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Internet-delivered cognitive control training as a preventive intervention for remitted depressed patients: Evidence from a double-blind randomized controlled trial study

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Abstract

Background. Cognitive control impairments may place remitted depressed (RMD) patients at increased risk for developing future depressive symptomatology by disrupting emotion regulation processes. Research has shown that directly targeting cognitive control has beneficial effects on high trait ruminators and clinically depressed patients. The current study tested whether internet-delivered cognitive control training (CCT) can be used as an intervention to increase resilience to depression in RMD patients.

Methods. Effects of CCT were assessed using a double-blind randomized controlled design. RMD patients performed 10 sessions of a working memory based CCT (N=34) or a low cognitive load training (N=34; active control condition) over a period of 14 days. Assessments took place prior to training, immediately following two weeks of training, and at three months follow-up. Brooding and depressive symptomatology were selected as primary outcome measures, alternative indicators for emotion regulation and residual symptomatology were selected as secondary outcome measures, along with indicators of functioning.

Results. Compared to an active control condition, CCT demonstrated beneficial effects on a cognitive transfer task, brooding, depressive symptomatology, residual complaints, self-reported use of general maladaptive emotion regulation strategies, and resilience after controlling for intention-to-treat. Furthermore, completers of the CCT reported a reduction in experienced disability and cognitive complaints. However, no beneficial effects were found for self-reported use of adaptive emotion regulation strategies.

Conclusions. These findings demonstrate the effectiveness of CCT as an intervention to reduce cognitive vulnerability, residual symptomatology, and foster resilience following recovery from depression. CCT thus holds potential as a preventive intervention for RMD patients.

Trial Registration: ClinicalTrials.gov identifier: NCT02407652

Keywords: cognitive control, depression, RCT, training, prevention

Public health significance statement

This RCT shows that online cognitive training targeting working memory functioning (cognitive control training) has beneficial effects on residual depressive symptomatology, maladaptive emotion regulation, and indicators of functioning in remitted depressed patients. These beneficial effects were observed immediately after training and at three months follow-up. Our findings indicate that cognitive control training holds potential as a preventive intervention for remitted depressed patients, decreasing cognitive vulnerability for recurrent depression and fostering resilience.

Achieving stable remission following major depressive disorder (MDD) remains an important challenge for current treatments of depression (Hardeveld, Spijker, De Graaf, Nolen, & Beekman, 2010). Given the high risk for new depressive episodes, studying causal mechanisms of depression vulnerability in remitted depressed individuals (RMD) is an important research priority. There is emerging evidence that RMD individuals are still characterized by impaired cognitive control as shown by behavioral (Lange et al., 2012; Levens & Gotlib, 2015) as well as neuroimaging data (Norbury, Godlewska, & Cowen, 2014; Vanderhasselt & De Raedt, 2009). The term cognitive control refers to executive processes such as shifting, inhibition and updating of information in working memory (Miyake et al., 2000).

Importantly, control over content in working memory may play a causal role in perseverative negative thinking concerning one's problems or feelings (i.e., depressive rumination or *brooding*) (Cohen, Mor, & Henik, 2015). Provided that engaging in maladaptive emotion regulation strategies such as depressive rumination has typically been linked to sustained negative affect and depressive symptomatology (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008; Treynor, Gonzalez, & Nolen-Hoeksema, 2003), cognitive control impairments place RMD patients at increased risk for recurrent depression (Demeyer, De Lissnyder, Koster, & De Raedt, 2012). As a result, it has been suggested that directly targeting these cognitive and neurobiological processes underlying vulnerability for depression may have beneficial effects (Segrave, Arnold, Hoy, & Fitzgerald, 2014; Siegle, Ghinassi, & Thase, 2007).

In this context, cognitive control training (CCT) has recently gained interest as a means to examine the causal influence of cognitive control on depressive symptoms as well as an adjunctive curative intervention for MDD. For instance, Siegle and colleagues (2007) introduced a variant of CCT combining an adaptive version of the Paced Auditory Serial Addition Task

(PASAT; Gronwall, 1977) and a task training selective attention (Wells' Attention Training; Wells, 2000). The non-adaptive PASAT has previously been used as an assessment task for executive functioning in multiple clinical populations (e.g., traumatic brain injury, multiple sclerosis, depression), and as a stress induction procedure given the high rate of errors that typically occur during the non-adaptive PASAT (for a review on the non-adaptive PASAT, please see Tombaugh, 2006). That is, during this task participants are presented with a continuous stream of digits and have to continuously respond to the sum of the last two heard digits, which has been proposed to activate the prefrontal cortex – a key cognitive control region (Cohen, 2001) – in a stressful context (Siegle et al., 2007, p. 245). Given the disturbed patterns of activation of frontal and limbic regions often reported in MDD (e.g., Davidson, Pizzagalli, Nitschke, & Putman, 2002; Pizzagalli, 2011), Siegle et al. (2007) developed an adaptive version of the PASAT during which task difficulty is modified based on the performance of the participant (i.e., every four consecutive correct responses are followed by a decrease in the inter-stimulus interval (ISI) of 100 ms, and vice versa). As a result, it has been suggested that during the adaptive PASAT participants have to recruit the dorsolateral prefrontal cortex (e.g., Lazeron, Rombouts, deSonneville, Barkhof, & Scheltens, 2003) while being exposed to interference from limbic pathways (Siegle et al., 2007). At the behavioral level, this may allow participants to gain control over thought processes upon confrontation with a stressor, potentially reducing perseverative negative thinking such as depressive rumination. Given that depressive rumination is a well-known cognitive risk factor for sustained and future depressive symptomatology (Nolen-Hoeksema et al., 2008; Treynor et al., 2003), this may then have beneficial effects on other depression-related outcomes (e.g., depressive symptomatology).

Indeed, combining six sessions of CCT with treatment as usual (TAU), Siegle and colleagues (2007) demonstrated beneficial effects on rumination (Siegle et al., 2007, 2014) and depressive symptomatology (Siegle et al., 2007) in a MDD sample compared to a TAU control group. Furthermore, in the year following the intervention, CCT showed beneficial effects on use of outpatient care services (Siegle et al., 2014), suggesting that CCT may have stable effects on depression-related outcomes and that these effects may be mediated by brooding. Confirming the suggested mechanisms underlying effects of CCT, Siegle et al. (2007) found that CCT may serve to reduce depression-related disruptions in amygdala and prefrontal activity.

