronger decrease in negative and b) stronger increase in positive affect from pre- to post-training and follow-up assessment compared to the control training, mixed-model ANOVAs with the factors group (CR vs. control training) and time (T1, T2, T3, T4, follow-up) will be conducted for the Negative Affect/ Positive Affect scale of the PANAS-C-SF. The same statistical model procedure will be applied for perceived stress (PSS-10).

[4] Detailed statistical information was derived from personal communication with corresponding author of this study; B. Denny, April 26th, 2017.

To test the hypothesis that over the course of the CR training, MD adolescents show an increased downregulation of the early and late LPP amplitude via CR, a mixed-model ANOVA with the factors 2(condition: negative-reappraise, negative-attend) x 4(training session: T1, T2, T3, T4) will be conducted separately for early and late LPP time windows. The same statistical procedure will be conducted for the affective ratings of negative pictures and the percent of gaze fixation duration in emotional areas of negative pictures. Correlation analyses will be performed between the percent of gaze fixation duration in emotional areas of negative pictures and ER success (downregulation of the LPP and affective ratings of negative pictures via CR).

To examine changes of the LPP, affective ratings of negative pictures and gaze fixations for the negative-attend condition in the control training group over the course of the training, additional exploratory ANOVAs will be conducted. Likewise, for the control training group, exploratory correlation analyses will be calculated to examine relationships between these measures and gaze fixation duration in emotional areas of negative pictures. Finally, moderation and mediation analyses will be applied to examine the role of mediating and moderating variables.

Patient and public involvement

Participants or their parents were not involved in designing the study. However, we will present the results of the study to parent and participant representatives to include their suggestions in the dissemination plan. Moreover, parallel to publication of the results, all participants and their families will receive a letter summarizing the main findings and conclusions in comprehensible language.

Discussion

This study will for the first time elucidate whether in adolescents with MD, a CR training shows beneficial effects both in and outside the laboratory. If the training proves effective, this approach might be a promising resource-effective intervention for adolescents with MD. Such an intervention could, e.g., be applied to bridge the often long waiting times for treatment of MD or as an adjunction to a treatment as usual. Moreover, after psychoeducation on CR and guided practice of this strategy in psychotherapy, the training could also be (online) applied as an adjunct to treatment as usual. In such a

context, the psychotherapist could monitor difficulties and progress in the use of CR, and promote the transfer of strategy into everyday life of the patient.

Building on the results from the present RCT, future investigations could additionally consider transfer effects to CR tasks other than the training tasks or to CR abilities in daily life e.g., based on ecological momentary assessment. Moreover, as a next step, it would be worthwhile to assess whether this training might prove effective in patients with other psychiatric disorders which are also characterized by deficient ER abilities, such as anxiety disorders and eating disorders.[68]

A limiting factor of the study is the short follow-up interval of two weeks. Thus, future studies should include a longer follow-up interval to also examine whether the effects of the training are long-lasting. Another limitation is that the study is single-blinded (participant-blinded) concerning the allocation to the CR training vs. control training. This single-blinding procedure entails the risk that the experimenters will transfer their expectations to the participants. However, as the participants will perform a comprehensive practice training that is guided by the experimenter, double-blinding would not be feasible. Finally, it should be stated the present study does not include the ecological momentary assessment of outcome measures. Expanding upon the present study, it would be important to also apply experience sampling methods in future work to be able to draw comprehensive conclusions regarding transfer effects of the CR training to daily live. Despite these caveats, the results of our study will be an important step towards larger scale, multi-center RCTs in MD adolescents to investigate whether a CR training increases the efficacy of standard treatments. Furthermore, the study will elucidate neurobiological changes that occur during training and whether these are linked to changes in training outcome. To this end, our protocol may also aid to identify potential biomarkers for monitoring and predicting treatment success and thereby spark further research into the direction of individualized treatment adaptation based on neurobiological parameters.

Ethics and Dissemination

Written informed consent/assent will be taken by the participating adolescents and their parents/legal custodians. The study protocol and the template informed consent/assent forms were approved (including two amendments) by the institutional review board of the local ethics committee (Ethics Committee of the Medical Faculty of the LMU Munich, Germany; study ID: 63-16) on 30th January 2019.

Study results will be presented at national and international confernces and published in peer-reviewed publications. Moreover, the particiants and their parents will receive a summary of the study results in layman's language.

Abbreviations

BAPS-Ado: Besançon Affective Picture Set-Adolescents; BAPS-Adult: Besançon Affective Picture Set-Adults; BDI-II: Beck depression inventory; CBCL 6-18R: Child Behavior Checklist for the ages 6-18; CFT-20-R (revidierte Grundintelligenztest Skala 2): Culture fair intelligence test; CBT: Cognitive-behavioral therapy; CR: Cognitive reappraisal; DFG (Deutsche Forschungsgemeinschaft): German Research Foundation; FEEL-KJ (Fragebogen zur Erhebung der Emotionsregulation bei Kindern und Jugendlichen): Questionnaire for the assessment of emotion regulation in children and adolescents; IAPS: International Affective Picture System; ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision; IQ: Intelligence Quotient; Kinder-DIPS (Diagnostisches Interview bei psychischen Störungen im Kindes- und Jugendalter): Diagnostic interview for psychiatric disorders for children and adolescents; LMU: Ludwig-Maximilians University; LPP: Late Positive Potential; MD: Major depression; PANAS-C-SF: Negative Affect Scale and Positive Affect Scale for Children Shortened Version for Children Shortened Version; PSS-10: Perceived Stress Scale 10; RSQ-D: German Version of the Response Styles Questionnaire; SAM: self-assessment manikin rating scale; SES-17: Social Desirability Scale; SPIRIT: Standard protocol items: recommendations for interventional trials; STAI: State-Trait-Anxiety Inventory; TAP (Testbatterie zur Aufmerksamkeitsprüfung): Test battery for executive functions; WISC-V: Wechsler Intelligence Scale for Children - Fifth Edition.

Declarations

Consent for publication

This manuscript does not contain any form of individual person's data, all data will be reported based on aggregated group data.

Availability of data and material

The datasets generated and/or analyzed during the current study are not publicly available due to sensitive patient information, such as sociodemographic information, birth date and comorbidities, but aggregated group data can be made available upon request.

Competing interests statement

The authors declare that they have no competing financial or non-financial interests.

Funding

This work was supported by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Grant GR4753/2-1 to E.G. The funding body played no role in the design of the study or writing of the manuscript or the decision to submit the report for publication.

Authors' contributions

EG, LF, GSK and CP contributed to the study design. Data management will be conducted by LF and EG and data analysis and interpretation will be performed by LF, EG, FO, GSK, JB, MSR and CP. EG and LF wrote the study protocol. All authors read and critically revised the draft of the paper and approved the final version of this manuscript.

Acknowledgements

We are grateful to Carolin Zsigo for the assistance during the implementation of the experiment. We wish to thank Petra Wagenbüchler for her assistance in data collection. We further would like to thank Dr. Lauriane Vulliez and Dr. Monika Szymanska for providing BAPS-Ado and BAPS-Adult picture sets.

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References

1. Kessler RC, Bromet EJ. The epidemiology of depression across cultures. Annu Rev Publ Health. 2013;34:119-38.
2. Avenevoli S, Knight E, Kessler RC, Merikangas KR. Epidemiology of depression in children and adolescents. In: Abela JRZ, Hankin BL, editors. Handbook of depression in children and adolescents. New York: Guilford; 2008. p. 6-32.
3. Kovacs M, Yaroslavsky I. Practitioner review: Dysphoria and its regulation in child and adolescent depression. J Child Psychol Psychiatry. 2014;55(7):741-57.
4. Ochsner KN, Gross JJ. The cognitive control of emotion. Trends Cogn Sci. 2005;9(5):242-9.
5. Ahmed SP, Bittencourt-Hewitt A, Sebastian CL. Neurocognitive bases of emotion regulation development in adolescence. Dev Cogn Neurosci. 2015;15:11-25.
6. Compton SN, March JS, Brent D, Albano AM, Weersing VR, Curry J. Cognitive-behavioral psychotherapy for anxiety and depressive disorders in children and adolescents: an evidence-based medicine review. J Am Acad Child Psy. 2004;43(8):930-59.
7. Curry J, Rohde P, Simons A, Silva S, Vitiello B, Kratochvil C, et al. Predictors and moderators of acute outcome in the Treatment for Adolescents with Depression Study (TADS). J Am Acad Child Psy. 2006;45(12):1427-39.
8. Thapar A, Collishaw S, Pine DS, Thapar AK. Depression in adolescence. Lancet. 2012;379(9820):1056-67.
9. Berking M, Ebert D, Cuijpers P, Hofmann SG. Emotion regulation skills training enhances the efficacy of inpatient cognitive behavioral therapy for major depressive disorder: a randomized controlled trial. Psychother Psychosom. 2013;82:234-45.
10. Berking M, Wupperman P, Reichardt A, Pejic T, Dippel A, Znoj H. Emotion-regulation skills as a treatment target in psychotherapy. Behav Res Ther. 2008;46:1230-7.
11. Cutuli D. Cognitive reappraisal and expressive suppression strategies role in the emotion regulation: an overview on their modulatory effects and neural correlates. Front Syst Neurosci. 2014;8:175.
12. Garnefski N, Kraaij V. The cognitive emotion regulation questionnaire: Psychometric Features and Prospective Relationships with Depression and Anxiety in Adults. Eur J Psychol Assess. 2007;23(3):141-9.
13. Joormann J, Gotlib IH. Emotion regulation in depression: relation to cognitive inhibition. Cognition Emotion. 2010;24(2):281-98.
14. Schäfer JÖ, Naumann E, Holmes EA, Tuschen-Caffier B, Samson AC. Emotion regulation strategies in depressive and anxiety symptoms in youth: A meta-analytic review. J Youth Adolescence. 2017;46(2):261-76.
15. Cohen N, Daches S, Mor N, Henik A. Inhibition of negative content - a shared process in rumination and reappraisal. Front Psychol. 2014; 5: 622.
16. Dillon DG, Pizzagalli DA. Evidence of successful modulation of brain activation and subjective experience during reappraisal of negative emotion in unmedicated depression. Psychiatry Res Neuroimaging. 2013;212(2):99-107.
17. Sheline YI, Barch DM, Price JL, Rundle MM, Vaishnavi SN, Snyder AZ, et al. The default mode network and self-referential processes in depression. P Natl Acad Sci. 2009;106(6):1942-7.
18. Zilverstand A, Parvaz MA, Goldstein RZ. Neuroimaging cognitive reappraisal in clinical populations to define neural targets for enhancing emotion regulation. A systematic review. Neuroimage. 2017;151:105-16.
19. Greimel E, Schulte-Ruether M, Fink GR, Piefke M, Herpertz-Dahlmann B, Konrad K. Development of neural correlates of empathy from childhood to early adulthood: an fMRI study in boys and adult men. J Neural Transm. 2010;117(6):781-91.
20. DeCicco JM, O'Toole LJ, Dennis TA. The late positive potential as a neural signature for cognitive reappraisal in children. Dev Neuropsychol. 2014;39(7):497-515.

21. Moser JS, Krompinger JW, Dietz J, Simons RF. Electrophysiological correlates of decreasing and increasing emotional responses to unpleasant pictures. Psychophysiology. 2009;46:17-27.
22. Paul S, Simon D, Kniesche R, Kathmann N, Endrass T. Timing effects of antecedent-and response-focused emotion regulation strategies. Biol Psychol. 2013;94(1):136-42.
23. Dennis TA, Hajcak G. The late positive potential: a neurophysiological marker for emotion regulation in children. J Child Psychol Psyc. 2009;50(11):1373-83.
24. Wessing I, Rehbein MA, Romer G, Achtergarde S, Dobel C, Zwitserlood P, et al. Cognitive emotion regulation in children: reappraisal of emotional faces modulates neural source activity in a frontoparietal network. Dev Cogn Neurosci. 2015;13:1-10.
25. Bylsma LM. Emotional Reactivity and Regulation in Current and Remitted Depression: An Event Related Potential Study [Dissertation]: University of South Florida; 2012.
26. Kudinova AY, Owens M, Burkhouse KL, Barretto KM, Bonanno GA, Gibb BE. Differences in emotion modulation using cognitive reappraisal in individuals with and without suicidal ideation: An ERP study. Cognition Emotion. 2016;30(5):999-1007.
27. Bebko GM, Franconeri SL, Ochsner KN, Chiao JY. Attentional deployment is not necessary for successful emotion regulation via cognitive reappraisal or expressive suppression. Emotion. 2014;14(3):504-12.
28. Manera V, Samson AC, Pehrs C, Lee IA, Gross JJ. The eyes have it: The role of attention in cognitive reappraisal of social stimuli. Emotion. 2014;14(5):833-9.
29. Strauss GP, Ossenfort KL, Whearty KM. Reappraisal and distraction emotion regulation strategies are associated with distinct patterns of visual attention and differing levels of cognitive demand. Plos One. 2016;11(11):e0162290.
30. Denny BT, Ochsner KN. Behavioral effects of longitudinal training in cognitive reappraisal. Emotion. 2014;14(2):425-33.
31. De Witte NA, Sütterlin S, Braet C, Mueller SC. Psychophysiological correlates of emotion regulation training in adolescent anxiety: Evidence from the novel PIER task. J Affect Disord. 2017;214:89-96.
32. World Health Organization. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines: Geneva: World Health Organization; 1992.
33. Schönfelder S, Kanske P, Heissler J, Wessa M. Time course of emotion-related responding during distraction and reappraisal. SCAN. 2014;9(9):1310-9.
34. Paul S, Simon D, Endrass T, Kathmann N. Altered emotion regulation in obsessive-compulsive disorder as evidenced by the late positive potential. Psychol Med. 2016;46(1):137-47.
35. Sarlo M, Ubel S, Leutgeb V, Schienle A. Cognitive reappraisal fails when attempting to reduce the appetitive value of food: an ERP study. Biol Psychol. 2013;94(3):507-12.
36. Greimel E, Piechaczek C, Schulte-Rüther M, Feldmann L, Schulte-Körne G. The role of attentional deployment during distancing in adolescents with major depression. BRAT. 2020;126:103554.
37. Bradley MM, Lang PJ. Measuring emotion: the self-assessment manikin and the semantic differential. J Behav Ther Exp Psy. 1994;25(1):49-59.
38. Suk H-J. Color and Emotion-a study on the affective judgment across media and in relation to visual stimuli [Dissertation]: Universität Mannheim; 2006.
39. Lang PJ. Behavioral treatment and bio-behavioral assessment: Computer applications. In: Sidowski JB, Johnson JH, Williams TA, editors. Technology in mental health care delivery systems. Norwood, NJ: Ablex; 1980. p. 119-37.
40. Musser ED, Galloway-Long HS, Frick PJ, Nigg JT. Emotion regulation and heterogeneity in attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2013;52(2):163-71.e2.
41. Reichel VA, Schneider N, Grünewald B, Kienast T, Pfeiffer E, Lehmkuhl U, et al. “Glass fairies” and “bone children”: Adolescents and young adults with anorexia nervosa show positive reactions towards extremely emaciated body pictures measured by the startle reflex paradigm. Psychophysiology. 2014;51(2):168-77.

42. Patrick CJ, Lavoro SA. Ratings of emotional response to pictorial stimuli: Positive and negative affect dimensions. Motiv Emotion. 1997;21(4):297-321.
43. Lang PJ, Bradley MM, Cuthbert BN. International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-8. Gainesville, FL: University of Florida; 2008.
44. Szymanska M, Monnin J, Noiret N, Tio G, Galdon L, Laurent E, et al. The Besancon affective picture set-adolescents (the BAPS-Ado): development and validation. Psychiatry Res. 2015;228(3):576-84.
45. Szymanska M, Comte A, Tio G, Vidal C, Monnin J, Smith CC, et al. The Besançon affective picture set-adult (BAPS-Adult): Development and validation. Psychiatry Res. 2019;271:31-8.
46. Margraf J, Cwik JC, Pflug V, Schneider S. Structured clinical interviews for mental disorders across the lifespan: Psychometric quality and further developments of the DIPS Open Access interviews. [Strukturierte klinische Interviews zur Erfassung psychischer Störungen über die Lebensspanne: Gütekriterien und Weiterentwicklungen der DIPS-Verfahren.]. Z Klin Psychol Psychopathol Psychother. 2017;46(3):176-86.
47. Margraf J, Cwik JC, Suppiger A, Schneider S. DIPS Open Access: Diagnostic Interview for Mental Disorders. [DIPS Open Access: Diagnostisches Interview bei psychischen Störungen.] Bochum: Mental Health Research and Treament Center; 2017.
48. Weiß RH. CFT 20-R, Grundintelligenztest Skala 2 - Revision (2. Auflage)2019.
49. Wechsler D. Wechsler Intelligence Scale for Children–Fifth Edition (WISC-V). Frankfurt/Main, Nürnberg, Leipzig: Pearson; 2017.
50. Kühner C, Huffziger S, Nolen-Hoeksema S. Response Styles Questionnaire-Deutsche Version: RSQ-D; Manual: Hogrefe; 2007.
51. Hautzinger M, Keller F, Kühner C. Das Beck Depressionsinventar II. Deutsche Bearbeitung und Handbuch zum BDI-II. Frankfurt am Main: Harcourt Test Services; 2006.
52. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24(4):385-96.
53. Ebesutani C, Regan J, Smith A, Reise S, Higa-McMillan C, Chorpita BF. The 10-Item Positive and Negative Affect Schedule for Children, Child and Parent Shortened Versions: Application of Item Response Theory for More Efficient Assessment. J Psychopathol Behav. 2012;34(2):191-203.
54. Stöber J. Die Soziale-Erwünschtheits-Skala-17 (SES-17): Entwicklung und erste Befunde zu Reliabilität und Validität. Diagnostica. 1999;45(4):173-7.
55. Koster EH, De Lissnyder E, Derakshan N, De Raedt R. Understanding depressive rumination from a cognitive science perspective: The impaired disengagement hypothesis. Clin Psychol Rev. 2011;31(1):138-45.
56. Sanchez-Lopez A, Everaert J, Van Put J, De Raedt R, Koster EHW. Eye-gaze contingent attention training (ECAT): Examining the causal role of attention regulation in reappraisal and rumination. Biol Psychol. 2019;142:116-25.
57. Cohen N, Ochsner KN. From surviving to thriving in the face of threats: the emerging science of emotion regulation training. Curr Opin Behav Sci. 2018;24:143-55.
58. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex “frontal lobe” tasks: A latent variable analysis. Cognitive Psychol. 2000;41(1):49-100.
59. Friedman NP, Miyake A, Young SE, DeFries JC, Corley RP, Hewitt JK. Individual differences in executive functions are almost entirely genetic in origin. J Exp Psychol Gen. 2008;137(2):201-25.
60. Zimmermann P, Fimm B. TAP Testbatterie zur Aufmerksamkeitsprüfung Version 2.3: Vera Fimm, Psychologische Testsysteme; 2012.
61. Grob A, Smolenski C. Fragebogen zur Erhebung der Emotionsregulation bei Kindern und Jugendlichen (FEEL-KJ). 2. Aktualisierte und ergänzte Auflage. Bern: Huber Verlag; 2009.
62. Axelson DA, Birmaher B. Relation between anxiety and depressive disorders in childhood and adolescence. Depress Anxiety. 2001;14(2):67-78.

