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Online cognitive control training for remitted depressed individuals: a replication and extension study

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Abstract

Background: Remitted depressed (RMD) individuals form a risk group for developing future depressive episodes. Improving cognitive control may reduce the risk to develop novel depressive symptoms, as beneficial effects of such training were demonstrated in RMD individuals.

Method: The current study attempted to replicate and extend these results. In this randomized controlled trial (ClinicalTrials.gov NCT03278756), 68 RMD individuals were allocated to a cognitive control training or an active control condition, each comprised of 10 homework sessions dispersed over two weeks. Primary outcome measures were depressive symptomatology and rumination. Assessment took place before and after training and at 3 and 6 month follow-up.

Results: This study showed training-related cognitive transfer and mixed effects on indicators of subjective cognitive functioning, depressive- and anxiety symptoms, as well as broader residual complaints. In addition, we failed to observe previously reported beneficial effects of CCT on indicators of emotion regulation and resilience.

Conclusions: Given the partial replication of previously reported effects of cognitive control training in RMD, further research is needed.

Cognitive impairments can be troublesome symptoms of a major depressive disorder (e.g., Austin, Ross, Murray, O'Carroll, Ebmeier, & Goodwin, 1992, Austin, Mitchell, & Goodwin, 2001; Porter, Bourke, & Gallagher, 2007; Snyder, 2013), that express themselves as problems with attention and memory, and moreover can lead to problematic psychosocial functioning (e.g., work or study problems). In turn, such problems can further decrease self-esteem and quality of life, causing a downward spiral of cognitive and affective processes. Importantly, these impairments often persist during remission from depression (Chen & Hergert, 2017), for instance reflected by attention and immediate memory problems (Baune, Miller, McAfoose, Johnson, Quirk, & Mitchell, 2010). Indeed, a recent meta-analysis showed that several cognitive impairments remain after successful treatment and worsen with the number of previous depressive episodes (Semkovska et al., 2019). In recent years, several theorists have argued that these impairments are not merely a side effect of major depressive disorder, but might form a risk factor for developing new depressive episodes (Joormann, Yoon, & Zetsche, 2007; Millan et al., 2012). It is argued that diminished activation in the prefrontal cortex, which may reflect cognitive control impairments (Collette & Van der Linden, 2002; Smith & Jonides, 1999), is linked to impaired inhibition of amygdala activity, resulting in prolonged limbic activation relating to cognitive processes such as rumination (Siegle, Steinhauer, Thase, Stenger, & Carter, 2002; De Raedt & Koster, 2010). In this context, cognitive control can be defined as processes responsible for adapting information processing and behavior in line with current goals (Braver, 2012; Koster, Hoorelbeke, Onraedt, Owens, & Derakshan, 2017). Furthermore, cognitive

control is negatively associated with depression (Harvey et al., 2004; Moriya & Tanno, 2008; Zetsche & Joormann, 2011; Snyder, 2013; Letkiewicz et al., 2014).

Supporting the view that impaired cognitive control might act as a risk factor for depression, cognitive control impairments have been observed in at-risk groups (e.g., Owens, Koster, & Derakshan, 2011; Levens & Gotlib, 2015), and have shown to predict other emotion regulation difficulties, such as depressive rumination and subsequent depressive symptoms (De Lissnyder, Koster, Goubert, Onraedt, Vanderhasselt, & De Raedt, 2012; Joormann & Gotlib, 2009; Ronold, Joormann, & Hammar, 2018). Furthermore, with every depressive episode, there is an increase in cognitive control impairments (Semkovska et al, 2019) and relapse risk (Beshai, Dobson, Bockting, & Quigley, 2011; Bockting, Spinhoven, Koeter, Wouters, & Schene, 2006). Therefore, there is an increasing interest in interventions that could remediate depression-related cognitive control impairments.

