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Augmenting neurocognitive remediation therapy to Preventive Cognitive Therapy for partially remitted depressed patients: protocol of a pragmatic multicentre randomised controlled trial

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ABSTRACT

Introduction Major depressive disorder (MDD) affects 163 million people globally every year. Individuals who experience subsyndromal depressive symptoms during remission (ie, partial remission of MDD) are especially at risk for a return to a depressive episode within an average of 4 months. Simultaneously, partial remission of MDD is associated with work and (psycho)social impairment and a lower quality of life. Brief psychological interventions such as preventive cognitive therapy (PCT) can reduce depressive symptoms or relapse for patients in partial remission, although achieving full remission with treatment is still a clinical challenge. Treatment might be more effective if cognitive functioning of patients is targeted as well since cognitive problems are the most persisting symptom in partial remission and predict poor treatment response and worse functioning. Studies show that cognitive functioning of patients with (remitted) MDD can be improved by online neurocognitive remediation therapy (oNCRT). Augmenting oNCRT to PCT might improve treatment effects for these patients by strengthening their cognitive functioning alongside a psychological intervention.

Methods and analysis This study will examine the effectiveness of augmenting oNCRT to PCT in a pragmatic national multicentre superiority randomised controlled trial. We will include 115 adults partially remitted from MDD with subsyndromal depressive symptoms defined as a Hamilton Depression Rating Scale score between 8 and 15. Participants will be randomly allocated to PCT with oNCRT, or PCT only. Primary outcome measure is the effect on depressive symptomatology over 1 year. Secondary outcomes include time to relapse, cognitive functioning, quality of life and healthcare costs. This first dual approach study of augmenting oNCRT to PCT might facilitate full remission in partially remitted individuals as well as prevent relapse over time.

Ethics and dissemination Ethical approval was obtained by Academic Medical Center, Amsterdam. Outcomes will be made publicly available.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Strengths are the national, pragmatic, multicentre, superiority randomised controlled trial design, with measurements focusing on various levels of patient functioning, where the outcome assessors are blinded to treatment allocation of the participants.
⇒ In our multimodal approach, we provide the patients who are partially remitted from a major depressive episode with preventive cognitive therapy with online neurocognitive remediation therapy, or only preventive cognitive therapy.
⇒ A limitation is that the study is single blinded and focuses on a specific group of patients.

Trial registration number NL9582.

INTRODUCTION

Major depressive disorder (MDD) affects 163 million people globally every year.[1] Approximately 28%–47% of patients treated with pharmacotherapy and 18%–45% of patients treated with psychotherapy and/or pharmacotherapy achieve no more than partial remission of MDD.[2–11] Approximately 16%–24% of these patients spend a substantial amount of time in partial remission, ranging from 5 to 10 years following the index depressive episode.[12 13] Partial remission has been defined as a period of improvement during which a patient no longer meets criteria for MDD yet continues to experience symptoms.[14–18] In line with this consensus statement, we define partial remission as the presence of subsyndromal depressive symptoms during the remission phase of MDD

with a Hamilton Depression Rating Scale (HAM-D) score in the range of 8–15.

Partial remission is associated with a high risk of relapse (76% experience a relapse within 15 months) as well as a fast return of the full episode, as the depressive episode returns on average within 3.7 months in the year following partial remission.[10] Aside from the symptoms and risks, partial remission is associated with impairment in work as well as (psycho)social impairment,[4 19 20] and lower quality of life.[4 21] The most persisting symptoms reported by patients in partial remission are cognitive problems.[22 23] Cognitive problems are present in 46% of patients in partial remission and 44% of the time[22 24] and might therefore be a target for novel treatments. Taken together, partial remission of MDD has a considerable impact on a person's life, which underscores the need for innovative strategies that tackle partial remission in MDD.

To treat partial remission, current guidelines recommend continuing, switch or add antidepressants, to switch to (another) psychotherapy, or to combine antidepressants with psychotherapy.[25 26] Previous randomised controlled trials (RCTs), including a variety of definitions of partial remission, demonstrated that cognitive–behavioural therapy (CBT),[27] mindfulness-based cognitive therapy (n=460)[28] and potentially rumination-focused CBT (n=60; n=42)[29 30] can further reduce depressive symptoms for patients in partial remission from MDD. CBT for this patient group improved psychological functioning as well as social functioning.[31] Alongside the effect on depressive symptoms, these treatments decreased relapse risk[27 29 32] and internet-based CBT increased time to relapse (n=84).[33] Furthermore, preventive cognitive therapy (PCT) has been shown to reduce depressive symptomatology[34–38] and relapse risk for up to 5.5–10 years in studies that included patients with partially and fully remitted MDD (HAM-D score below 10 or 14).[34–36 39–42]

Interestingly, most psychological treatments do not focus on improving cognitive functioning, whereas cognitive problems are the most persistent symptoms in partial remission.[22 24] Deficits in cognitive functioning are present during the acute phase of MDD and often remain during remission,[43–46] and predict poor treatment response and worse functioning.[47–49] These deficits in emotion-independent information processing are also referred to as 'cold cognition' deficits.[50] Rather than focusing on deficits in cold cognition, psychological treatments for partial remission address so-called 'hot cognitions', defined as emotion-dependent thinking (eg, self-schemata).[50 51] Targeting cold cognition (ie, improving cognitive functioning) alongside hot cognition in a combined treatment might facilitate full remission in individuals with partial remission.

Available evidence-based treatments for cold cognition include neurocognitive remediation therapy (NCRT), which involves exercises to train cognitive functions. Recent meta-analyses demonstrated that NCRT enhances attention, processing speed, executive functioning, working memory and verbal memory in (remitted) depressed patients.[52–56] For patients in partial remission specifically, NCRT improved attention.[57] NCRT also decreased depressive symptomatology in patients with (remitted) MDD,[52 54–56] although the robustness of the effect on depressive symptomatology is questionable as the beneficial effect disappeared when only high-quality studies were included.[52] Despite these inconsistent effects on depressive symptomatology, beneficial effects of NCRT on cognitive functioning (ie, cold cognition) throughout several stages of MDD have been demonstrated.

Previous studies show that NCRT may enhance the effect of psychotherapy that targets hot cognitions.[58] Targeting cold cognition with NCRT augmented to targeting hot cognitions using PCT might promote full remission for patients in partial remission. Therefore, in a nationwide pragmatic multicentre superiority RCT, we will compare PCT with online NCRT (oNCRT) to PCT alone (1:1 allocation) to assess if augmenting oNCRT to PCT further reduces depressive symptoms in partially remitted depressed patients over 1 year. We hypothesise that over a period of 1 year, augmentation of oNCRT to PCT further reduces depressive symptoms, reduces the risk of relapse and time to relapse, strengthens cognitive functioning, increases overall quality of life and decreases healthcare costs.

METHODS AND ANALYSIS

The HERSTEL (Dutch for 'recovery') study is funded by the Dutch Brain Foundation (Hersenstichting). The study has been approved by the Medical Research Ethics Committee of the Academic Medical Center, Amsterdam.

Study design

This study is a national pragmatic multicentre superiority RCT with a 1:1 parallel group design. In total, 115 partially remitted depressed adults will be randomised to adding oNCRT to PCT (PCT+ group) or PCT alone (PCT– group). Both groups will be assessed monthly up to 1 year after baseline assessment. Total duration of participation in the study is 12 months. Allocation of participants is concealed for study assessors to ascertain independent assessments. An overview of the study design is provided in figure 1.

Participants

Recruitment

Participants will be recruited in participating mental healthcare centres and hospitals across the Netherlands, and through advertisements, (social) media and websites. A full list of participating centres is available on request.

Inclusion and exclusion criteria

Eligible patients must fulfil the following criteria at randomisation: (1) are currently in remission from MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[59] for at least 8

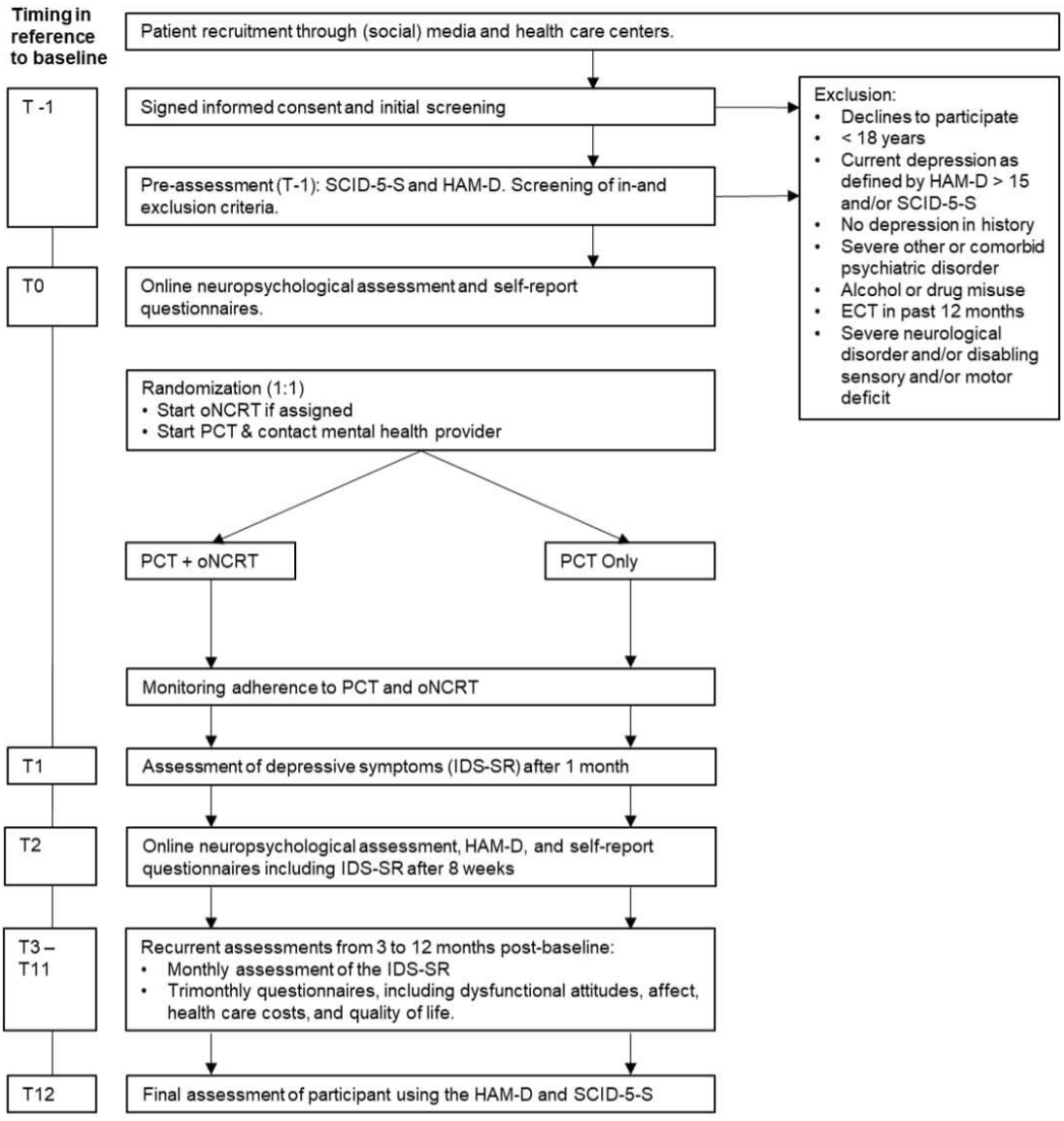

Figure 1 Study flow chart. ECT, Electroconvulsive Therapy; HAM-D, Hamilton Depression Rating Scale; IDS-SR, Inventory of Depression Symptomatology Self-Report; oNCRT, online neurocognitive remediation therapy; PCT, preventive cognitive therapy; SCID-5-S, Structured Clinical Interview for DSM-5 Disorders.

weeks and no longer than 2 years, as assessed with the Structured Clinical Interview for DSM-5 Disorders (SCID-5-S);[60] (2) have HAM-D[61] scores of ≥8 and ≤15; (3) are aged 18 years or older; and (4) speak Dutch or English. Exclusion criteria are current (hypo)mania or a history of bipolar illness, any psychotic disorder, substance misuse, primary anxiety disorder diagnosis, electroconvulsive therapy in the previous 12 months, neurological disorder, or a disabling sensory and/or motor deficit. Patients must provide written informed consent before the study procedures occur.

Informed consent and assessment of eligibility

Patients who either declare interest in the study or are referred by a healthcare provider will first be informed about the study by one of the researchers. Patients who are interested in the study will receive an information letter and an informed consent form. After informed consent is obtained, patients will be screened for inclusion and exclusion criteria using the SCID-5-S, HAM-D and additional questions regarding age, language, current and previous treatments of DSM-5 disorders and neurological disorders. The screening results will be discussed with an experienced mental health professional to decide if a participant is eligible. Eligible participants will continue with a baseline assessment, consisting of various questionnaires and neuropsychological tests. See table 1 and 'outcomes' for an overview of all assessments. On completion of the baseline assessment, participants will be randomised.

Randomisation

In total, 115 participants will be randomised with a 1:1 allocation ratio to PCT with oNCRT (PCT+) or PCT alone (PCT). To that end, an independent researcher will use a computer-generated block randomisation scheme with

Table 1 Overview of schedule of enrolment, interventions and assessments

		Study period													
		Entry	Baseline	Postallocation											Last assessment
Time point	Description	T-1	T0	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
Enrolment															
Eligibility screen		X													
Informed consent	Before T-1 assessments	X													
Allocation	Randomisation after baseline assessments		X												
Interventions															
PCT+oNCRT			⟷	⟷	⟷										
PCT alone			⟷	⟷	⟷										
Assessments															
Clinical interviews			X												
SCID-5-S	DSM-5 disorders	X													X
HAM-D	Depressive symptoms	X			X										X
Patient characteristics and psychiatric history			X												X
Self-reports															
IDS-SR			X	X	X	X	X	X	X	X	X	X	X	X	X
EPCL			X			X			X			X			X
DAS			X			X			X			X			X
CTQ			X												
TiC-P			X			X			X			X			X
EQ-5D-5L			X			X			X			X			X
WHODAS 2.0			X			X			X			X			X
PANAS			X			X			X			X			X
Neuropsychological tests															
TOMM			X		X										
Wordlist Learning			X		X										
Place the Beads			X		X										
Connect the Dots I and II			X		X										
Digit Sequences I and II			X		X										
Stroop Color-Word Interference Test			X		X										
Computer skills			X		X										
Adherence															

Continued

Table 1 Continued

Time point	Description	Study period												
		Entry	Baseline	Postallocation										Last assessment
		T-1	T0	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
PCT			X	X	X										
oNCRT			X	X	X										

All assessments will be conducted online. T0=baseline, T1=1 month, T2=directly post-treatment (8 weeks), T3–T11=3–11 months, T12=1 year follow-up.
CTQ, Childhood Trauma Questionnaire; DAS, Dysfunctional Attitude Scale; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; EPCL, Everyday Problem Checklist; EQ-5D-5L, 5-Level version of EuroQol-5 Dimension (EuroQol Group 5 dimensions questionnaire for health-related quality of life); HAM-D, Hamilton Depression Rating Scale; IDS-SR, Inventory of Depression Symptomatology Self-Report; oNCRT, online neurocognitive remediation therapy; PANAS, Positive and Negative Affect Scale; PCT, preventive cognitive therapy; SCID-5-S, Structured Clinical Interview for DSM-5 Disorders; TiC-P, questionnaire on healthcare utilisation and productivity losses in patients with a psychiatric disorder; TOMM, Test of Memory Malingering; WHODAS, WHO Disability Assessment Schedule.

randomly varying block size (eg, 2, 3 or 4), stratified for number of previous depressive episodes (1 vs ≥2). After randomisation, the participants will be informed by one of the coordinating researchers on their treatment allocation. Allocation of participants is concealed for the outcome assessors. Participants are requested not to share treatment allocation with the outcome assessor. If the blinding is violated, this will be registered.

Interventions

Preventive cognitive therapy

All participants will receive PCT, which consists of eight weekly individual PCT sessions. PCT is an adapted form of cognitive therapy that was developed to prevent relapse in patients with remitted MDD and with recurrent MDD.[62] During PCT, patients identify and evaluate presumed vulnerability factors of MDD recurrence (ie, dysfunctional beliefs).[63] Furthermore, patient's autobiographical memory and retrieval of positive experiences is trained in PCT. In addition, patients create a tailored relapse prevention plan. A recent RCT (n=195) showed that PCT is effective in patients with partial remission.[36] PCT was also evaluated in several RCTs which demonstrated that PCT reduces the risk of relapse over 12 months up to 10 years.[34–36 38–40 42 64–66]

PCT will be delivered via a videoconferencing programme by trained and licensed healthcare and clinical psychologists at one of the participating centres. Treatment delivered via videoconferencing yields similar results as face-to-face treatment,[67] and a previous study demonstrated that using a videoconferencing programme for PCT is feasible.[37] Therapists who deliver PCT will follow a 1-day training in PCT and subsequent monthly group supervision. To assess adherence to the PCT protocol, therapists will be asked to complete a checklist after every PCT session, and the number of sessions attended by the participants will be noted.

Neurocognitive remediation therapy

Participants assigned to the PCT+ group will receive oNCRT alongside PCT during the same 8-week period as the PCT. oNCRT is provided by CogniFit and targets cognitive abilities that are often diminished in patients with MDD (ie, (working) memory, executive functioning (task shifting) and attention (divided attention, inhibition and updating)).[68] Engaging game-like cognitive exercises are played to strengthen these cognitive abilities. The difficulty level of the exercises adjusts to the participant's performance level. Participants will play three sessions of these exercises per week, with a duration of 45 min per session, over a period of 8 weeks. oNCRT is delivered as an online programme that can be accessed at home at the participant's own computer. We will register the number of sessions completed to assess adherence.

Concomitant care

Psychiatric medication or any other medication is allowed during the entire study if necessary, which is in line with

the pragmatic nature of the trial. However, patients and healthcare providers will be asked not to change or switch medication during the trial. Medication use and potential changes will be recorded.

Withdrawal

Participants can withdraw from the treatment or from the study at any time without consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Participants who withdraw from treatment are asked if they are willing to complete the remaining assessments.

Outcome measures and timeline

Data will be collected at baseline, post-treatment and at several time points over 1 year (see figure 1 and table 1 for an overview). To proceed with the study and comply with (potential) COVID-19 restrictions, all assessments are completed without any face-to-face contact (eg, assessments via secured online videoconferencing, telephone calls, online questionnaires). The outcome assessors will be blinded to treatment allocation.

Primary outcome

The primary outcome measure is change in depressive symptomatology as assessed monthly with the Inventory of Depression Symptomatology Self-Report (IDS-SR) over a 1-year follow-up period.[69] See table 1 for an overview of all assessments.

Secondary outcomes

Time-related proportion of relapse/recurrence within a year will be examined with the SCID-5-S.[60] The SCID-5-S will be administered at baseline (T-1) and 1-year follow-up (T12). The HAM-D will be administered at baseline (T-1), post-treatment (T2) and 1-year follow-up (T12) to assess clinician-rated depressive symptoms.[70]

At baseline (T0) and post-treatment (T2), cognitive functioning will be assessed with tests from the Amsterdam Cognition Scan (ACS)[71] and PowerPoint presentations via a secured online videoconferencing assessment. The following neuropsychological tests from the ACS are included: Wordlist Learning, Delayed Recall and Recognition to assess verbal learning; Connect the Dots II to measure mental flexibility (inhibition and set-shifting ability); Digit Sequences I and II for verbal working memory; Place the Beads and Connect the Dots I to assess planning and processing speed. Using a videoconferencing meeting, the Stroop Color-Word Interference Test will be used to test mental flexibility, and the Test of Memory Malingering[72] to assess malingering. Online cognitive functioning assessment can be an alternative to traditional pen-and-paper tests that yield similar results.[71 73 74]

Participants will be asked to complete the online questionnaires every 3 months during the 1-year study period (T0, T3, T6, T9, T12) to assess among others quality of life and healthcare costs. The following questionnaires are included: health-related quality of life as measured with the 5-Level version of EuroQol-5 Dimension,[75] positive and negative affects measured with the Positive and Negative Affect Scale,[76] dysfunctional attitudes assessed with the Dysfunctional Attitude Scale,[77] daily hassles using the Everyday Problem Checklist,[78] disability with the WHO Disability Assessment Schedule 2.0[79] and healthcare and associated costs and costs from productivity loss measured using the Treatment Inventory of Costs in Psychiatric Patients (TIC-P).[80]

Additional outcomes

At baseline, we will furthermore assess sociodemographic and participant characteristics, including age, gender, socioeconomic status and psychiatric history. At baseline, childhood trauma will be measured as well using the Childhood Trauma Questionnaire, a self-report 28-item questionnaire that measures five types of maltreatment: emotional, physical, and sexual abuse, and emotional and physical neglect.[81]

Sample size

A power analysis based on a linear mixed (fixed and random) effects model analysis (intraindividual r=0.5)[82] indicated that a sample size of 92 is needed to detect a moderate (Cohen's *d*: 0.5) effect size on the primary outcome with 90% power and using a two-sided 5% significance level. To account for an expected 20% dropout, 115 participants will be included.

Statistical analysis

Our primary hypothesis is that PCT with oNCRT will lead to a larger decrease in depressive symptoms (measured with the IDS-SR) over the course of 1 year, as compared with PCT alone.