63. Laux L, Glanzmann P, Schaffner P, Spielberger C. Das State-Trait-Angstinventar Weinheim, Germany: Beltz; 1981.
64. Döpfner M, Achenbach TM, Plück J, Kinnen C, Plück J. CBCL/6-18R-TRF/6-18R-YSR/11-18R: Deutsche Schulalter-Formen der Child Behavior Checklist von Thomas M. Achenbach: Elternfragebogen über das Verhalten von Kindern und Jugendlichen (CBCL/6-18R), Lehrerfragebogen über das Verhalten von Kindern und Jugendlichen (TRF/6-18R), Fragebogen für Jugendliche (YSR/11-18R). Göttingen: Hogrefe; 2014.
65. Moran TP, Jendrusina AA, Moser JS. The psychometric properties of the late positive potential during emotion processing and regulation. Brain Res. 2013;1516:66-75.
66. Siegle GJ, Price RB, Jones NP, Ghinassi F, Painter T, Thase ME. You gotta work at it: Pupillary indices of task focus are prognostic for response to a neurocognitive intervention for rumination in depression. Clin Psychol Sci. 2014;2(4):455-71.
67. Murrar S, Brauer M. Mixed model analysis of variance. In: Frey BB, editor. The SAGE encyclopedia of educational research, measurement, and evaluation. Thousand Oaks: SAGE Publications, Inc.; 2018. p. 1075-8.
68. Aldao A, Nolen-Hoeksema S, Schweizer S. Emotion-regulation strategies across psychopathology: A meta-analytic review. Clin Psychol Rev. 2010;30(2):217-37.
69. Adornetto C, In-Albon T, Schneider S. Diagnostik im Kindes-und Jugendalter anhand strukturierter Interviews: Anwendung und Durchführung des Kinder-DIPS. Klin Diagnostik u Evaluation. 2008;1(4):363-77.
70. Dolle K, Schulte-Körne G, O'Leary AM, von Hofacker N, Izat Y, Allgaier A-K. The Beck Depression Inventory-II in adolescent mental health patients: Cut-off scores for detecting depression and rating severity. Psychiat Research. 2012;200(2-3):843-8.
71. Stockings E, Degenhardt L, Lee YY, Mihalopoulos C, Liu A, Hobbs M, et al. Symptom screening scales for detecting major depressive disorder in children and adolescents: a systematic review and meta-analysis of reliability, validity and diagnostic utility. J Affect Disorders. 2015;174:447-63.
72. Löwe B, Kroenke K, Gräfe K. Detecting and monitoring depression with a two-item questionnaire (PHQ-2). J Psychosom Res. 2005;58(2):163-71.
73. Klein EM, Brähler E, Dreier M, Reinecke L, Müller KW, Schmutzer G, et al. The German version of the Perceived Stress Scale–psychometric characteristics in a representative German community sample. BMC Psychiatry. 2016;16:159.
74. Conway M, Csank PA, Holm SL, Blake CK. On assessing individual differences in rumination on sadness. J Pers Assess. 2000;75(3):404-25.
75. Stöber J. The Social Desirability Scale-17 (SDS-17): Convergent validity, discriminant validity, and relationship with age. Eur J Psychol Assess. 2001;17(3):222-32.

Table 1. Overview over diagnostic measures and all variables of the study

Function	Measure	Instrument	Reliability/Validity	T0 Baseline/ Diagnostics	T1	T2	T3	T4	2-week Follow-up
Diagnostic	Diagnosis	Kinder-DIPS (A)	Retest-Reliability for depressive disorders=.95 (Kappa) for the predecessor version of the Kinder-Dips for DSM-IV diagnoses in children and adolescents[69]	X					
	Intelligence quotient (IQ)	CFT-20-R (A) (part 1)	Cronbach's α=.92 for the first part in children, adolescents and adults[48]	X					
Primary Outcome	Depressive Symptoms	BDI-II (A)	Cronbach's α=.94 in an adolescent population[70]; pooled estimate for internal reliability: .86; discriminative validity - pooled estimate for sensitivity and specifity: .81; based on meta-analytic data in non-clinical and clincal child and adolescent populations[71]	X				X	
	Negative and positive Affect	PANAS-C-SF (A)	Cronbach's α=.86 for positive affect scale and Cronbach's α=.82 for negative affect scale; divergent validity - correlation between positive and negative affect scales: -.13; based on data in an adolescent population[53]		X	X	X	X	X
	Perceived Stress	PSS-10 (A)	Cronbach's α=.84; construct validity of .59 with the PHQ-2 [Patient Health Questionnaire; 72]; based on a sample of adolescents and adults for the original version of the PSS-10[73]		X	X	X	X	X
	Rumination	RSQ-D (A)	Cronbach's α=.77 for self-focused rumination scale and Cronbach's	X				X	X

			α=.88 for symptom-focused rumination; convergent validity of .52 for symptom-focused rumination and .72 for self-focused rumination with the RSS [Rumination on Sadness Scale; 74]; based on depressed adult patients[50]						
Secondary Outcome	Affective behavioral responses to pictures	SAM Rating Scale (A) of valence	Cronbach´s α for SAM ratings of the stimuli applied in the current study will be calculated based on the present sample		X	X	X	X	
	LPP (Late Positive Potential)	(A)	n.a.		X	X	X	X	
	Gaze fixations in emotional areas of interest	(A)	n.a.		X	X	X	X	
Confounding Variables	Social Desirability	SES-17 (A)	Cronbach's α=.78 in a young adult population[54, 75]	X					
Mediators	State rumination during training	Questionnaire (A) applied in A Sanchez-Lopez, J Everaert, J Van Put, R De Raedt and EHW Koster [56]	Cronbach´s α=.72 to .73; based on data in a young adult population[56]		X	X	X	X	
	Habitual emotion regulation strategies	FEEL-KJ (A)	Cronbach's α=.93 for Adaptive emotion regulation scale and Cronbach's α=.82 for Maladaptive emotion regulation scale in children and adolescents[61]	X					
	Executive Function abilities (Set shifting, Working Memory, Inhibition)	TAP 2.3 (A)	Odd–even– Reliability for reaction times in adolescents: .791 for working memory, .952 for flexibility, .911 for Go/nogo for trials applied in the current study[60]	X					

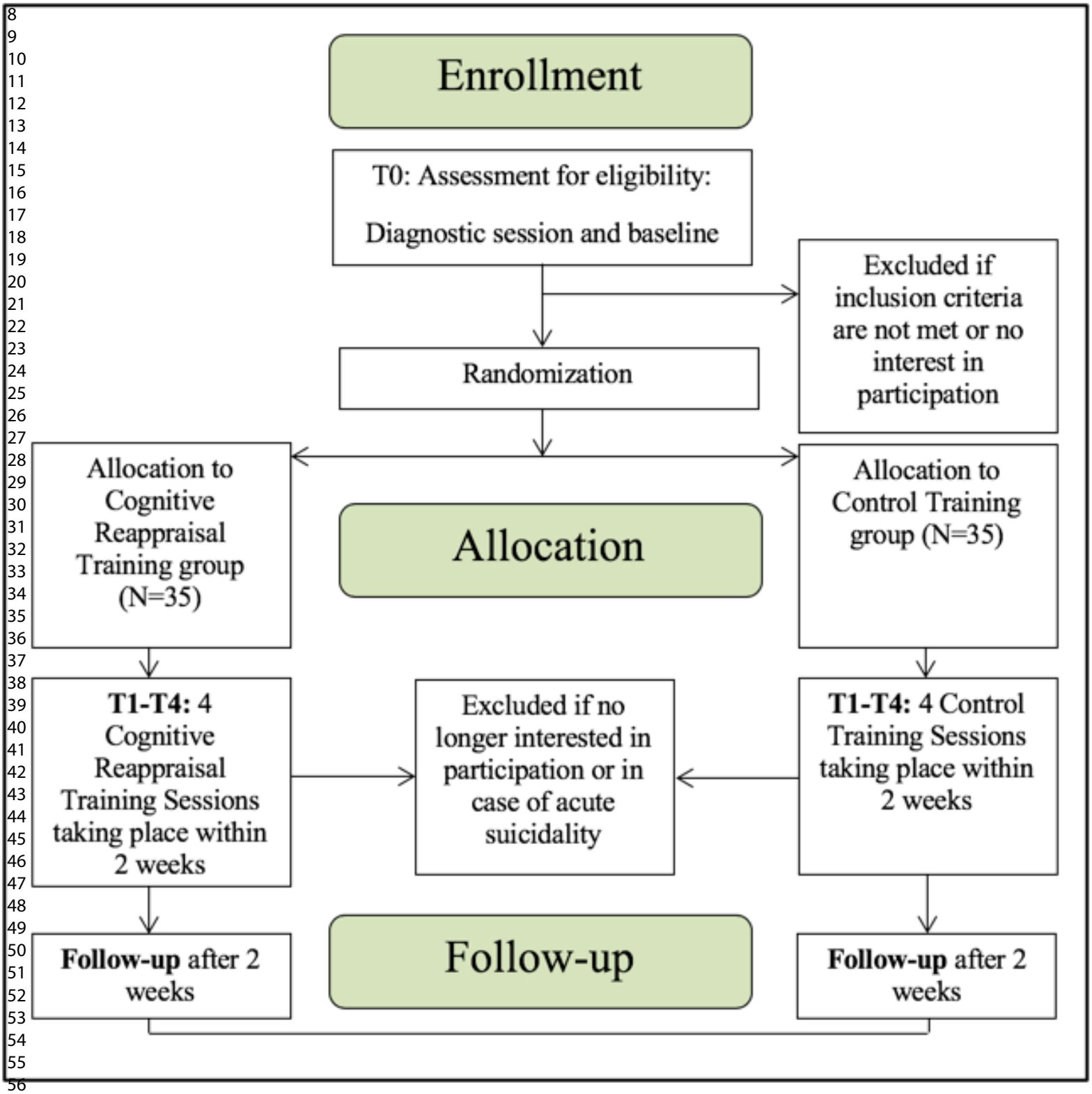
Moderators	Trait and state anxiety	STAI (A)	Cronbach's α=.91 for STAI-S scale and Cronbach's α≥.89 for STAI-T scale in adolescents/young adults[63]	X					
	Psychopathology	CBCL 6-18R (P)	Cronbach's α=.93 for total behavior problem scale based on a sample of children and adolescents[64]	X					

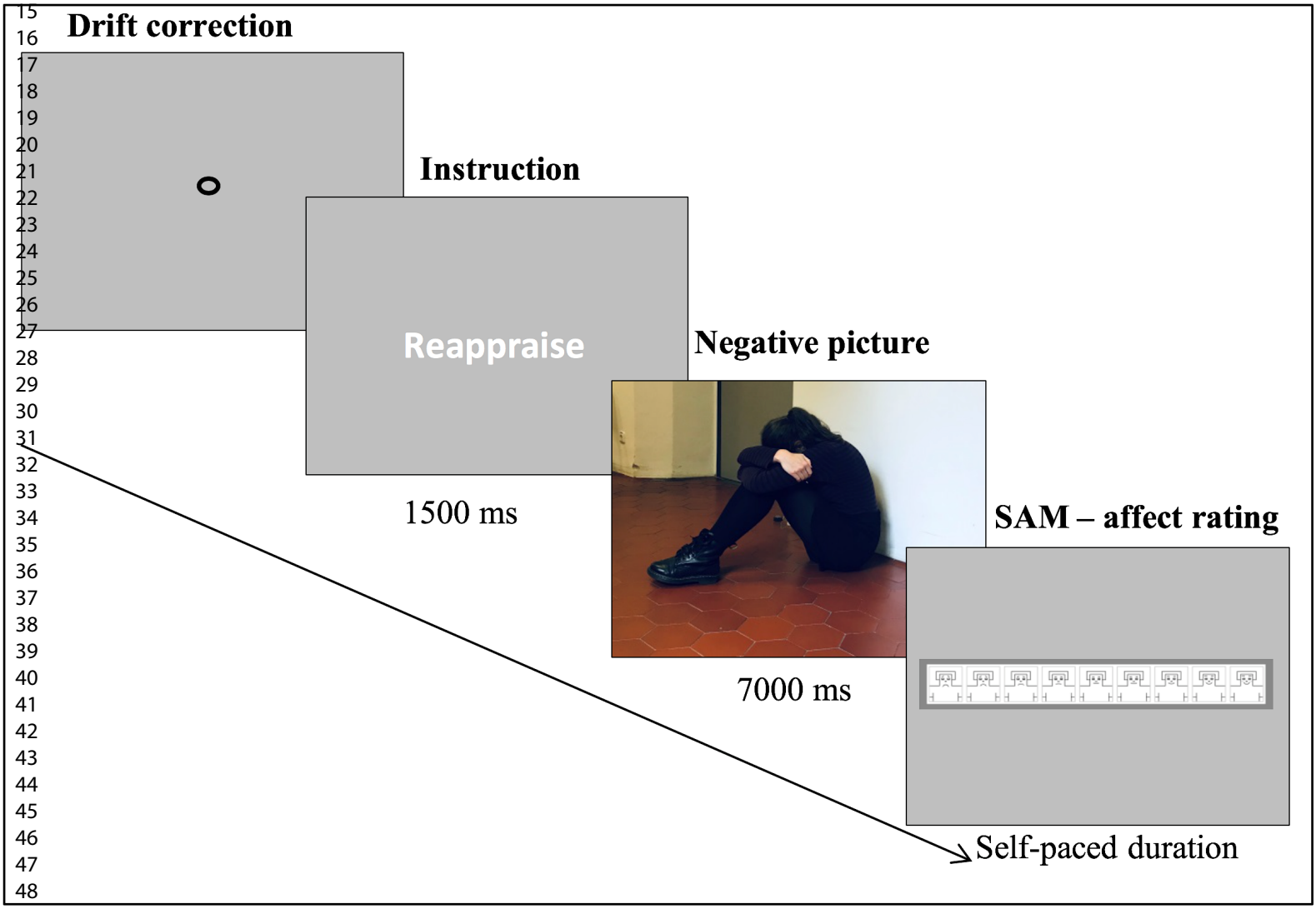
Note. Applied to A=Adolescent P=Parent; Abbreviatons: Kinder-DIPS (Diagnostisches Interview bei psychischen Störungen im Kindes- und Jugendalter): Diagnostic interview for psychiatric disorders for children and adolescents; CFT-20-R (revidierte Grundintelligenztest Skala 2): Culture fair intelligence test; BDI-II: Beck depression inventory; PANAS-C-SF: Negative Affect Scale and Positive Affect Scale for Children Shortened Version for Children Shortened Version; PSS-10: Perceived Stress Scale 10; RSQ-D: German Version of the Response Styles Questionnaire; SAM: self-assessment manikin rating scale; n.a.: not applicable; SES-17: Social Desirability Scale; FEEL-KJ (Fragebogen zur Erhebung der Emotionsregulation bei Kindern und Jugendlichen): Questionnaire for the assessment of emotion regulation in children and adolescents; TAP (Testbatterie zur Aufmerksamkeitsprüfung): Test battery for executive functions; STAI: State-Trait-Anxiety Inventory; CBCL 6-18R: Child Behavior Checklist for the ages 6-18.