Training Paradigm

In this context, cognitive control training (CCT) may be of particular interest. That is, CCT can be implemented in several ways (e.g., in terms of training paradigm, timing and length of training sessions, number of training sessions; for a review, see Koster et al., 2017). The most frequently used task to this aim is the Paced Auditory Serial Addition Task (PASAT, Gronwall, 1977; Siegle, Ghinassi, & Thase, 2007). In this task, participants hear digits (1-9) and are tasked with indicating the sum of the last two digits, on a trial-by-trial basis. In a standardized, non-adaptive PASAT (naPASAT),

multiple blocks with different but fixed intertrial intervals of the digits are presented. In an adaptive PASAT (aPASAT), the intertrial interval is dependent on the performance of the participant and decreases or increases throughout the task. Regardless of version, the PASAT loads on frontal brain regions such as the dorsolateral prefrontal cortex (Lazeron, Rombouts, de Sonneville, Barkhof, & Scheltens, 2003) and relies heavily on working memory, attention and processing speed (for a review, see Tombaugh, 2006). The naPASAT has typically been used to measure cognitive control functioning, while the aPASAT is utilized as a training task, given that difficulty is set at an adaptive yet challenging individual level (e.g., Siegle et al., 2007; Siegle, Price, Jones, Ghinassi, Painter, & Thase, 2014). This task will also be used in the current study.

Research Findings

There has been some evidence for effectiveness of cognitive training for depression. In a meta-analysis by Motter, Pimontel, Rindskopf, Devanand, Doraiswamy and Sneed (2016), small to moderate effects were reported on depressed mood, daily functioning, attention, working memory, and global functioning, but lacking for verbal memory or executive functioning. In terms of clinical outcomes, PASAT-based training seems the most promising where depressive symptomatology has shown to be decreased in multiple studies (e.g., Siegle et al., 2007; Segrave, Arnold, Hoy, & Fitzgerald, 2014; Calkins, McMorran, Siegle, & Otto, 2015) and positive effects on depressive rumination have been found (Siegle et al., 2014; Hoorelbeke, Koster, Vanderhasselt, Callewaert, & Demeyer, 2015).

In a particularly promising double-blind randomized controlled trial (RCT), Hoorelbeke and Koster (2017) investigated whether applying CCT in a remitted

depressed sample could reduce cognitive vulnerability (protocol in Hoorelbeke, Faelens, Behiels, & Koster, 2015). This RCT compared ten sessions of aPASAT with an active control training, over the course of two weeks. Assessments were conducted at baseline, immediately following training, and three months later. Beneficial effects of CCT were found in terms of reduced depressive symptomatology, rumination, residual complaints, and maladaptive emotion regulation strategies. These effects were observed directly after training and were maintained at a three-month follow-up. Interestingly, CCT also had an impact on positive outcomes. That is, the experimental group reported an increase in resilience scores from baseline to three months follow-up, reflecting an overall protective effect of CCT (Hoorelbeke & Koster, 2017). This demonstrates that PASAT-based CCT holds promise as a preventive intervention for remitted depressed individuals.

While this RCT provided important and clinically relevant information as a first study of effects of CCT in remitted depressed patients, it also has several limitations. First, user experiences were suboptimal. That is, the original training procedure relied on an experimental paradigm that was modified to be conducted online. Assessment of user experiences in a limited subset of the sample indicated that the training procedure could be more engaging (Vervaeke, Van Looy, Hoorelbeke, Baeken, & Koster, 2018). This is particularly noteworthy, as user engagement has been found to be a predictor of CCT effectiveness (Siegle et al., 2014). Second, the original study included a follow-up period of three months, which is commendable. However, follow-up studies exploring effects of CCT over a longer time period are needed to examine the duration of beneficial effects.

Bearing these limitations in mind, we developed a novel CCT platform with end-user involvement, which provides an integrated way to administer questionnaires and present standardized and training tasks, in order to assess participants fully online (for more information regarding the development process, see Vervaeke et al., 2018). The aim of the current study was to conceptually replicate and extend the previous RCT by Hoorelbeke & Koster (2017), using the same methodology, similar measures but a new platform, to assess the stability of the findings. Important novel aspects of our study are the novel online training and assessment platform, inclusion of measures of task engagement, broader measures of psychopathology (e.g., assessment of level of anxiety and stress symptoms, in addition to level of depressive symptoms), and an extended follow-up period.

Based on the findings of Hoorelbeke & Koster (2017), we preregistered the following hypotheses (ClinicalTrials.gov identifier: NCT03278756): Our primary hypothesis is that CCT will result in a decrease in depressive symptomatology and rumination. More specifically, in RMD - if remaining cognitive impairments disrupt emotion regulation - this will increase the risk for depressive symptoms in the group without the active intervention relative to the CCT group, especially at 3 and 6 months follow-up. Furthermore, we expect maladaptive emotion regulation strategies and residual symptomatology to decrease, while adaptive emotion regulation strategies and quality of life will remain unaffected. Lastly, resilience in the CCT group is thought to show an increase. Given that we also wanted to extend the results, we included effortful control as an outcome, where we expect an increase on the attentional control scale.

Method

Participants

Participants were recruited through media advertisements. In order to be eligible for participation in this study, volunteers had to (a) be between 18 and 65 years old, (b) report a history of depressive episodes in the context of major depressive- or bipolar disorder in absence of an ongoing depressive episode for at least three months, (c) report no history of psychosis, substance abuse or cognitive complaints after brain injury, (d) report using no or a stable dose of medication, (e) report receiving no or stable therapeutic maintenance contact (one session every three weeks, or less), (f) have reliable internet access, and (g) own a functional computer and external mouse or tablet computer. To assess eligibility, a telephone screening was conducted beforehand, where the criteria for current and past depressive episode from the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998; Overbeek, Schruers, & Griez, 1999) were used.

Based on a power analysis conducted for the RCT of Hoorelbeke and Koster (2017; Hoorelbeke, Faelens et al., 2015), 68 participants were enrolled in the study, and randomized to one of two conditions in a double-blind fashion (see Figure 1 for the CONSORT participant flow diagram). Sample characteristics can be found in Table 1. All participants provided written informed consent.

Randomization and Blinding

The random allocation of participants to one of two conditions was performed using the software package RandList, by a researcher that had no contact with participants (KH). By doing so, the researcher in charge of assessing participants (JV)

was blind during the phase of data collection. Therefore, all information provided during baseline assessment regarding the training phase and other study steps was identical for the two conditions, ensuring blinded participants. Successful blinding of participants was evaluated at baseline and post-training assessment with the Credibility/Expectancy Questionnaire (CEQ; Devilly & Borkovec, 2000). In addition, JV remained blind for training condition during the phase of data-analysis. That is, KH provided a list grouping the subjects in two non-informative conditions and data from the primary and secondary outcome measures were analyzed separately from data from the training tasks.

Design

The full study protocol was approved by the medical ethical committee and preregistered on ClinicalTrials.gov (identifier code NCT03278756). It consisted of the following phases: (1) telephone screening, (2) screening and baseline assessment in the lab, (3) training phase, (4) online post-training assessment, (5) online follow-up assessment, and (6) final follow-up assessment in the lab. Except for the training procedure used, all phases were identical for the two conditions. As an experimental manipulation of cognitive control, participants repeatedly completed a cognitive control or active control task. All participants were instructed to start training within two weeks following the baseline assessment (BA), and to complete the post-training assessment (PA) within one week of the last training session. The online follow-up assessment (FU 3M) was scheduled three months after completion of the final training session. The final follow-up lab assessment (FU 6M) took place six months after completion of the training procedure.

Outcome Variables

All questionnaires and tasks were provided in Dutch and administered at every assessment, unless specified otherwise. For a full overview of all variables that were assessed at the different time points, see Table 2. For the primary outcome measures, higher scores reflect more symptoms or maladaptive processes. In terms of secondary outcome measures, this was reversed, with higher scores being indicative of more positive outcomes or adaptive processes, except for the maladaptive emotion regulation strategies and remission from depression.

Primary outcome measures. *Depressive symptomatology* was measured with the Depression Anxiety Stress Scales (DASS; