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ORIGINAL ARTICLE

A Cognitive Control Training as Add-On Treatment to Usual Care for Depressed Inpatients

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Abstract

Background There is a growing body of research supporting the potential therapeutic value of the Cognitive Control Training (CCT) for depression, even though more research including a control condition is necessary to investigate its working mechanisms.

Methods The aim of this randomized, double-blind, placebo-controlled trial was to investigate the adjunctive effects of CCT to treatment-as-usual, compared to a sham-training, in patients with Major Depressive Disorder. Hundred-and-fifteen inpatients were randomly assigned to complete ten sessions of either an active working-memory based CCT ($n=56$) or a comparable sham-training ($n=59$). Changes in depressive symptoms and rumination were assessed from baseline to post-training, and at 1 year follow-up. Secondary outcome measures included alternative indices of maladaptive emotion regulation strategies, state-rumination in response to a worry induction, a cognitive transfer task and self-reports of work-status and well-being at 1 year follow-up.

Results Our results show no evidence for short-term beneficial effects of CCT in depressed inpatients when added to TAU.

Conclusion Although other studies suggest that CCT may hold potential as an add-on intervention for depression, our findings point to the importance of investigating individual differences and conditions predicting training response.

Keywords Major depression · Cognitive control training · PASAT · Rumination · RCT

Major Depressive Disorder (MDD) is one of the most common mental disorders, and besides the serious emotional and personal costs for those affected, depression places an enormous economic burden on the healthcare system and on society (National Collaborating Centre for Mental Health 2010). According to the World Health Organization, MDD is the leading cause of disability (World Health Organization 2015). Unfortunately, despite the range of available evidence-based treatments for depression (Bauer et al. 2007; National Collaborating Centre for Mental Health 2010), less than half of the patients show response and remission after psychotherapy (Cuijpers et al. 2014) or pharmacotherapy (Carvalho et al. 2007; Thase et al. 2001). Given the low response and remission rates (Carvalho et al. 2007; Thase et al. 2001) and the high risk of relapse (Hardeveld et al. 2010; Keller et al. 1983; Solomon et al. 2000), it has been suggested that existing treatments do not sufficiently target the underlying vulnerability factors which maintain the depression and predispose individuals to experience new episodes repeatedly (De Raedt and Koster 2010).

There is emerging evidence that impairments in cognitive control, which are observed in depression (De Raedt and Koster 2010; Goeleven et al. 2006; Gotlib and Joormann

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2010), even after remission from an episode (Demeyer et al. 2012; Paelecke-Habermann et al. 2005; Siegle et al. 2007a, b; Vanderhasselt and De Raedt 2009) may be a causal factor for depression vulnerability (for reviews, see De Raedt and Koster 2010; Koster et al. 2017). Cognitive control refers to executive processes such as mental set shifting, inhibition of irrelevant content or proponent responses, as well as updating and monitoring of information in working memory (Miyake et al. 2000). In particular, the difficulty to update and inhibit irrelevant mood-congruent negative information from working memory has been linked to rumination, a perseverant negative emotional processing style typically found in depression (De Raedt and Koster 2010; Nolen-Hoeksema et al. 1993). The use of maladaptive emotion regulation strategies such as ruminative thinking, instead of more adaptive regulatory processes such as positive reappraisal (Gross and John 2003), has been linked to poorer mood-regulation, and hence to prolonged negative affect and depressive symptoms (De Raedt and Koster 2010; Gotlib and Joormann 2010; Joormann and D'Avanzato 2010), making it an important risk factor for depression recurrence (Nolen-Hoeksema et al. 2008).

Based on the evidence for the role of impaired cognitive control and maladaptive emotion regulation strategies in depression vulnerability (e.g., Joormann and D'Avanzato 2010), it has been suggested that reducing cognitive control deficits should have beneficial effects on treatment outcome for depression (Siegle et al. 2007a, b). As a result, there has been an increasing number of studies that investigate the effects of modified trainings implying working memory processes to improve cognitive control, also referred to as Cognitive Control Training (CCT). The most frequently used CCT-task in this context is the adaptive Paced Auditory Serial Addition Task (aPASAT; see Koster et al. 2017), which in some studies was combined with a sustained attention training (e.g., Siegle et al. 2007a, b; Moshier and Otto 2017). During the aPASAT, participants hear a random stream of digits, and they have to respond to these digits by continuously indicating the sum of the last two digits they heard, creating interference with updating the last presented digits in working memory. To train cognitive control in a challenging context, the pace with which the numbers are presented is adapted to participants´ performance, leading to increasing task-difficulty with increasing task performance. This task has been developed by Siegle et al. (2007a; b) as an adjusted version of the original PASAT by Gronwall (1977; for a review, see Tombaugh 2006) in order to increase activity in the dorsolateral prefrontal cortex (DLPFC), which is typically underactivated in depression (Baxter et al. 1989; Fales et al. 2008; Ochsner and Gross 2005; Zhong et al. 2011).

The DLPFC is thought to play an important role in emotion regulation by recruiting cognitive control resources, while inhibiting emotional processing in limbic regions such as the amygdala (Davidson et al. 2000; Ochsner et al. 2004; Siegle et al. 2007a, b). Disrupted prefrontal activity is thus associated with sustained activation of the amygdala in response to stress, and decreased inhibitory control over negative stimuli. This leads to prolonged elaboration on negative materials during rumination, and hence to prolonged negative affect (De Raedt and Koster 2010). Accordingly, the aim of the adaptive PASAT is to increase prefrontal activity to promote cognitive control over information in working memory. This happens while being exposed to negative affect (i.e., slight frustration, as the aPASAT is highly challenging and evokes frequent errors), thus during interference from limbic pathways (Koster et al. 2017; Siegle et al. 2007a, b). This may result in increased control over thought processes in response to stress, possibly attenuating the perseverant negative thinking in depression.

There is a growing body of research supporting the potential therapeutic value of the aPASAT for depression (for a review, see Koster et al. 2017). In a first study, Siegle et al. (2007a; b) showed that combining 2 weeks (6 sessions) of Cognitive Control Training (involving two tasks, namely the aPASAT and a sustained attention task) with treatment as usual (TAU), lead to greater reductions of rumination and depressive symptoms in clinically depressed patients compared to TAU only. Even more promising results were found in a comparable study (Siegle et al. 2014) where adjunctive CCT did not only reduce depressive rumination, but also the need for outpatient care services at 1 year follow-up. In support of the neurobiological mechanisms underlying CCT effects, Siegle et al. (2007a, b) could demonstrate that this task is related to the neurocircuit underlying emotional control, enhancing activation of the Dorsolateral Prefrontal Cortex during a cognitive task, and decreasing activation in the amygdala during an emotional task.