The secondary hypotheses are that, compared with PCT alone, PCT plus oNCRT will lead to: longer time to depressive relapse; improved neuropsychological functioning; higher self-reported health-related quality of life; less self-reported disability; lower healthcare and associated costs and costs from productivity loss; changes in positive and negative affects, dysfunctional attitudes and stress.

The primary analyses will be intention to treat, that is, participants will be analysed according to their randomised allocation, regardless of the actual treatment and time in the study after baseline. Secondary analyses will be per protocol, defined as at least six PCT sessions and 6 weeks of oNCRT (in case of PCT+oNCRT allocation).

The effect of PCT+ relative to PCT− will be estimated using linear mixed models for fixed (treatment) and random effects (for patient, and possibly for centre) for all continuously distributed outcome variables. Continuous measures that are measured once, for instance, results of neuropsychological tests, will be compared using unpaired t-tests. Categorical outcomes will be tested with χ^2 tests. Time to depressive relapse (as measured by the SCID-5-S) will be graphically analysed using the Kaplan-Meier method and the curves will be statistically

compared between the randomised groups using the log rank test. To obtain an HR as a measure of effect size for the time to relapse outcome we will construct a Cox proportions hazards model to enable adjustment in the analyses of time to relapse. Prior to performing Cox regression, we will check the proportional hazards assumption graphically by creating log minus log plots.

In each analysis, adjustment will be performed for the stratification variable. If despite randomisation other prognostically important factors differ between the groups, they will be adjusted for in supplemental analyses. This will be done by adding them as covariates to the linear mixed models and the Cox regression model. Results are considered statistically significant at a two-sided significance level of alpha <0.05.

To deal with missing data, we will perform multiple imputation (MI) to avoid potential bias and decreased statistical power associated with complete case analysis. MI will be done by chained equations under the assumption that missing values were missing at random or missing completely at random. The missing data mechanism will be studied to as much as possible substantiate these assumptions. The amount of missing data and reasons for non-participation or non-response will be reported and a complete case analysis will be added as a sensitivity analysis.

ETHICS AND DISSEMINATION

The study was approved by the Medical Research Ethics Committee of the Academic Medical Center, Amsterdam, before study onset (protocol ID: NL74547.018.20, trial register: https://www.trialregister.nl/trial/9582 (URL). Registered on 9 July 2021). The procedures listed above are in accordance with the Declaration of Helsinki. All participants will be informed about the study and will consent with participation before assessments. Only staff members (eg, clinical interns, clerical personnel) authorised by the principal investigators, monitoring agency of the AMC and the Health and Youth Care Inspectorate will be allowed access to the data. Data will be shared anonymised with other researchers on reasonable request and after a data sharing agreement has been signed. The (anonymised) results of the study will be shared with the participating centres. The results will be presented on seminars and published in peer-reviewed journals.

DISCUSSION

Partial remission of MDD is prevalent,[4 5 8–11 83] and is associated with a fast return to the full depressive episode,[10] a high risk of relapse,[17 18] work and (psycho)social impairment[4 19 20] and lower quality of life.[4 21] This considerable burden highlights the importance of effective treatment for partial remission. Brief psychological interventions, including PCT, seem to reduce depressive symptoms and relapse.[29 30 32 34–40 42 64 66] However, achieving full remission is still a clinical challenge. Treatment might be more effective if cognitive functioning of patients is targeted as well since cognitive deficits are present in (remitted and partially remitted) MDD[43 45 46 84] and predict poor treatment response and worse functioning.[47–49] Cognitive functioning of patients with (remitted) MDD can be improved by NCRT.[52–56] Therefore, this study will examine the effectiveness of a multimodal approach, that is, adding oNCRT to PCT in a pragmatic RCT. To our knowledge, the current study is the first to assess if augmenting oNCRT to PCT further reduces depressive symptoms in partially remitted depressed patients. Our approach could provide an effective multimodal treatment for partially remitted individuals, for which currently few evidence-based treatments are available.

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Contributors CB, HB, GJG, MB, AML and MS were responsible for the funding. CB is the principal investigator and wrote the draft of the manuscript with JGJvdS and MB. MB and CB were responsible for the coordination of the project. CB designed the PCT intervention. MB, JGJvdS and AML were responsible for data collection, inclusion of participants, monitoring of the study and continued ethical approval. CB, AML, JGJvdS, GJG, MS, HB, IOB, NL, DAJPD and MB were involved in the design and ethical approval of the study. NL was involved in the patient perspective of the study. CB, AML, JGJvdS, GJG, MS, HB, IOB, NL, DAJPD and MB read, commented and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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