Interestingly, recent work indicates that CCT specifically targeting working memory functioning (the adaptive PASAT component) shows potential in reducing rumination (Vanderhasselt et al., 2015) and depressive symptomatology (Brunoni et al., 2014) in absence of Wells' Attention Training in MDD patients. However, initial studies in clinical populations often lack an adequate control group to control for motivational effects of undergoing CCT (e.g., Brunoni et al., 2014; Siegle et al., 2007) and findings in non-clinical samples have been mixed (e.g., Calkins, Deveney, Weitzman, Hearon, & Siegle, 2011; Calkins, McMorran, Siegle, & Otto, 2015; Hoorelbeke, Koster, Demeyer, Loeys, & Vanderhasselt, 2016; Hoorelbeke, Koster, Vanderhasselt, Callewaert, & Demeyer, 2015; Moshier, Molokotos, Stein, & Otto, 2015). Furthermore, previous studies are often characterized by a unilateral focus on indicators of dysfunctioning. As a result, it has not been tested whether effects of CCT may extend to broader indicators of functioning in clinical samples. Additionally, to our knowledge no previous study has explored effects of adaptive PASAT training in RMD patients, nor has the suggested mediation effect (i.e., increase in cognitive control affects depressive symptomatology via

depressive rumination) been directly tested, which is crucial to advance our understanding of the preventive potential of CCT.

Current Study

Given that cognitive impairments and residual depressive symptoms often persist during remission from depression and form an important vulnerability factor, we tested whether CCT targeting working memory functioning can be used to reduce cognitive vulnerability for depression in a RMD sample, in order to prevent recurrence of depressive symptomatology. We conducted a double-blind randomized controlled trial (RCT) study comparing effects of CCT to an active control condition.

We hypothesized that: (a) CCT would have beneficial effects on primary outcome measures brooding and depressive symptomatology (Time 2 and 3); (b) It has been suggested that effects of cognitive control manipulation on depressive symptomatology (Time 3) may be mediated by depressive rumination (Time 2) (Siegle et al., 2014). We provided a test of this assumption; (c) We further extended previous work by broadening the scope of training effects to indicators of functioning, predicting beneficial effects on adaptive emotion regulation (Time 2 and 3), resilience, quality of life, disability, and a self-report measure for remission from depression (Time 3).

Methods

Design and Power

The study was pre-registered on ClinicalTrials.Gov (identifier: NCT02407652) and the complete protocol of this 2 (Condition) x 3 (Time) double-blind RCT was submitted for open access publication prior to data-collection (Hoorelbeke, Faelens, Behiels, & Koster, 2015). The study was approved by the local ethics committee and written informed consent was obtained for all participants. Sixty eight RMD patients were recruited to detect effects of CCT approaching those reported in previous studies (Hoorelbeke, Koster, et al., 2015; Siegle et al., 2014, 2007) with 80% power on primary outcome measures depressive rumination and symptomatology. Following baseline assessment, RMD patients were randomly assigned to 10 sessions (two weeks) of CCT (N=34) or a low cognitive load training (active control condition; N=34). Effects were assessed post-training and at three months follow-up.

Randomization and Blinding

Randomization over training condition (simple randomization, CCT vs. low cognitive load training; allocation ratio = 1:1) took place using automated randomization software (RandList; randomisation.eu). To ensure blinding of researchers, using RandList an independent researcher linked subject numbers (used during the lab assessments by the researchers for the questionnaires and cognitive transfer task) with training identification codes (used at home by the participants to perform the training). Based on the training identification codes – which were presented in a sealed envelope containing a personalized training manual – participants performed the CCT or low cognitive load training. This prevented awareness of training condition allocation. Technical queries that could reveal training condition were also resolved by the independent researchers. Furthermore, during data-analysis the researchers remained blind to training task condition. Specifically, the independent researcher provided the researchers with a list grouping the subject numbers in two non-informative conditions and analysis of training-related process measures

were separated from analysis of training effects on outcome measures. Successful blinding of participants was evaluated at baseline and immediately following training using the Credibility/Expectancy Questionnaire (CEQ; Devilly & Borkovec, 2000). Furthermore, at three-months follow-up participants completed a one-item measure assessing whether participants experienced the intervention as being a 'placebo'.

Participants

Participants (adults aged 23 – 65) were recruited via advertisements and a lab database. The study was conducted at the Faculty of Psychology and Educational Sciences of Ghent University. Following a brief telephone screening to assess eligibility, participants were invited for a more extensive structured clinical interview (Mini-International Neuropsychiatric Interview, MINI; Sheehan et al., 1989). Participants with a history of depression showing stable remission (≥ 6 months) were deemed eligible if: (a) the episode did not occur in the context of a bipolar disorder, (b) there was no history of psychosis, extensive substance abuse, or brain injury, nor were there current comorbid disorders, and (c) use of antidepressant medication was kept stable and therapeutic contact was limited to maintenance contact (< 1 / 3 weeks).

Interventions

Following a psycho-education session at baseline to foster task engagement (Siegle et al., 2014), participants performed 10 online sessions of the adaptive PASAT (*CCT condition*) or a low cognitive load training (*active control condition*) over a period of two weeks. Each session was performed online in-browser on the personal computer of the participant using a Millisecond software Web license, allowing participants to receive the complete intervention at home (e.g., Hoorelbeke et al., 2016) rather than in a lab context (e.g., Calkins et al., 2015; Siegle et al.,

2014). It is noteworthy that recent meta-analytic findings indicate that performing CCT at home (instead of in the lab) does not affect cognitive transfer (Au et al., 2015), while performing the intervention online provides a more ecological valid training context which may foster transfer on depression-related outcomes.

Importantly, participants were only allowed to perform 10 sessions of CCT during the two-week training period, which was monitored online. Breach of protocol (performing less than 10 sessions over the two-week training period or continuing training following the post-training assessment) was seen as non-compliance to the intervention and taken into account for the intention-to-treat (ITT; cf. infra) and completers-only analysis. None of the participants continued training outside the training period. Due to technical difficulties two participants in the active control condition completed 11 sessions during the training period.[1] To increase compliance, participants received a training manual following the psycho-education session and automated daily reminders via text message during the two-week training period (using SurveySignal software; Hofmann & Patel, 2015).

In both conditions participants were confronted with a continuous stream of auditory digits. In the CCT condition participants were instructed to continuously respond to the sum of the last two heard digits (stimuli: 1 – 9) by clicking on the corresponding response button (ranging from 1 – 18), whereas participants performing the low cognitive load task (Hoorelbeke et al., 2016) had to immediately respond to the last heard digit. To train cognitive functioning, speed of number presentation was adapted based on participants' performance: each training session started with an ISI of 3000 ms, which decreased / increased with 100 ms following every four consecutive correct / incorrect responses. In each condition, participants performed 400 training trials per session, providing an equal amount of training opportunities per participant

(independent of training task performance; e.g., Hoorelbeke et al., 2016). Overall, when taking into account increased task performance over the 10 training sessions in this sample, which – due to the adaptive nature of the task (see Supplemental material Table 1 for mean ISI per session per condition) – reduces the length of the training sessions over the two-week period, on average participants completed the CCT intervention in 142.82 minutes (not taking into account practice trials). In line with previous studies, individual progress on the training tasks over time was assessed using median ISI levels per session.

Outcome Measures

Cognitive transfer. *Near transfer* (i.e., transfer of cognitive training on performance on tasks that are similar to the training task) was assessed at baseline, post-training, and follow-up using accuracy scores of a non-adaptive version of the PASAT (Gronwall, 1977) during which participants performed three blocks of increasing difficulty (ISI block 1 = 3000 ms; ISI block 2 = 2000 ms; ISI block 3 = 1500 ms). Participants performed a total of 180 test trials (60 trials per block) following a practice phase of 10 trials. Furthermore, *cognitive complaints* were assessed using the Global Executive scale of the Behavior Rating Inventory of Executive Function Adult Version (BRIEF-A; range: 70 – 210; Scholte & Noens, 2011). The Global Executive scale of this 75-item self-report questionnaire combines experienced difficulties for a broad range of cognitive functions in daily life, providing estimates of executive and working memory functioning (e.g., experienced difficulties in daily life situations with inhibition, shifting, emotional control, working memory).

Primary outcome measures. *Depressive rumination* (range: 5 – 20) was assessed using the Brooding subscale of the Ruminative Response Scale (RRS; Nolen-Hoeksema & Morrow,

1991; Treynor et al., 2003) and *depressive symptomatology* using the Beck Depression Inventory (BDI-II, range: 0 – 63; Beck, Steer, & Brown, 1996; Van der Does, 2002). Both primary outcome measures were assessed at baseline, post-training, and three months follow-up, with higher scores indicating more symptoms or maladaptive processes.

Secondary outcome measures. The Cognitive Emotion Regulation Questionnaire (CERQ; Garnefski, Kraaij, & Spinhoven, 2001) was used as an alternative measure for *maladaptive emotion regulation* (next to the RRS; compound score maladaptive emotion regulation, range: 16 – 80) and *adaptive emotion regulation* processes (compound score adaptive emotion regulation, range: 20 – 100) at baseline, post-training, and follow-up. Furthermore, as indicators of general functioning, we assessed *disability* (World Health Organization Disability Assessment Schedule 2.0, WHODAS 2.0; Üstün, Kostanjsek, Chatterji, & Rehm, 2010), *quality of life* (Quality of Life in Depression Scale, QLDS; range: 0 – 34; Hunt & McKenna, 1992; Tuynman-Qua, de Jonghe, & McKenna, 1997), *resilience* (Resilience Scale, RS; range: 25 – 100; Portzky, 2008; Wagnild & Young, 1993), and *remission from depression* (Remission of Depression Questionnaire, RDQ; range: 0 – 82; Peeters, Nicolson, Wichers, & Hacker, 2013; Zimmerman et al., 2013) at baseline and follow-up. For all secondary outcome measures, except for resilience and adaptive emotion regulation, a higher score is indicative for more maladaptive processes.

Other measures. Potential confounders such as life events, treatment credibility and expectancy were assessed using the List of Threatening Experiences (LTE; Brugha & Cragg, 1990; Rosmalen, Bos, & de Jonghe, 2012) and the Credibility/Expectancy Questionnaire (CEQ; Devilly & Borkovec, 2000). An additional item assessed whether participants experienced the

training as being a bogus training (placebo: yes / no) and intake of antidepressants and other forms of therapy was monitored.

Procedure

Following a telephone screening, potential participants were invited to the lab for a more extensive structured clinical interview. If all criteria were met, participants were randomized and entered the baseline assessment (Time 1) where they gave written informed consent, received psycho-education, and completed the baseline cognitive task and self-report questionnaires. After receiving training instructions, participants performed ten online sessions of CCT or a low cognitive load version over a two week period after which they returned to the lab for a post-training assessment (Time 2) of the primary outcome measures, (mal)adaptive emotion regulation, cognitive functioning, and treatment expectancy/credibility. At three months follow-up (Time 3), participants returned to the lab where the baseline measures were re-assessed. Please see Hoorelbeke, Faelens, et al. (2015) for a more thorough description of the protocol. No deviations from the pre-registered protocol were made throughout the study.

Statistical Analysis

In line with the Consolidated Standards of Reporting Trials (CONSORT; Moher et al., 2010), effects of CCT on primary and secondary outcome measures will be tested using intention-to-treat (ITT) analysis. This allows a more stringent test of effects of CCT, taking into account each participant that was randomized to CCT or low cognitive load training when evaluating training effects. Specifically, in line with the pre-registered protocol (Hoorelbeke, Faelens, et al., 2015), missing data and/or non-compliance to the treatment protocol were handled using the Last-Observation-Carried-Forward (LOCF) method. Effects of CCT will be tested

using Repeated Measures ANOVA's with follow-up independent and paired samples *t*-tests (two-sided, $\alpha = .05$) to further elucidate interaction effects. As secondary analysis, we will also perform completers-only analyses. Explorative within-group mediation analysis will be performed using the Preacher and Hayes bootstrapping method (Preacher & Hayes, 2004), testing whether increase in cognitive control predicts lower levels of depressive symptomatology at three-months follow-up via depressive rumination (brooding) immediately following two weeks of training.[2]

Results

Group Characteristics

Participants were randomly allocated to a CCT (N=34) or active control condition (N=34; see Figure 1 for the CONSORT patient flow diagram). Both groups did not differ concerning demographic variables, variables specific to history of depression (e.g., age of onset, amount / duration of episodes), or amount of days between completion of each assessment phase (see Table 1). Importantly, independent samples *t*-tests indicate that both groups did not significantly differ at baseline concerning cognitive transfer- and outcome measures (all *t*s<1.73; see Table 2).

Training Task Process Measures

Progress on training task. Training task progress was assessed using participants' median ISI scores per session (Hoorelbeke, Koster, et al., 2015). Due to the different nature of both training tasks, for each group we performed a Repeated Measures ANOVA to explore whether progress was made over the ten training sessions. In line with our expectations, both groups showed a significant increase in task performance throughout the two week training

period, as shown by a decrease in ISI (CCT: $F(9, 20)=18.95$, $p<.001$, $\eta_p^2=0.90$; active control: $F(9, 23)=4.82$, $p=.001$, $\eta_p^2=0.65$; see Supplemental material Table 1).

Perception of the training as an intervention. As expected, results from 2 (Time: Pre- vs. Post-training) x 2 (Group: CCT vs. active control) Mixed ANOVA's indicate that both groups did not significantly differ concerning self-reported credibility of the intervention and expectancy (as shown by the absence of an interaction effect for both measures in Table 3; see Table 2 for descriptives). Furthermore, the proportion of participants that perceived the intervention as a placebo was limited (ratio "placebo" : "no-placebo"; CCT: 3:31; active control: 4:30) and did not differ between both groups ($\chi^2=0.16$, $p=.690$). This indicates that blinding of participants was successful.

Effects of Training

Effects of CCT on cognitive transfer measures (cognitive task performance and self-reported cognitive complaints), primary outcome measures (depressive rumination and depressive symptomatology) and secondary outcome measure (mal)adaptive emotion regulation (CERQ) were assessed using 3 (Time: Pre-training, Post-training, Follow-up) x 2 (Group: CCT vs. active control) Mixed ANOVA's. Given that some of the secondary outcome measures were only assessed at baseline and three months follow-up, effects on secondary outcome measures quality of life, resilience, disability and remission were explored using 2 (Time: Pre-training vs. Follow-up) x 2 (Group: CCT vs. active control) Mixed ANOVA's. Effects are reported in Table 3 taking into account ITT. Where the expected interaction effects were not found using ITT analysis, we then proceeded with a secondary completers-only analysis.

Cognitive transfer effects. Using ITT analysis, we found an effect of CCT on *cognitive task performance*, as indicated by the significant Time x Group interaction effect (see Table 3). Follow-up paired samples *t*-tests indicate that both groups continued to perform well at the three month follow-up compared to the baseline assessment of cognitive functioning (CCT: $t(33)=10.80$, $p<.001$, $d=1.85$, 95% CI [21.75, 31.85]; active control: $t(33)=8.19$, $p<.001$, $d=1.40$, 95% CI [11.33, 18.83]), with cognitive task performance at both the post-training assessment (independent samples *t*-test, $t(66)=4.78$, $p<.001$, $d=1.16$, 95% CI [11.35, 27.64]) and the follow-up assessment ($t(66)=2.76$, $p=.007$, $d=0.67$, 95% CI [3.18, 19.83]) significantly higher in the CCT group than in the active control condition (see Table 2). The results were similar when not taking into account ITT and including completers only (see Supplemental material Table 2).

We did not find differential effects of training on *self-reported cognitive complaints* when taking into account ITT: we only found a general decrease in cognitive complaints over time (Baseline: $M=118.40$, $SD=23.54$; Post-training: $M=115.32$, $SD=24.60$; Follow-up: $M=112.65$, $SD=25.32$; see Table 3). However, results for completers only do show a near significant effect of CCT on cognitive complaints (Time x Group interaction: $F(2, 54)=2.70$, $p=.076$, $\eta_p^2=0.09$), with follow-up paired samples *t*-tests suggesting a marginal significant decrease in cognitive complaints from baseline to the post-training assessment in the CCT group ($t(28)=2.03$, $p=.053$, $d=0.38$, 95% CI [-0.05, 9.16]), and a significant decrease in cognitive complaints from the post-training assessment to three months follow-up ($t(27)=2.72$, $p=.011$, $d=0.51$, 95% CI [1.72, 12.28]), which was not the case in the active control condition (all *t*s<0.96, see Supplemental material Table 2). However, this did not result in a significant group difference in self-reported cognitive complaints at three months follow-up, $t(55)=1.71$, $p=.094$, $d=0.45$, 95% CI [-1.92, 23.85].

Effects on primary outcome measures: brooding and depressive symptomatology. Taking into account ITT, we found beneficial effects of CCT on both *brooding* and *depressive symptomatology* as shown by the significant Time x Group interactions (see Table 3 and Figure 2A/B). Follow-up paired samples *t*-tests indicate that the immediate beneficial effects of CCT on depressive symptomatology (from baseline to the post-training assessment; $t(33)=2.83$, $p=.008$, $d=0.49$, 95% CI [0.95, 5.82]) remained stable from post-training to the three month follow-up ($t(33)=0.88$, $p=.385$, $d=0.15$, 95% CI [-1.16, 2.92]). In contrast, no change in depressive symptomatology occurred in the active control condition (all ts<1.58). Independent samples *t*-tests indicate that the CCT group reported significantly lower levels of depressive symptomatology than the active control condition at three months follow-up ($t(66)=3.15$, $p=.002$, $d=0.76$, 95% CI [1.75, 7.84]), whereas there was a tendency towards a group difference immediately following two weeks of training ($t(66)=1.94$, $p=.057$, $d=0.47$, 95% CI [-0.11, 7.94]). Similarly, only the CCT condition showed an immediate reduction in brooding (from baseline to the post-training assessment; CCT: $t(33)=2.97$, $p=.006$, $d=0.51$, 95% CI [0.66, 3.52]; active control: $t(33)=0.91$, $p=.371$, $d=0.16$, 95% CI [-0.44, 1.14]). Furthermore, although both groups reported a significant reduction in brooding from post-training to three months follow-up (CCT: $t(33)=2.63$, $p=.013$, $d=0.45$, 95% CI [0.25, 1.93]; active control: $t(33)=2.62$, $p=.013$, $d=0.45$, 95% CI [0.28, 2.25]), independent samples *t*-tests indicate that brooding levels were significantly lower in the CCT condition at post-training ($t(66)=3.42$, $p=.001$, $d=0.83$, 95% CI [1.04, 3.96]) and follow-up ($t(54.24)=3.59$, $p=.001$, $d=0.87$, 95% CI [1.03, 3.62]; see Table 2). These interaction effects were also found when performing completers-only analysis.[3]

Effects on secondary outcome measures.

(Mal)Adaptive emotion regulation. Results for ITT analysis on the alternative measure

for *maladaptive emotion regulation* are in line with the above reported beneficial effects on brooding. That is, we found a significant Time x Group interaction effect for CERQ maladaptive emotion regulation (see Table 3 and Figure 2C), with follow-up paired samples *t*-tests indicating immediate beneficial effects of CCT (from baseline to post-training assessment; $t(33)=3.72$, $p<.001$, $d=0.64$, 95% CI [2.53, 8.65]), and a further decrease in maladaptive emotion regulation from post-training to the three month follow-up ($t(33)=2.56$, $p=.015$, $d=0.44$, 95% CI [0.83, 7.29]). In line with the results for brooding, the active control condition only showed a decrease in maladaptive emotion regulation from post-training to follow-up (from baseline to post-training: $t(33)=0.35$, $p=.728$, $d=0.06$, 95% CI [-1.41, 2.00]; from post-training to follow-up: $t(33)=2.65$, $p=.012$, $d=0.45$, 95% CI [0.70, 5.36]). Importantly, in absence of baseline group differences, compared to the active control condition the CCT condition reported deploying less maladaptive emotion regulation strategies immediately following training ($t(66)=2.17$, $p=.034$, $d=0.53$, 95% CI [0.43, 10.22]) and at three months follow-up ($t(66)=3.01$, $p=.004$, $d=0.73$, 95% CI [2.14, 10.57]; see Table 2). In contrast to the beneficial effects on maladaptive emotion regulation processes, CCT did not affect self-reported use of *adaptive emotion regulation strategies* (see Table 2, Table 3). Similar interaction effects were found when deploying completers-only analysis.

Other indicators of functioning. CCT had beneficial effects on *resilience* and *remission from depression* (see Table 3). In contrast to the active control condition ($t(33)=0.03$, $p=.979$, $d=0.01$, 95% CI [-2.20, 2.26]), follow-up paired samples *t*-tests revealed that participants in the CCT condition showed a significant increase in resilience ($t(33)=4.31$, $p<.001$, $d=0.74$, 95% CI [3.44, 9.62]; see Table 2 and Figure 2D), resulting in a significant group difference in self-reported resilience levels at three months follow-up in favor of the CCT condition (independent

samples *t*-test, $t(66)=2.60$, $p=.011$, $d=0.63$, 95% CI [1.72, 13.10]). Furthermore, the CCT group showed a significant reduction in residual symptomatology (RDQ; $t(33)=2.31$, $p=.027$, $d=0.40$, 95% CI [0.65, 10.35]) while participants from the active control condition reported an increase in residual symptoms at three months follow-up ($t(33)=2.43$, $p=.021$, $d=0.42$, 95% CI [0.91, 10.15]; see Table 2). In line with the findings for our primary outcome measure for depressive symptomatology (BDI-II), participants from the CCT condition reported significantly lower levels of residual symptomatology (RDQ) at three months follow-up (independent samples *t*-test, $t(66)=3.10$, $p=.003$, $d=0.75$, 95% CI [3.86, 17.79]).

We found a marginal significant interaction for *Quality of Life* (see Table 3), which turned significant when performing completers-only analyses (Time x Group interaction: $F(1, 55)=4.63$, $p=.036$, $\eta_p^2=0.08$). However, follow-up paired samples *t*-tests suggest that Quality of Life remained stable in both groups (all ts<1.66; see Supplemental material Table 2). Moreover, both groups did not significantly differ in self-reported Quality of Life at three months follow-up ($t(55)=1.43$, $p=.158$, $d=0.38$, 95% CI [-0.72, 4.32]). Completers-only analysis also yielded a significant Time x Group interaction effect for *WHODAS disability score* (Time x Group interaction: $F(1, 55)=7.05$, $p=.010$, $\eta_p^2=0.11$), with follow-up paired samples *t*-tests suggesting a significant increase in functioning (a decrease in disability) in the CCT group only (CCT: $t(27)=3.30$, $p=.003$, $d=0.62$, 95% CI [2.34, 10.01]; active control: $t(28)=0.61$, $p=.545$, $d=0.11$, 95% CI [-2.99, 5.54]; see Supplemental material Table 2). As a result, in absence of baseline group differences, the CCT group reported significantly lower levels of experienced disability at three months follow-up (independent samples *t*-test, $t(55)=2.58$, $p=.012$, $d=0.69$, 95% CI [2.01, 15.87]).

Mediation Hypothesis

We conducted multiple regression analyses to test whether effects of cognitive control on depressive symptomatology were mediated by brooding. To ensure sufficient variability in change in cognitive control over time and to have the necessary power to detect mediation effects, we relied on the sample of participants used for the primary analyses (N = 68). Increase in cognitive control from baseline to post-training (Δ non-adaptive PASAT task performance) entered the model as the independent variable. Post-training brooding was selected as mediator and follow-up depressive symptomatology as dependent variable. Effects of baseline depressive symptomatology (B=0.29, t=3.21, p=.002) and baseline brooding (B=-0.03, t=0.15, p=.879) on the dependent variable were controlled for by entering both variables as covariates in the model (see Figure 3).

Results indicate that initial increase in cognitive control (Δ non-adaptive PASAT task performance) predicted lower post-training brooding levels (A-path; B=-0.05, t=2.13, p=.037) and less depressive symptomatology at three months follow-up (C-path; B=-0.13, t=3.11, p=.003). Furthermore, post-training brooding predicted more future depressive symptomatology (B-path; B=0.94, t=4.10, p<.001). Given that both A- and B-paths were significant, we continued the mediation analysis via the Preacher and Hayes bootstrapping method (Preacher & Hayes, 2004) with bias-corrected confidence estimates, using 5000 bootstrap resamples to obtain the 95% confidence interval (CI) of the indirect effect (Preacher & Hayes, 2008). Results confirmed the mediating role of brooding for the effect of cognitive control on depressive symptomatology (B=-0.04; 95% CI [-0.10, -0.01]). Given that the direct effect of cognitive control on depressive symptomatology remained significant when controlling for the mediator (C'-path; B=-0.09, t=2.30, p=.025), these findings suggest partial mediation.

Discussion

This RCT study demonstrates the preventive potential of CCT following recovery from depression. We found near transfer of training on a cognitive transfer task, suggesting successful manipulation of cognitive control. Moreover, participants completing the CCT intervention reported a reduction in cognitive complaints over time. In line with our first hypothesis, findings indicated immediate and lasting beneficial effects of CCT on primary outcome measures brooding and depressive symptomatology, even after controlling for ITT. The finding that similar effects were obtained for alternative measures of maladaptive emotion regulation (CERQ) and residual depressive symptomatology (RDQ) adds to the validity of the reported effects. These moderate to strong effects are in line with previous studies exploring the preventive and curative potential of CCT in at-risk and MDD populations (Calkins et al., 2015; Hoorelbeke, Koster, et al., 2015; Siegle et al., 2014). Furthermore, in contrast to Siegle et al. (2014), participants in the CCT condition showed the tendency to report less depressive symptomatology immediately following training. This between-group difference in depressive symptomatology turned significant at three months follow-up. Interestingly, this is in line with previous findings suggesting that beneficial effects of CCT may gradually develop over time. Confirming our second hypothesis, effects of cognitive control on depressive symptomatology were partially mediated by brooding, suggesting both direct and indirect beneficial effects of CCT on depressive symptomatology. Importantly, CCT also showed transfer to indicators of functioning (e.g., resilience, disability), confirming our third hypothesis. However, in accordance with previous experimental studies (Hoorelbeke et al., 2016), CCT did not exert effects on adaptive emotion regulation strategies. Similarly, effects on quality of life were limited.

The lack of training effects on adaptive emotion regulation may indicate that cognitive control is less crucial to deployment of adaptive emotion regulation strategies once recovery from depression has occurred. Alternatively, it is possible that – while stimulating cognitive control may provide individuals with the necessary cognitive resources to disengage from perseverative negative thinking processes – in order to adopt more adaptive emotion regulation strategies in daily life, combining CCT with other therapeutic interventions may be warranted (e.g., emotion regulation skill training). Furthermore, a growing literature suggests that the extent to which engaging in a certain emotion regulation strategy is adaptive depends on the flexible deployment of that emotion regulation strategy within a given context (Aldao, Sheppes, & Gross, 2015; Aldao, 2013; Bonanno, Papa, Lalande, Westphal, & Coifman, 2004). Moreover, previous findings indicate the importance of taking into account the interaction between both adaptive and maladaptive emotion regulation strategies in relation to psychopathology (e.g., Aldao, Jazaieri, Goldin, & Gross, 2014; Aldao & Nolen-Hoeksema, 2012; Conklin et al., 2015), whereas we have explored the effects on adaptive and maladaptive emotion regulation separately.

On a theoretical level, these experimental findings confirm the causal role of cognitive control in maladaptive emotion regulation as a vulnerability factor for (residual) depressive symptomatology. Furthermore, these findings indicate that cognitive control may contribute to resilience and functioning. Although it has been proposed that cognitive control may play a role in resilience via adaptive emotion regulation strategies, the current findings indicate that other mechanisms may underlie the observed relation between cognitive control and resilience. These findings have significant clinical implications, suggesting that directly targeting cognitive control via cognitive training reduces residual symptomatology and holds the potential to contribute to the prevention of recurring depressive episodes.