Figure Legends

Figure 1. Overview of the KONNI study design

Figure 2. Experimental time course. Exemplary illustration of a trial belonging to the CR training (negative-reappraise condition). The picture shown is exemplary and not part of the picture databases used in the study. Abbreviations: SAM: self-assessment manikin rating scale (as a portrait version).


Enrollment
T0: Assessment for eligibility:
Diagnostic session and baseline
Excluded if inclusion criteria are not met or no interest in participation
Randomization
Allocation to Cognitive Reappraisal Training group (N=35)
Allocation
Allocation to Control Training group (N=35)
T1-T4: 4 Cognitive Reappraisal Training Sessions taking place within 2 weeks
Excluded if no longer interested in participation or in case of acute suicidality
T1-T4: 4 Control Training Sessions taking place within 2 weeks
Follow-up after 2 weeks
Follow-up
Follow-up after 2 weeks


Drift correction
Instruction
Reappraise
1500 ms
Negative picture
7000 ms
SAM – affect rating
Self-paced duration

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **(p. 1 Title)**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **(p. 2 "Trial Registration")**
	2b	All items from the World Health Organization Trial Registration Data Set **(throughout the entire study protocol)**
Protocol version	3	Date and version identifier **(n.a., first version of the protocol)**
Funding	4	Sources and types of financial, material, and other support **(p. 18, section "funding")**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **(p. 18, section "author's contributions")**
	5b	Name and contact information for the trial sponsor **(p. 18, section "trial sponsor")**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities **(p. 18, section "funding")**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) **(n.a.)**
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **(pp. 3-5; sections: "Introduction", "Cognitive reappraisal in depressed individuals", "Trainability of cognitive reappraisal", "Aim of the study")**

	6b	Explanation for choice of comparators **(p. 9, section "Control training")**
Objectives	7	Specific objectives or hypotheses **(p. 5, section "Aim of the study")**
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **(p. 6, section "Design")**
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **(p. 6, section "Recruitment")**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **(pp. 6-7, sections "Participants", "Procedure")**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **(pp. 8-9, sections "Cognitive Reappraisal Training", "Control Training")**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **(pp. 7-8, section "Procedure"; Fig. 1)**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **(p. 9, section "Cognitive Reappraisal Training")**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **(p. 8, section "Procedure")**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **(p. 10, sections "Primary outcomes", "Secondary outcomes")**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) **(Table 1; Fig. 1)**

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **(pp. 12-13, section "Calculation of sample size")**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **(p. 6, section "Recruitment")**

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **(pp. 6-7, section "Procedure")**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned **(pp. 6-7, section "Procedure")**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **(pp. 6-7, section "Procedure")**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **(p. 7, section "Procedure")**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **(p. 7, section "Procedure")**

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **(pp. 8-10, sections Cognitive Reappraisal Training", "Control training" "Diagnostic measures"; Table 1)**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **(p. 7-8, section "Procedure")**

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **(p. 13, section "Data management and confidentiality")**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **(pp. 14-15, section "Statistical analysis")**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **(p. 15, section "Statistical analysis")**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **(p. 14, section "Statistical analysis")**
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **(n.a. A data monitoring is not needed as the training (cognitive reappraisal training) and the control training are expected to carry no risks.)**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **(n.a., As the training (cognitive reappraisal training) and the control training are expected to carry no risks, there are no stopping guidelines and interims analyses planned.)**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **(p. 8, Section "Procedure")**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **(n.a.)**
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **(p. 17, section "Ethics approval")**

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **(p. 5, section "Methods and analysis")**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **(p. 6, section "Procedure")**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **(pp. 6-7, section "Procedure")**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial **(p. 13, section "Data management and confidentiality")**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **(p. 18, section "Competing interests")**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators **(p. 13, section "Data management and confidentiality")**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **(n.a.)**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **(p. 2, section "Ethics and Dissemination")**
	31b	Authorship eligibility guidelines and any intended use of professional writers **(n.a., no intended use of professional writers; author's contribution are summerized on p. 18)**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical **(p. 18, section "Availability of data and material")**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **(n.a., documents in German)**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **(n.a.)**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.