In a study with depressed patients by Vanderhasselt et al. (2015), the aPASAT was combined with or without transcranial direct current stimulation (tDCS), a biological technique that can directly alter prefrontal activity. Improvements in working memory over the course of the training were associated with greater reductions in depressive rumination from before to after the intervention, irrespective of the stimulation condition. Similar research showed that 10 sessions of the aPASAT alone or combined with tDCS can decrease depressive symptoms up to 4 weeks later (Brunoni et al. 2014) and that the training even improves antidepressant outcomes of tDCS at 3 weeks follow-up (Segrave et al. 2014).

A more recent line of research supports the potential preventive effects of training using the aPASAT for depression in remission (Hoorelbeke and Koster 2017). Compared to an active control condition, the aPASAT training proved to be more effective in reducing rumination and depressive

symptoms as well as experienced disability and cognitive impairments up to 3-months later in remitted depressed patients. Interestingly, effects of the training on depressive symptoms were partially mediated by brooding (i.e., the depressive subtype of rumination). Promising effects were also found in studies with non-clinical samples, suggesting that CCT may reduce negative mood in adults (e.g., Calkins et al. 2015) or attenuate state rumination and negative mood in response to lab stressors and naturalistic stressors in high-trait ruminators (Hoorelbeke et al. 2015).

Considering the above-mentioned research, there is cumulative evidence suggesting that systematic training with the aPASAT might be of therapeutic value for depression. However, except for the RCT in remitted depressed patients by Hoorelbeke and Koster (2017), previous studies in clinical samples lacked an adequate control condition (Brunoni et al. 2014; Siegle et al. 2007a, b; Vanderhasselt et al. 2015). This raises the question whether the observed effects are actually due to changes in cognitive processes or rather reflect demand or placebo effects of the intervention. In fact, the only study which compared CCT consisting of the aPASAT (Siegle et al. 2007a, b) or attentional control training (Papageorgiou and Wells 2000) to a non-active control condition in clinically depressed patients did not find any adjunctive effects to a four-session behavioral activation treatment (i.e., brief behavioral activation treatment for depression, BATD; Moshier and Otto 2017). It is important to mention, though, that the CCT in this trial was administered less frequently compared to previous studies (i.e., once per week for 4 weeks only), which might have been insufficient to activate prefrontal areas and improve cognitive control to the degree that it may actually affect clinical symptoms or BATD treatment effects.

In addition, most trials made use of cognitive tasks that were very similar to the training task to assess near cognitive transfer (e.g., Hoorelbeke and Koster 2017) and further focused on the effects on clinical outcome only. To further explore the proposed underlying working mechanisms of the training, studies investigating transfer effects to working memory tasks different from the PASAT (i.e., far transfer effects) are needed. To address these limitations, we conducted a randomized, double-blind, placebo-controlled trial (RCT), investigating the effectiveness of the aPASAT training as an add-on intervention to treatment-as-usual (TAU) in clinically depressed inpatients. Hundred-and-fifteen patients were randomly assigned to either the active-training (i.e., the aPASAT) or to a sham-training condition. The latter was similar to the training, but did not require high cognitive working memory load, because participants simply had to react to the last heard digit, rather than adding it to the one before. Patients completed 10 training sessions during a period of 2 weeks. As a manipulation check, it was expected, that participants in the CCT group would show an increase in cognitive control, as reflected by a significant decrease in the inter-stimulus-interval (ISI) from the first to the last training session.

We hypothesized that compared to the sham-training group, the active-training group would show a significant decrease in the primary outcome measures of depressive symptoms and maladaptive emotion regulation strategies, in particular ruminative thinking, from before to after the training. Changes in depressive symptoms were expected to be maintained up to 1 year follow-up. State ruminative thinking was also measured (using self-reported levels of state rumination) before and after a stressful worry induction. We further extended previous research by measuring far-transfer effects on other measures of cognitive control, using the Random Number Generation Task which is loading on inhibition and working memory. We hypothesized that only the active-training group would show an increase in cognitive control capacity in this task. Finally, as an exploratory research outcome measure, participants' expectations and the experienced credibility of the training were investigated. Although active/sham-control conditions are superior to waiting-list control groups in controlling for placebo effects, it has been argued that it is only possible to ascribe treatment effects to the intervention if the treatment group and the sham-training group have the same expectations regarding improvement (Boot et al. 2013).

Methods

Compliance with Ethical Standards

This RCT was pre-registered at the Nederlands Trial Register (http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5030).[1] The study received ethical approval from the Ethics Committee of the University of Chemnitz, Germany. All procedures performed in the study involving human participants were in accordance with the ethical standards of the ethics committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

[1] It should be noted that the pre-registration wrongly mentioned BDI < 11 as an inclusion criterium. Moreover, we have added the BDI as a primary outcome measure, even though it was listed as a secondary outcome measure in the pre-registration. Based on new insights in the field of cognitive remediation, we also consider depressive symptoms and emotion regulation as primary outcome variables, and changes in rumination as a potential mediator. Finally, after an initial pilot test, it became clear that the burden of the pre-registered original protocol was too high for the patients. Therefore, the Internal Shift Task was replaced by the Random Number Generation task.

Participants

Participants were 43 male and 72 female adult patients (age: $M = 51.31$, $SD = 7.39$; age range 27–63 years old) with a major depressive episode, who were admitted to a 5-weeks inpatient treatment at the [The Salus Clinic Lindow] clinic in Germany. This is a "psychosomatic clinic" that admits patients with moderate to severe symptom levels who are still highly functioning, and it is not comparable to a psychiatric in-patient clinic. The study was powered for the primary outcome measures, which were assessed both before and immediately after the active-training and the sham-training. We assumed a medium effect size ($f = 0.25$) for the training group by time interaction. This may be a somewhat conservative assumption, given that both Siegle et al. (2014) and Vanderhasselt et al. (2015) reported large effects. With a total of 115 participants, an alpha error of $p = 0.05$, and a correlation among repeated measures of $r = 0.50$, the sample size yields excellent power of $1 - \beta = 0.99$. For a small interaction effect ($f = 0.10$), however, this sample size yields only power of $1 - ß = 0.56$.

To be eligible for participation, patients had to meet the criteria for a diagnosis of MDD, first or recurrent, according to the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 2013). Exclusion criteria included a history of neurological dysfunctions, acute suicidal risk, any psychotic disorder (current or previous), alcohol dependence, and a BDI-II score < 12 (Steer et al. 1993). Patients were informed about the study and the option to withdraw from it, without any consequences for their treatment at the clinic. All included patients provided written informed consent for participation.

Instruments and Materials

Intervention

Cognitive Control Training: aPASAT The cognitive control training consisted of an adaptive version of the Paced-Auditory-Serial-Addition Task (PASAT; Gronwall 1977; Siegle et al. 2007a, b). During this task, participants were presented with a random auditory stream of digits ranging from 1 to 9. The participants' task was to respond to these digits by continuously summing up the last two digits they heard and to indicate each sum by clicking on a corresponding response button (labeled 1 to 18) on the computer screen, using the computer mouse. To train cognitive control in a slightly demanding context, the pace with which the numbers were presented changed according to the performance of the individual participant. The task began with an Inter-Stimulus-Interval (ISI) between digits of 4000 ms. Upon four consecutive correct responses, the ISI was decreased by 100 ms, such that task difficulty increased slightly. Similarly, the ISI increased by 100 ms after every four consecutive incorrect responses. During the whole task, participants received feedback (in a feedback box presented in the upper part of the screen) about their current ISI and the amount of consecutive correct and incorrect responses. The computer recorded participant's responses and response times (RT). In line with previous research, the median ISI per session was used as an indicator of the participants' task performance. Each session consisted of four blocks of 100 trials each, and it took about 20–30 min, with short breaks between blocks.

Sham-Training Control Condition The sham-training consisted of a low-cognitive-load version of the aPASAT. The task was very similar to the aPASAT in terms of stimuli, responses, feedback on task performance, and modification of task difficulty (i.e., via adaptation of the ISI). The only difference was that, unlike in the active version of the task, participants did not have to compute the sum of the last two digits. Instead, they simply reacted to the last digit they heard by clicking on the corresponding response button on the screen. To keep the possible responses comparable to responses in the active version, the auditory stream of digits ranged from 1 to 18.

Primary Outcome Measures

Depressive Symptoms Depressive symptoms were assessed with the 21-item revised German version of the revised version of the Becks Depression Inventory, BDI-II (Hautzinger et al. 2006). In the current study, the internal reliability of the questionnaire was good (Cronbach's α's (both groups) BDI pre > 0.82, Cronbach's α's (both groups) BDI post > 0.90), & Cronbach's α's (both groups) BDI follow-up > 0.92.

Trait Rumination Rumination was assessed using the German version of the rumination subscale of the Response Style Questionnaire (RSQ) by Nolen-Hoeksema (1991; RSQ-D; Bürger and Kühner 2007). The RSQ assesses cognitive and behavioral coping style in response to dysphoric mood, including rumination, which refers to the repetitive and continuous thinking about depressive symptoms, their possible causes and consequences. Next to rumination, the RSQ provides a measure of distraction, referring to behavioural and cognitive distraction from the negative mood, it's possible causes and consequences. Whereas rumination is assumed to maintain and increase depressed mood, distraction is presumed to attenuate it. The German version of the RSQ has good psychometric properties. In the current study, the internal reliability of the questionnaire was good

(Cronbach's α's (both groups) RSQ rumination subscale pre > 0.84, Cronbach's α's (both groups) RSQ rumination subscale post > 0.89.

Cognitive Emotion Regulation The German version of the Cognitive Emotion Regulation Questionnaire (CERQ; Garnefski and Kraaij 2007; Loch et al. 2011) was used as a measure of maladaptive and adaptive emotion regulation strategies in response to stress. The CERQ measures nine conceptually distinct emotion regulation strategies in response to stressful life events: self-blame, other-blame, rumination, catastrophizing (generally maladaptive strategies), putting into perspective, positive refocusing, positive reappraisal, acceptance, and planning (generally adaptive strategies). The questionnaire contains 36 items, with four items per subscale. The German version of the CERQ has good psychometric properties, as well as adequate external validity. In line with Vanderhasselt et al. (2014), a compound score was calculated for adaptive and maladaptive emotion regulation. In the current study, the internal reliability of the questionnaire was good (cronbach's α's (both groups) CERQ adaptive ER pre > 0.79, cronbach's α's (both groups) CERQ adaptive ER post > 0.87; cronbach's α's (both groups) CERQ maladaptive ER pre > 0.85, cronbach's α's (both groups) CERQ maladaptive ER post > 0.87).

State Rumination

Breathing Focus Task

The Breathing Focus Task (BFT; Borkovec et al. 1983; Hirsch et al. 2009; Ruscio and Borkovec 2004) was used as behavioural measure of state worry. The task contained three phases of 5 min each: (1) pre-worry breathing focus, (2) instructed worry period, and (3) post-worry breathing focus. During each of the two breathing focus periods, participants were instructed to focus their attention on their breathing. The computer generated 12 tones at random intervals between 20 and 30 s and participants were instructed to indicate per tone, whether their attention was focused on their breathing or whether they had a thought intrusion. In case of a thought intrusion, participants briefly indicated the valence of their thoughts (i.e., negative, neutral or positive) and provided a brief description of it (e.g., "positive – dinner tonight"). After the first breathing focus period, the instructed-worry period followed, during which participants had to identify a personally relevant, negative, future-related topic and were asked to silently worry about this topic for 5 min. Thereafter, the second breathing focus period followed.

During a subsequent interview, participants provided fuller descriptions of each of the reported thought intrusions during the two breathing focus periods. All answers were briefly noted by the experimenter as well as digitally recorded for later ratings by an assessor. Two independent raters rated the valence of each intrusion. Kappa for inter-rater variability was (kappa value, approximate significance value): Phase 1 baseline: 0.03, $p = 0.55$; phase 3 baseline: 0.35, $p < 0.001$; Phase 1 post-training: 0.38, $p = 0.003$; Phase 3 post-training: 0.35; $p < 0.001$.

Momentary Ruminative Self-focus Inventory (MRSI)

To assess state rumination in response to the BFT, a prior version of the Brief State Rumination Inventory (Marchetti et al. 2018) was administered before and after the BFT. The MRSI used in this study contains six items, measuring momentary self-focused rumination (e.g., "Right now, I am thinking about the possible meaning of the way I feel"). Items are rated on a 7-point scale, ranging from "totally not agree" to "totally agree". The MRSI has been shown to have good reliability and validity and to be sensitive enough to pick up changes in response to experimental manipulations. In the current study, the internal reliability of the questionnaire was good (Cronbach's alpha's pre (both groups) > 0.80, post (both groups) > 0.80.