Demonstrating the efficacy of CCT as a neurobehavioral intervention for RMD patients, this RCT is the first study to provide experimental evidence for the causal role of cognitive control in cognitive vulnerability for depression and resilience following recovery from a depressive episode. Other strengths of this study are the use of an active control condition that is closely matched to the intervention, extending the focus to a wide range of indicators of functioning (among which alternative measures for the primary outcome measures), and repeated assessment of cognitive transfer effects at three months follow-up. Although participants maintained their training-related improvements, we observed a subtle reduction. This could indicate that booster sessions may be warranted to increase long-term beneficial effects of CCT on stable remission.

Certain limitations should be taken into account. This study is the first to explore effects of CCT in a RMD population whereas previous studies have typically explored effects in healthy, at-risk (student) samples, or MDD patients (e.g., Brunoni et al., 2014; Calkins et al., 2015; Hoorelbeke, Koster, et al., 2015; Segrave et al., 2014; Siegle et al., 2014). Despite these promising results, replication is warranted. Furthermore, effects were assessed using self-report questionnaires until three months follow-up. Future studies should explore long-term effects using structured interviews to directly assess the efficacy of CCT in reducing recurrence of depressive episodes. Additionally, to further enhance our understanding of the mechanisms underlying beneficial effects of CCT on depression vulnerability, future studies could combine CCT with experience sampling (e.g., Hoorelbeke et al., 2016) in clinical samples. Third, we relied on a cognitive task showing high resemblance to the training task to assess close cognitive transfer. As a result, strategy learning may have confounded the cognitive transfer effects. Future studies could deploy multiple transfer tasks. Importantly, there is increasing evidence for the

neural underpinnings of effects of CCT (Cohen et al., 2016; Schweizer, Grahn, Hampshire, Mobbs, & Dalgleish, 2013; Siegle, Ghinassi, & Thase, 2007) and cognitive transfer effects of the training procedure used in this study have also been established using a dual n-back task (Hoorelbeke et al., 2016). In the current study we instead added a measure for the clinical experience of the patient (self-reported cognitive complaints). Finally, due to sample size restrictions, we did not explore potential moderators of training success (e.g., medication use). It is likely that beneficial effects of CCT may be increased using a stepped-care and individually tailored training approach. Overall, although this is an interesting initial test of the potential of CCT as a preventive intervention for recurrent depression, replication in a larger sample of RMD patients is desirable following-up participants over a clinically more meaningful timeframe in terms of exploring effects on recurrence of depression.

Conclusion

This double-blind RCT study provides evidence for the effectiveness of a working memory based CCT in reducing cognitive vulnerability for depression and increasing resilience in RMD patients. Compared to an active control condition, CCT demonstrated beneficial effects on cognitive functioning, brooding, and depressive symptomatology immediately following training and at three months follow-up. Similar findings were obtained using alternative measures of maladaptive emotion regulation and residual symptomatology. In line with existing theories, improvement in cognitive control predicted lower future levels of depressive symptomatology, which was partially mediated by brooding. Additional beneficial effects were found on resilience and disability. However, no effects were found on indicators of adaptive emotion regulation. Overall, these findings demonstrate the potential of CCT as a preventive intervention following recovery from depression.

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The design was set-up by KH and EK. Data was collected by KH, assisted by students Lien Faelens, Jeffrey Behiels, and Sylvie Van Paemele. KH analyzed the data. KH and EK were involved in writing the manuscript. Both authors agree to the final version of this manuscript. None of the authors report competing interests. We thank Ineke Demeyer and Laura de Putter for overseeing the blinding procedure and Stephanie Stevens for proofreading the manuscript.

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Footnote(s)

(1) Excluding these two participants from the primary analyses did not affect our main findings indicating beneficial effects of CCT.

(2) Effects of (potential) violations of test assumptions due to the distribution of variables were evaluated using transformation. However, the main analysis proved to be robust, adding to the validity of the reported findings.

(3) Effects of CCT on the primary outcome measures remained after controlling for change in process measures of training session experience (i.e., rated mood and thoughts during and immediately following completion of an online training session; for a complete description of the protocol, please see Hoorelbeke, Faelens, et al., 2015). This indicates that training effects may not be reduced to habituation to stress.

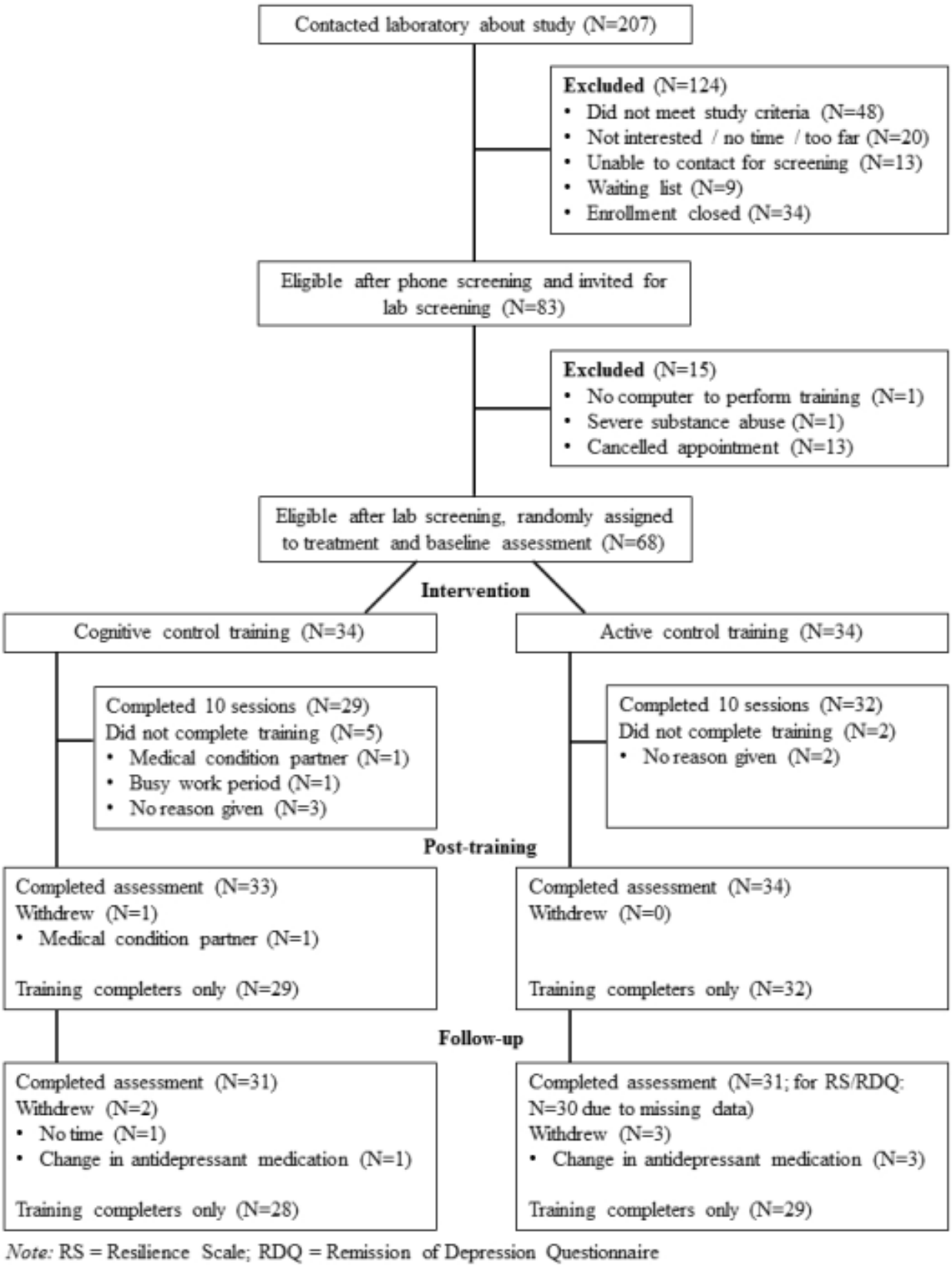
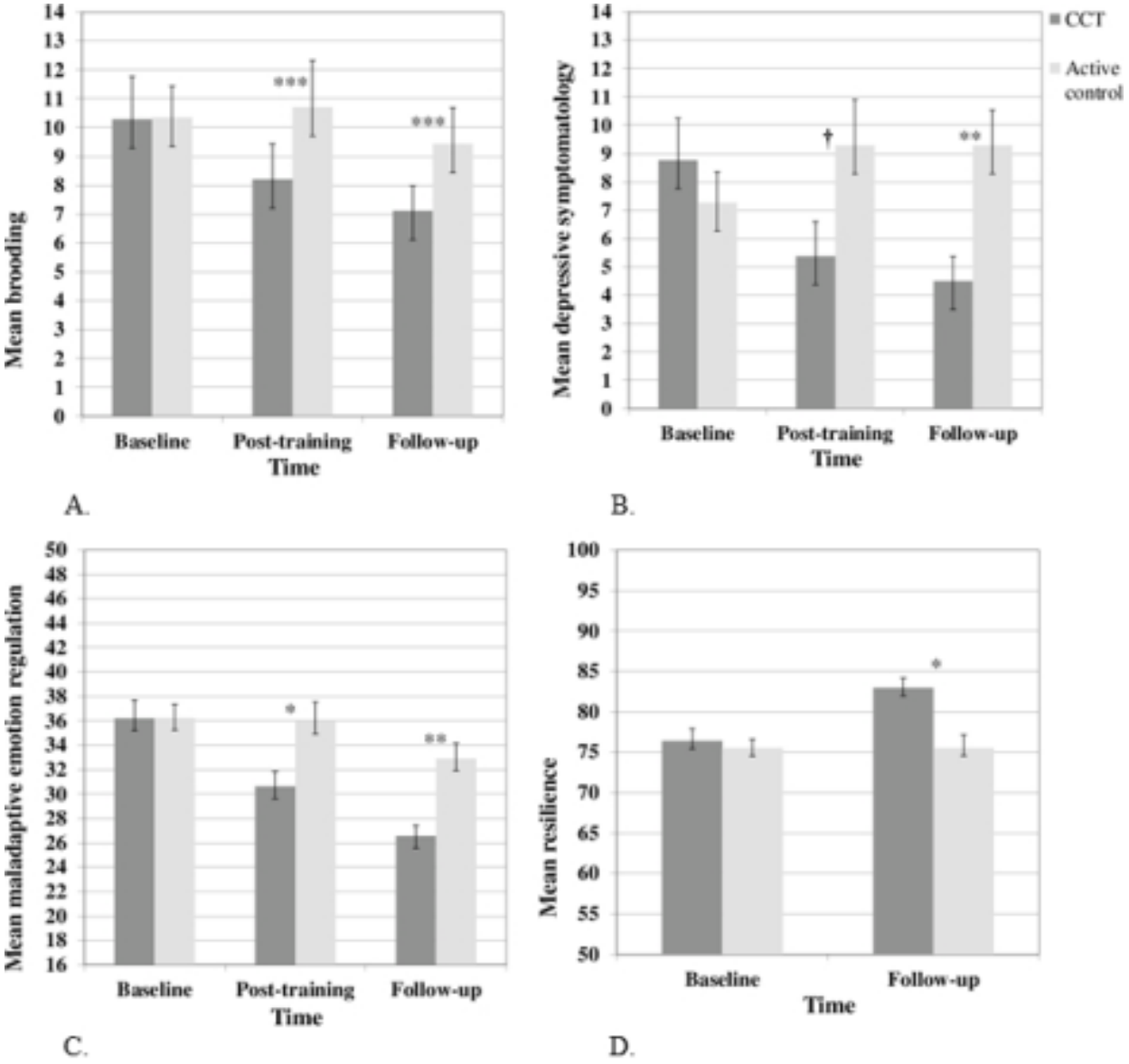
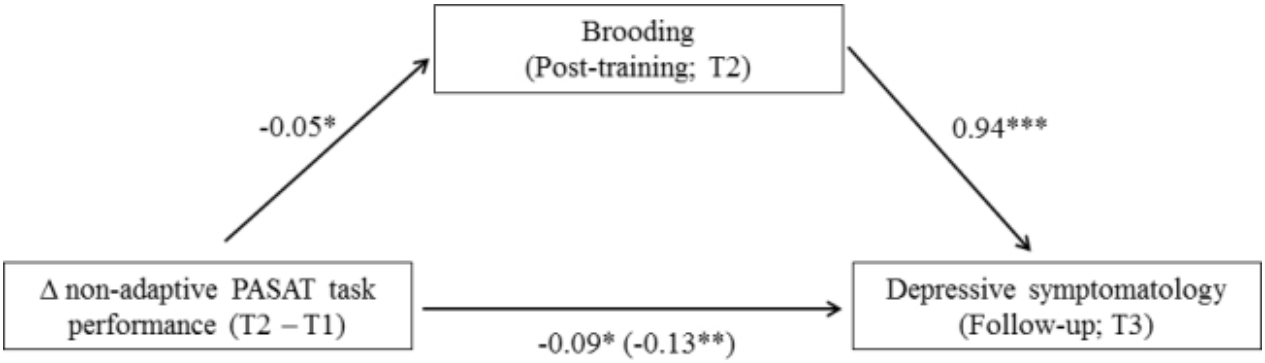


Figure 1. Consort diagram for flow of participants



Note: Independent samples t-tests, † = p<0.100, * = p<0.050, ** = p<0.010, *** = p≤0.001;
A. Time x Group effect on brooding; B. Time x Group effect on depressive symptomatology;
C. Time x Group effect on maladaptive emotion regulation; D. Time x Group effect on resilience

Figure 2. Effects of training on the primary outcome measures, maladaptive emotion regulation and resilience (M, SE)



Covariates: Baseline Brooding (T1; -0.03)
Baseline Depressive symptomatology (T1; 0.29**)

Note: * = p<0.050, ** = p<0.010, *** = p<0.001

Figure 3. Mediation model

Table 1

Demographic and study progress information by group

	Training condition				
	Cognitive control (*N*=34)	Active control (*N*=34)	Statistic	df	*p*
Age (M ± SD)	46.12 ± 10.80	47.82 ± 12.20	t=0.61	66	.544
Gender (male : female)	12 : 22	11 : 23	χ^2=0.07	1	.798
Age of onset (M ± SD)	28.77 ± 11.63	25.82 ± 13.98	t=0.94	66	.349
Amount of depressive episodes (M ± SD)	2.79 ± 3.28	3.79 ± 5.05	t=0.97	66	.337
Episode length in months (M ± SD)	6.81 ± 4.06	7.19 ± 5.26	t=0.34	66	.738
Time since previous episode in years (M ± SD)	6.49 ± 7.05	5.91 ± 5.64	t=0.37	66	.710
Received inpatient treatment (yes : no)	10 : 24	14 : 20	χ^2=1.03	1	.310
Current use of antidepressant medication (yes : no)	11 : 23	17 : 17	χ^2=2.19	1	.139
Therapeutic maintenance contact (yes : no)	4 : 30	9 : 25	χ^2=2.38	1	.123
Days from baseline to post-training assessment[a]	14.09 ± 0.98	13.97 ± 1.00	t=0.50	65	.621
Days from post-training assessment to follow-up[b]	90.88 ± 8.32	88.82 ± 6.84	t=1.10	64	.277

Note: [a] For these values, CCT (N=33) and active control (N=34), not taking into account exclusion due to change in antidepressants use; [b] For these values, CCT (N=32) and active control (N=34), not taking into account exclusion due to change in antidepressants use

Table 2

Group characteristics as a function of training condition

	Training condition											
	Cognitive control (N=34)						Active control (N=34)					
	Time 1		Time 2		Time 3		Time 1		Time 2		Time 3	
Variables	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Cognitive transfer measures												
Cogn. task accur.	50.82	17.89	82.53	16.72	77.61	17.04	51.03	12.91	63.04	16.90	66.11	17.33
Cogn. complaints	117.15	24.84	112.62	25.47	107.97	24.10	119.65	22.47	118.03	23.77	117.32	25.99
Primary outcome measures												
Depressive sympt.	8.77	8.65	5.38	7.10	4.50	5.10	7.27	6.28	9.29	9.37	9.29	7.28
Trait rumination	43.00	11.88	34.71	10.01	30.06	6.72	43.29	12.27	44.29	12.58	40.35	14.06
Brooding	10.29	3.77	8.21	2.57	7.12	1.95	10.35	2.91	10.71	3.40	9.44	3.23
Reflection	9.59	3.46	8.12	3.07	7.00	2.32	9.85	3.56	9.79	3.49	9.21	3.84
Secondary outcome measures												
Adaptive ER	59.15	13.34	58.88	15.87	55.71	17.16	56.65	14.31	54.82	14.19	56.00	14.86

Maladaptive ER	36.21	9.41	30.62	9.69	26.56	7.88	36.24	10.86	35.94	10.51	32.91	9.47
Quality of Life	4.24	6.28	/	/	2.79	4.20	3.32	4.55	/	/	4.59	5.44
Disability	17.23	13.73	/	/	14.71	14.82	19.66	11.41	/	/	20.97	14.34
Resilience	76.41	10.37	/	/	82.94	11.98	75.50	11.32	/	/	75.53	11.52
Remission	19.44	15.61	/	/	13.94	11.96	19.24	14.87	/	/	24.77	16.46
Other variables												
Credibility	0.21	2.74	0.48	2.74	/	/	-0.21	2.32	-0.50	2.57	/	/
Expectancy	0.54	2.64	0.51	2.55	/	/	-0.54	2.52	-0.52	2.72	/	/
Stressful events	1.27	1.40	0.47	0.66	0.74	0.93	1.15	1.26	0.50	0.86	0.85	1.11

Note: ER = Emotion Regulation; These descriptives represent information on Group level at the Baseline- (Time 1), Post-training- (Time 2), and Follow-up assessment (Time 3) taking into account intention-to-treat. Independent samples *t*-tests indicate that both groups did not significantly differ at Time 1 concerning the cognitive transfer and outcome measures (all *t*s<1.73). Furthermore, independent samples *t*-tests indicate that participants did not differ in amount of experienced stressful / life events from one year prior to participation to the study until the follow-up assessment (all *t*s<0.49)

Table 3

Evidence for training effects from Mixed ANOVA's

	Main effect of Time				Main effect of Group				Time x Group interaction			
Variables	*F*	*df*	*p*	η_p^2	*F*	*df*	*p*	η_p^2	*F*	*df*	*p*	η_p^2
Cognitive transfer measures												
Non-adaptive PASAT accuracy[a]	93.86	2, 65	< .001	0.74	7.87	1, 66	.007	0.11	18.52	2, 65	< .001	0.36
Cognitive complaints[a]	3.65	2, 65	.032	0.10	1.09	1, 66	.300	0.02	1.20	2, 65	.308	0.04
Primary outcome measures												
Brooding[a]	12.10	2, 65	< .001	0.27	7.85	1, 66	.007	0.11	4.70	2, 65	.012	0.13
Depressive symptomatology[a]	0.79	2, 65	.459	0.02	2.56	1, 66	.115	0.04	7.04	2, 65	.002	0.18
Secondary outcome measures												
Maladaptive emotion regulation[a]	17.39	2, 65	< .001	0.35	3.60	1, 66	.062	0.05	5.79	2, 65	.005	0.15
Adaptive emotion regulation[a]	0.66	2, 65	.519	0.02	0.45	1, 66	.505	0.01	0.87	2, 65	.425	0.03
Resilience[b]	12.30	1, 66	.001	0.16	2.60	1, 66	.111	0.04	12.08	1, 66	.001	0.16
Remission from depression[b]	0.00	1, 66	.993	0.00	2.76	1, 66	.101	0.04	11.21	1, 66	.001	0.15
Disability[b]	0.14	1, 66	.714	0.00	2.30	1, 66	.134	0.03	1.36	1, 66	.249	0.02

Quality of Life[b]	0.02	1, 66	.904	0.00	0.19	1, 66	.668	0.00	3.46	1, 66	.067	0.05
Other measures												
Credibility[b]	0.00	1, 66	.982	0.00	1.88	1, 66	.176	0.03	0.56	1, 66	.455	0.01
Expectancy[b]	0.00	1, 66	.984	0.00	3.58	1, 66	.063	0.05	0.01	1, 66	.927	0.00

Note: The presented statistics take into account intention-to-treat analysis; [a] Represents results of 3 (Time) x 2 (Group) Mixed ANOVA's; [b] Represents results of 2 (Time) x 2 (Group) Mixed ANOVA's