Secondary Outcome Measures

Transfer Effects To assess transfer effects of the training to a different working memory measure, the *Random Number Generation Task* (RNGT; Peters et al. 2007) was used. During this task, participants were requested to generate a sequence of 100 numbers, using the digits between 1 and 9 in a random order. The speed with which participants had to provide their answers was paced by a metronome, set to 40 answers per minute (i.e., 100 answers within 2.5 min). The concept of randomness was explained in a standard procedure, using instructions based on the analogy of selecting and replacing numbered pieces of paper from a box. Participants were asked to name one digit per tone, which was recorded by the experimenter. Based on the analyses reported by Peters et al. (2007), three scores that loaded most on the three different factors of randomness were calculated: (1) *Cluster ratio (loaded most on factor seriation),* that is, the variance of 100 successive responses in the diagram matrix. It represents the frequency with which each digit is followed by each possible digit. In a series with n digits, there are n^2 possible pairings. In the current study, this score had a retest reliability in the control group of $r = 0.473$, $p < 0.001$. (2) *GAP (loaded most on factor cycling),* a measure of cycling through the set of 9 digits. This measure is obtained by counting the number of gaps between two identical digits. The median of this number is then calculated. In the current study, this score had a retest reliability in the control group of $r = 0.327$, $p = 0.012$. (3) *Repetition (loaded most on factor*

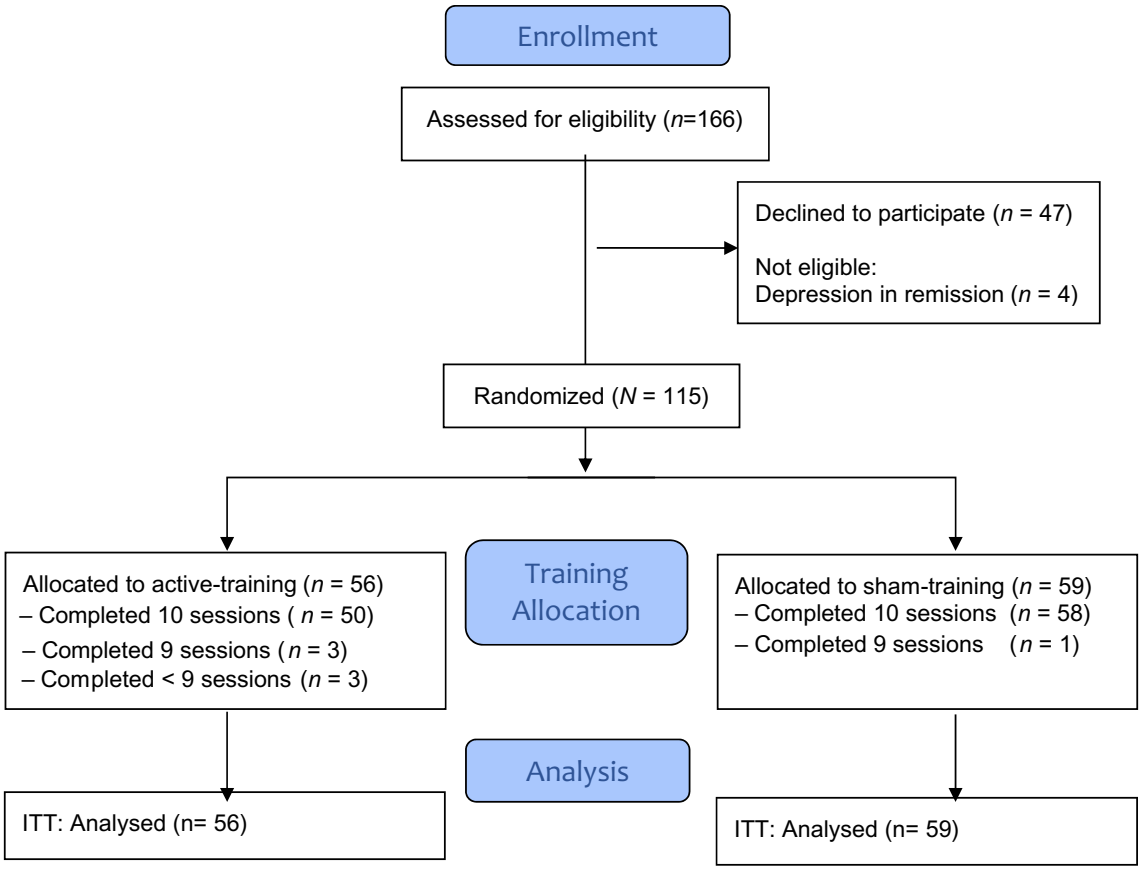

Fig. 1 Consort flow diagram

repetition), that is the number of identical consecutive digits (e.g., 4,4). The score is the sum of these identical pairs. In the current study, this score had a retest reliability in the control group of $r = 0.324$, $p = 0.013$.

Exploratory Outcome Measures

Credibility and Expectancy of the Intervention To control for possible placebo effects of the intervention, a translated version of the Credibility/Expectancy Questionnaire (CEQ; Devilly and Borkovec 2000) was used. The CEQ is a short self-report questionnaire that measures how credible and convincing the patient finds the intervention, and what the patient expects from it. It comprises 3 questions regarding the credibility of the intervention (items 1–3) and 3 questions assessing participants' expectations (items 4–6). Besides two items of the "expectancy" subscale, which are rated on a 11-point scale from 0 to 100%, all other items are answered on a 9-point likert scale (1 = *not at all* to 9 = *very much*).

Follow-up questionnaires. To get a further indication of potential long-term effects of the CCT, the following outcome-variables, which are part of the standard 1-year follow-up treatment-outcome questionnaire of the [The Salus Clinic Lindow] clinic, were explored: self-reported status (1 = *very much better* to 7 = *very much worse*), work/education impairment (1 = *not at all* to 5 = *very heavily*), inability to work, and weeks of being unable to work.

Procedure

Participants were recruited at the [The Salus Clinic Lindow], where they received care as usual (TAU), which included both individual and group sessions, for an average of 2 months. For the CONSORT flow diagram, see Fig. 1.

During the first week of therapy, all patients took part in the standard intake procedure of the clinic. During this diagnostic phase, a range of questionnaires were administered, including the baseline BDI-II, RSQ, and CERQ. Afterwards, patients were randomly allocated to either the active-training group receiving the aPASAT, or to the sham-training active control group described above. Before the training started, participants completed another baseline session during which the BFT and RNGT were administered. This session was followed by 10 training sessions within

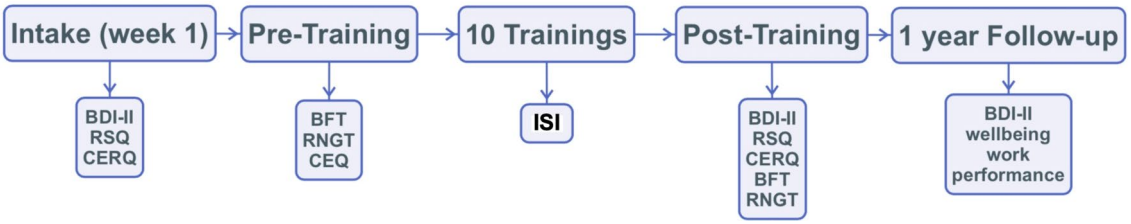

Fig. 2 Overview of procedure and measures. Note: *BDI-II* Revised Beck's Depression Inventory, *RSQ* Response Style Questionnaire, *CERQ* Cognitive Emotion Regulation Questionnaire, *BFT* Breathing Focus Task, *RNGT* Random Number Generation Task, *CEQ* Credibility/Expectancy Questionnaire, *ISI* Inter-Stimulus-Interval

2 weeks (i.e., 5 training sessions per week). The first session was completed individually, in order to allow for thorough explanation of the training instructions and for answering participants' questions. All other training sessions were completed in groups of a maximum of 5 participants per session. To measure participants' expectancies regarding the training, the CEQ was administered directly after the first training session. The 2 weeks of training were followed by a post-test, during which participants again filled in all questionnaires and completed the BFT and RNGT. As part of the standard procedure at the clinic, the BDI-II was administered at discharge, and the exploratory outcome measures regarding self-reported status of patients' well-being and work, as well as the BDI-II, were administered 1 year post-treatment. Please see Fig. 2 for an overview of the procedure and the measures of the study.

Results

Data Preparation

Missing baseline data were imputed by the mean of all patients' baseline scores subtracted by its standard deviation, which resulted in imputed data in the BDI-II ($n=2$), RRS ($n=6$); CERQ ($n=8$); RNGT ($n=8$); and MRSI ($n=5$ pre; $n=5$ post-training).

Data were analyzed using the Intention-To-Treat (ITT) approach, with the last observation carried forward (LOCF). Hence, missing data of post-training BDI-II ($n=5$), RRS ($n=9$), CERQ ($n=11$), MRSI ($n=2$ pre; $n=3$ post training) were replaced by the score at baseline. When both pre-and post-test data were missing (BFT $n=4$), missing data were not imputed, and when the ITT approach was applied, the baseline score was always available. Additional sensitivity analyses—including only participants of whom we had the data for each time-point were conducted for the primary outcome variables.

Demographics

Patients in the active-training condition ($n=56$) and in the sham-training condition ($n=59$) did not differ significantly concerning demographic variables or most baseline questionnaires, besides on distraction scores of the RSQ ($p=0.044$; all other $ps>0.08$) (see Table 1).

Manipulation Check

Training effects on the aPASAT were assessed by testing whether the ISI decreased significantly across the 10 training sessions. To that end, two separate one-way ANOVAs with the factor Time (Session 1 to 10) were computed on the mean ISIs, one for the active-training condition and another one for the sham-training condition. In the active-training condition, a significant effect of *Time* occurred, $F(9,441)=105.79$, $p<0.0001$, $\eta_p^2=0.68$ (Greenhouse–Geisser corrected), showing a significant linear trend of reduced ISI (i.e., reflecting an increase in cognitive control) across the 10 sessions, $F(1,49)=217.42$, $p<0.0001$, $\eta_p^2=0.82$. No significant effect of *Time* was observed in the sham-training condition, $F(9,513)=1.59$, $p=0.20$, $\eta_p^2=0.03$, indicating no changes in ISI over time. See Fig. 3 for an overview of the ITI over the ten sessions, plotted per training condition.

Training Effects on Primary Outcome Measures

(1) To investigate training effects on trait rumination (RSQ, rumination subscale), 2 (*Time*: baseline, post-training) × 2 (*Training Group*: active-training, sham-training) mixed-factors ANOVA was performed. This analysis yielded a main effect of *Time*, $F(1,112)=5.75$, $p=0.02$, $\eta_p^2=0.05$, indicating a significant reduction in rumination scores across groups from before to after the training. The crucial *Time* x *Training Group* interaction, however, was not significant, indicating that the reduction in ruminative thinking did not differ between groups, $F(1,112)=0.46$, $p=0.50$, $\eta_p^2=0.004$. The main effect of *Training Group* was not significant either, $F(1,112)=0.47$, $p=0.495$, $\eta_p^2=0.004$. For means and standard deviations, see Table 2. Sensitivity

Table 1 Group differences on demographic variables

	Active-training ($n=56$)	Sham-training ($n=59$)	$N=115$
Age (M, *SD*)	52.54 (6.74)	50.15 (7.84)	$t(113)=1.74$, $p=.08$
Gender (*n*, %)			$\chi^2(1)=.631$, $p=.447$
Male	23 (20)	20 (17.39)	
Female	33 (28.70)	39 (33.91)	
Relationship status (*n*, %)			$\chi^2(4)=7.38$, $p=.117$
Unmarried	18 (15.65)	12 (10.43)	
Married	24 (20.87)	25 (21.74)	
Divorced	10 (8.70)	21 (15.88)	
Widowed	2 (1.74)		
Other/unknown	2 (1.74)	1 (0.65)	
Educational level (*n*, %)			$\chi^2(3)=3.24$, $p=.357$
Low	3 (2.61)	3 (2.61)	
Medium	38 (33.04)	36 (31.30)	
High	10 (8.70)	9 (7.83)	
Unknown	4 (3.48)	11 (5.57)	

BDI-II Revised Becks Depression Inventory (BDI-II), *RSQ* Response Style Questionnaire, *CERQ* Cognitive Emotion Regulation Questionnaire

analyses revealed similar effects, namely a main effect of *Time*, $F(1,97)=11.23$, $p<0.01$, $\eta_p^2=0.10$; but no main effect of *Training Group,* $F(1,97)=0.44$, $p=0.51$, or interaction between both, $F(1,97)=0.00$, $p=0.959$. No main effects or interactions were observed for the RSQ subscale Distraction either, $Fs<3.11$, $ps>0.08$.[2]

(2) To investigate training effects on depression (BDI-II) scores, 2 (*Time*: baseline, post-training)×2 (*Training Group*: active-training, sham-training) mixed-factors ANOVA was performed on. This analysis yielded a main effect of *Time* $F(1,113)=45.84$, $p<0.01$, $\eta_p^2=0.29$, indicating—across all participants—a significant reduction in depressive symptoms after as compared to before the intervention. This reduction, however, was not larger in the active-training group than in the sham-training group, $F(1,113)=0.19$, $p=0.666$, $\eta_p^2=0.002$. The main effect of *Training Group* was not significant either, $F(1, 113=2.17$, $p=0.144$, $\eta_p^2=0.019$. Sensitivity analyses revealed similar effects, namely a main effect of *Time*, $F(1,107)=45.14$, $p<0.01$, $\eta_p^2=0.30$; but no effect of *Training Group*, $F=1.99$, $p=0.16$; $\eta_p^2=0.011$, and no interaction between them, $F(1,107)=0.04$, $p=0.847$; $\eta_p^2=0.004$.

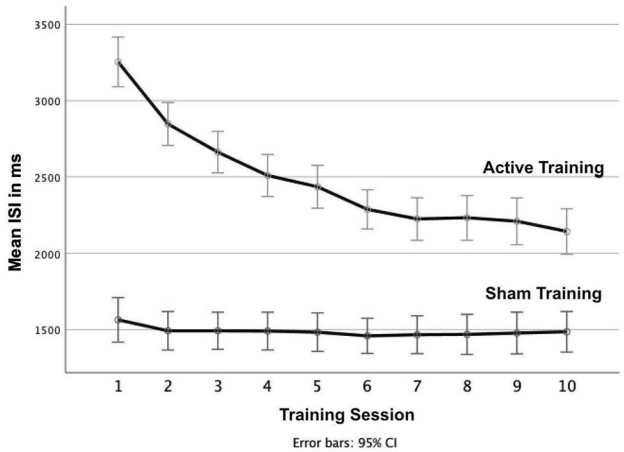

Fig. 3 Mean Inter-Stimulus-Intervals across the 10 training sessions, plotted per training condition

[2] Results of the analyses on the RSQ subscale Distraction may be affected by the significant baseline between-group difference on this scale.

Adding the BDI at follow-up to the analysis, the 3 (*Time)*×2 (*Training Group)* ANOVA again reveals non-differential changes in depression levels between the groups, $F(2,33)=1.9$, $p=0.16$, $\eta_p^2=0.11$. The main effect of *Time* was significant though, $F(2,33)=19.59$, $p<0.01$, $\eta_p^2=0.54$, indicating a reduction of depressive symptoms over time. Importantly, as return-rates of the BDI-II were very low ($n=35$), the samples size of this analysis is too small, to yield (i.e., expect) a significant interaction effect here.

(3) Cognitive emotion regulation (CERQ). The additional measure of emotion regulation strategies (the CERQ), was analyzed by means of a 2 (*Time*: baseline, post-training)×2 (*Training Group*: active-training, sham-training) mixed-factors MANOVA of the compound scores of adaptive and maladaptive emotion regulation. The MANOVA revealed a significant main effect of *Time*, $F(2,110)=4.18$, $p=0.018$, $\eta_p^2=0.071$, for which the univariate tests showed a significant reduction of maladaptive emotion regulation strategies, $F(1,111)=7.93$, $p=0.006$, $\eta_p^2=0.067$, but not a significant increase in adaptive emotion regulation strategies,

Table 2 Group characteristics at pre and post-test as a function of training group

	Active-training ($n=56$)		Sham-training ($n=59$)	
	Baseline	Post-test	Baseline	Post-test
BDI–II (M, *SD*)	21.81 (7.81)	17.28 (9.50)	24.56 (9.32)	19.40 (11.58)
RSQ (M, *SD*)				
Rumination	52.12 (8.70)	50.23 (10.24)	53.95 (9.74)	51.25 (13.48)
Distraction	23.46 (5.00)	24.07 (5.63)	21.56 (4.97)	22.31 (5.90)
CERQ (M, *SD*)				
Maladaptive	26.63 (9.34)	23.06 (9.83)	29.09 (10.08)	24.49 (13.01)
Adaptive	33.07 (10.60)	30.40 (10.89)	29.57 (12.46)	29.80 (13.22)

Because the time between administration of the BDI-II at post-test and dismissal varied greatly between participants and was often less than a week, the BDI-II data that patients filled in at their dismissal could not serve as follow-up measure and hence was not included in the analyses. Due to low return rates of the BDI-II at follow up, the sample size is lower for this variable: active-training$_n=19$, sham-training$_n=17$

$F(1,111)=0.65$, $p=0.422$, $\eta_p^2=0.006$, across groups. The crucial *Time-by-Training Group* interaction was not significant, $F(2, 110)=0.51$, $p=0.602$, $\eta_p^2=0.009$, and neither was the main effect of *Training Group*, $F(2,110)=2.11$, $p=0.126$,$\eta_p^2=0.04$), indicating no differential changes in emotion-regulation strategies between groups. For means and standard deviations, see Table 2.

(4) State rumination (self-report and behavioural measures) after a worry induction.

(4.1) MRSI. To investigate whether the training affected self-reported state rumination in response to the worry induction of the Breathing Focus Task (BFT), a *Time* (pre, post-training) x *BFT* (pre, post-BFT) x *Training Group* mixed-effects ANOVA on the MRSI scores was conducted. This analysis revealed a significant main effect of *Time*, $F(1,113)=22.46$, $p<0.0001$, $\eta_p^2=0.166$, indicating a general reduction in self-reported rumination post versus pre training. Also, the main effect of *BFT* was significant $F(1,113)=38.90$, $p<0.001$, $\eta_p^2=0.256$, implying that self-reported rumination increased post versus pre-worry induction. In contrast, neither the main effect of *Training Group* nor any interaction with it reached significance, all Fs <3.50, ps >0.064, suggesting that the training did not affect how the worry induction affected self-reported rumination.

(4.2) Breathing Focus Task.[3] To further investigate training effects on a behavioral measure of state-rumination in response to the worry induction, non-parametric tests (independent samples, Mann–Whitney-U-test) were performed on the dependent variables of the BFT (frequency of focus on breathing, negative, positive and neutral thoughts). Overall, no differences between the two conditions were observed (all $Z<1.52$, all $p>0.128$), except for the number of positive thoughts before the BFT, post training, $Z=2.73$, $p=0.006$. However, this effect did not survive the correction for multiple comparisons ($p=0.096$). For descriptives, see Table 3.

Training Effects on Secondary Outcome Measures

(1) Random Number Generation Task. Transfer effects of the training, were investigated using a MANOVA with *Time* (baseline, post-training) as within-subjects factor and *Training Group* (active-training, sham-training) as between-subjects factor, using the three dependent variables of the RNGT (cluster ratio, GAP and repetition). Results of this MANOVA yielded a main effect of *Time*, $F(3, 108)=4.19$, $p=0.008$, $\eta_p^2=0.104$, but neither an interaction of *Time* and *Training Group*, $F(3, 108)=1.91$, $p=0.132$, $\eta_p^2=0.050$, nor a main effect of *Training Group*, $F(3,108)=0.581$, $p=0.629$, $\eta_p^2=0.02$), indicating that the training did not affect cognitive control capacity as measured by the RNGT. For descriptives, see Table 4.

Training Effects on Exploratory Outcome Measures

(1) Treatment outcome at 1-year follow-up. Exploratory analyses were conducted to assess patients' self-reported status (i.e., well-being and work-related status) at the clinic's routine 1-year follow-up measurement. Status at follow-up was measured with the question "How do you feel now compared to before your stay at the clinic?", with answer options ranging from 1 (very much better) to 7 (very much worse). Results revealed that patients in the active-training group ($n=55$; $M=3.13$; $SD=1.48$), as compared to the sham-training group ($n=47$; $M=3.85$; $SD=1.85$), reported a better status at follow-up, $t(100)=2.21$, $p=0.03$. Work-education impairment was measured with the question "How much are you currently impaired in your work or education?" with answer options ranging from 1 (not

[3] We had planned to use both self-judgments and rater-judgments of the intrusions. However, the inter-rater reliability was so low (none to slight or fair agreement for the different phases of the task) that only the self-judgments could be used.

Table 3 State-rumination and thought intrusions during the breathing focus task as a function of training group, test time, and task phase

	Baseline		Post-test	
	Pre-worry (M, *SD*)	Post-worry (M, *SD*)	Pre-worry (M, *SD*)	Post-worry (M, *SD*)
Active-training				
MRSI	27.55 (8.29)	29.24 (6.61)	22.75 (8.64)	27.54 (9.08)
Focused breathing				
Breathing negative thoughts	5.60 (2.62)	5.21 (3.51)	5.85 (2.79)	5.20 (3.60)
	4.32 (2.77)	3.87 (3.63)	1.94 (2.13)	3,78 (3.72)
Positive thoughts	2.79 (1.99)	1.58 (2.08)	2.77 (2.67)	1.27 (1.73)
Neutral thoughts	2.89 (2.21)	1.23 (1.80)	1.42 (1.82)	1.71 (2.20)
Sham-training				
MRSI	24.83 (7.80)	19.14 (7.66)	21.34 (8.83)	25.44 (8.40)
Focused breathing				
Breathing negative thoughts	6.39 (3.55)	4.93 (3.31)	6.51 (3.49)	6.24 (3.43)
	3.71 (2.09)	3.64 (3.03)	2.27 (2.41)	3.24 (3.00)
Positive thoughts	3.15 (2.34)	1.71 (2.15)	2.02 (2.88)	1.19 (1.37)
Neutral thoughts	2.71 (2.41)	1.71 (2.44)	1.19 (1.49)	1.29 (1.93)

MRSI Momentary Ruminative Self-Focus Inventory*; Focused breathing* Frequency of Breathing, negative, positive and neutral thoughts during the 5 min breathing-phase of the Breathing Focus Task, *Pre-worry* 5 min breathing-period before the worry induction; *Post-worry* 5 min breathing-period after the worry induction; The MRSI was administered before and after the BFT, hence for the MRSI, *Pre-Worry Pre-BFT* and *Post-worry Post-BFT*

Table 4 Means (standard deviations) of RNGT indices at baseline and post-test as a function of training group

	Active-training ($n=54$)		Sham-training ($n=58$)	
	Baseline	Post-test	Baseline	Post-test
Cluster ratio	.36 (.05)	.36 (.10)	.38 (.08)	.38 (.08)
GAP	8.61 (.39)	8.78 (.20)	8.66 (.30)	8.69 (.24)
Repetition	.86 (1.92)	.78 (1.73)	1.21 (1.64)	.78 (1.27)

RNGT Random Number Generation Task

at all) to 5 (very heavily). The two groups responses to this question did not differ significantly (active: $M=2.48$, $SD=1.06$; sham: $M=2.60$; $SD=1.00$): $p=0.68$. Patients were also asked "How many weeks were you unable to work during the last year?". This did not differ between the groups (active: $M=11.74$, $SD=17.12$; sham: $M=16.03$; $SD=19.47$): $p=0.31$. Finally, they were asked if they were currently unable to work (Yes or No). The percentage of patients being unable to work did not differ between groups (active: $M=57\%$; sham: $M=47\%$): $\chi^2=0.33$.

(2) Expectancy Effects. To investigate whether the groups differed in their expectations and in the experienced credibility of the training, the scores on these two dependent variables of the CEQ were analyzed with two separate ANOVAs, using *Training Group* (active-training, sham-training) as between-subjects factor. The ANOVAs did not show significant group differences on the two subscales, indicating that the active-training and sham-training group did not differ in their expectations (active-training: $M=13.49$, $SD=6.25$; sham-training: $M=13.17$, $SD=6.08$; $F(1, 102)=0.07$, $p=0.791, =0.001$), and neither in the experienced credibility of the task (active-training: $M=17.22$, $SD=6.08$; sham-training: $M=14.95$, $SD=6.12$, $F(1, 107)=3.47$, $p=0.057, =0.034$.[4]

Discussion

With this RCT, we aimed at investigating the adjunctive effects of ten sessions of CCT (i.e., the aPASAT) to TAU, compared to a sham-training control condition, in clinically depressed inpatients. Only the active-training group showed an improvement in training-task performance (i.e., a decrease in the ISI throughout the 10 sessions), supposedly indicating increased cognitive control in this training group. However, besides this difference in cognitive performance during the sessions between training groups, patients in both groups showed a significant decrease in trait rumination and depressive symptoms after as compared to before

[4] Due to missing data on single items of both subscales, the *n* of the two subscales differs slightly (Expectancy: Active-Training$_n=47$, Sham-Training$_n=57$, Credibility: Active-Training$_n=50$, Sham-Training$_n=57$).

the training. There was no association between the change in ISI and the outcome measures. This reduction in depression and rumination levels was not stronger for the active-training group than for the sham-training group. The same result was obtained for changes in depression levels when including the 1-year follow-up,[5] as well as for maladaptive strategies of emotion regulation or state-rumination in response to the BFT (MRSI). Also, the training did not affect the number of negative and positive thought intrusions in response to the worry induction of the BFT. Finally, both the active-training and sham-training resulted in an increase in cognitive control capacity as measured by the RNGT, but with no difference between groups. In sum, results of this randomized, double-blind, placebo-controlled pre-registered trial do not show adjunctive immediate effects of the CCT as compared to a sham-training, when added to TAU in patients with MDD. These absent clinical effects are not in line with our expectations and there are a number of possible explanations that should be considered.

Our findings suggest that the aPASAT did not enhance TAU effects when compared to an active control-condition that does not require working memory capacities. However, due to the absence of a no-training control condition, we cannot exclude the possibility that our study underestimated CCT effects, that is, the sham-training may have been more active than intended. Indeed, as we did not have a no-training control group, it remains impossible to measure whether the significant decrease in clinical outcome measures in the two groups can be explained by comparable beneficial effects of both training versions (active and sham), or by TAU only (i.e., neither training had an additive effect). Possibly previous studies with neither a no-training control group nor a sham-training group might have overestimated CCT effects, and the reported results may have reflected placebo effects rather than effects of adding a cognitive training to TAU (or other factors associated with CCT). On the other hand, more recent research in non-clinical samples (e.g., trait ruminators; Hoorelbeke et al. 2015) or remitted depressed patients (Hoorelbeke and Koster 2017), with adequate control conditions, including the one used in our study, did show that CCT with the aPASAT may decrease stress reactivity and rumination in response to stress or residual symptoms following depression recovery.

A second explanation for the lack of clinical effects might be that our training did not improve cognitive control in the first place. Given the lack of transfer effects of the current training on the RNGT (i.e., secondary outcome measure), it is conceivable that the observed decrease in the ISI in the training group reflects a task-specific learning effect rather than an actual improvement of cognitive control. The absence of a training-related improvement in the sham-training, on the other hand, could be explained by a floor effect, due to the easier instructions of this task. If cognitive control was indeed not improved, changes in clinical outcomes cannot be expected because evidence suggests that changes in working memory are the working mechanism of the training. For instance, an increase in working memory function has been shown to be associated with levels of rumination and resilience after training (Hoorelbeke et al. 2015), as well as with greater reductions in rumination from before to after training (Vanderhasselt et al. 2015).

Third, earlier research suggests that it is important to take into account individual differences in baseline levels of cognitive control when evaluating CCT effects (Hoorelbeke et al. 2016). It is conceivable that the degree to which patients benefit from the training, both on cognitive and clinical symptom levels, may depend on pre-existing levels of cognitive control (i.e., impaired working memory functioning; Koster et al. 2017) and actual hypoactivation of the DLPFC, both of which have not been evaluated in this study. On the other hand, it has been argued that the relation between cognitive control impairments and CCT effects might be a non-linear one, such that CCT may not be sufficient for inducing changes in individuals with extensive cognitive control deficits (Koster et al. 2017). Siegle et al. (2014) showed that higher levels of task-engagement predicted stronger training effects. In line with this, one may argue that severely depressed patients who may be particularly unable to allocate sufficient attentional control to the task might benefit less from the training (see Moshier and Otto 2017). Indeed, De Raedt et al. (2015) have suggested that currently depressed individuals may not be able to exert enough DLPFC activity to benefit from the CCT, and that the combination with neurostimulation might be a possible solution. Future research should further investigate the predictive role of individual differences in cognitive processes and symptom severity for training utility. It should be examined whether a more individualized approach in which baseline variables serve as selection criteria for training participation is more promising.

Another potential explanation for the lack of clinically relevant training effects may be related to the timing of our measurements. It has been suggested that the training first induces changes in rumination, which subsequently lead to a reduction of depressive symptoms, but not vice versa (Siegle et al. 2007a, b). In support of this assumption, training effects on depressive symptoms in the study by Hoorelbeke and Koster (2017), were partially mediated by depressive rumination. Moreover, between-group differences in depression became significant only at 3 months follow-up, suggesting that training effects on depressive symptoms can only be detected after a longer period of time. In our study, due to

[5] Due to the small sample-size the analysis of the BDI-II follow-up data was based on, this analysis is not considered reliable.

insufficient follow-up data (return rates of the BDI-II were very low), the analyses of the BDI follow-up data cannot be expected to yield significant results, which may also explain why our results regarding the clinical outcome are in contrast with previous studies. Considering the absence of changes in any measures of rumination at post-training, however, it does seem unlikely that effects on depression would have developed over time. On the other hand, exploratory analyses of the standard treatment-outcome questionnaire of the clinic suggest that although patients in the two groups did not differ in their work-related status, patients in the active-training group showed slightly, but significantly higher levels of subjective well-being than patients in the sham-training group. Despite the small sample size this analysis was based on, the results may allow for the very tentative conclusion that clinical effects of CCT may indeed manifest themselves only after a longer period of time, as has been suggested in earlier studies (e.g., Hoorelbeke and Koster 2017). Therefore, future research should include long-term measures of depression to allow for the detection of delayed CCT effects on depressive symptoms. Moreover, they should be studied in larger samples, taking into account low return rates. Also, future studies should include follow-up measures of cognitive control, to assess the temporal stability of the modified cognitive processes. Regarding the latter, Hoorelbeke and Koster (2017) found that, although cognitive transfer effects were maintained at 3-months follow-up, there was a subtle reduction, suggesting the possible need for booster sessions to increase long-term effects of CCT.

There are a number of additional methodological limitations to consider. First, due to the heterogeneity of our sample (i.e., we did not exclude patients with psychiatric comorbidities; TAU included different types of treatment, selected individually by therapists and patients) our sample size may still have been too small to detect any additional effects of CCT on top of the variable effects of the different types of TAU. Second, due to practical issues, not all participants completed the training within 2 weeks, and the timing of the pre- and post-measurements also varied between participants. Third, the use of medication and the number of psychotherapy sessions could not be monitored either, and hence could not be controlled for. Although a meta-analysis by Motter et al. (2016) did not find moderating effects of medication status, suggesting that CCT can be combined with other evidence-based treatments, future research should either try to keep medication use constant during the study, or investigate type of medication and other relevant treatment variables as potential moderators of CCT training effects.

Fourth, as an indicator of changes in cognitive control, we analyzed changes in the ISI throughout the ten training sessions. Next to the far-transfer measure of working memory functioning (RNGT), our study may have benefitted from using a near-transfer cognitive task showing high resemblance with the training, like the non-adaptive PASAT used in the study by Hoorelbeke and Koster (2017). In this task, however, strategy learning may also confound the transfer effects, therefore multiple cognitive transfer tasks should be used, including the O-Span task or dual n-back tasks. These have successfully been used to demonstrate transfer effects (Hoorelbeke et al. 2015, 2016). Finally, although emotion regulation is considered an important mediating factor of CCT (Koster et al. 2017), like most earlier studies, we did not examine the mediating role of rumination in training effects on depressive symptoms. At least one study by Hoorelbeke and Koster (2017) showed that, in remitted depression, increased cognitive control predicted post-training levels of rumination, which partially mediated effects on depressive symptoms at 3-months follow-up. As recommended in a recent review (Koster et al. 2017), future studies should add such measures of potential mediating variables at multiple time points to examine mediation, for instance by using experience sampling (Hoorelbeke et al. 2016).

To conclude, the results of our study did not yield any evidence for the hypothesis that ten sessions of CCT with the aPASAT, when added to TAU, would have beneficial short-term effects on depressive symptoms or rumination in depressed inpatients. Considering the limitations of the present study and the previously reported beneficial effects of the training on working memory function and depressive symptoms in MDD (Koster et al. 2017; Motter et al. 2016), we consider it premature to conclude that CCT has no therapeutic value for depression at all. In the context of the exploratory finding that at 1-year post-treatment, the self-reported status of patients' well-being was slightly better in the active-training group, it is conceivable that changes in depressive symptoms as a result of the training appear only after a longer period of time. Still, the results may suggest that effects might be less robust than previously suggested (Moshier and Otto 2017), at least for severely depressed patients. Future studies should investigate individual differences that may predict training response, such as levels of task engagement (Siegle et al. 2014) or actual levels of DLPFC activity and cognitive control, to allow for more tailored and potentially more effective treatments.

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Compliance with Ethical Standards

Conflict of Interest Gina R. A. Ferrari, Marie-Anne Vanderhasselt, Mike Rinck, Ineke Demeyer, Rudi De Raedt, Silvia Beisel, Johannes Lindenmeyer and Eni S. Becker declare that they have no conflict of interest.

Ethical Approval This RCT was pre-registered at the Nederlands Trial Register (http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=5030). The study received ethical approval from the Ethics Committee of the University of Chemnitz, Germany. All procedures performed in the study involving human participants were in accordance with the ethical standards of the ethics committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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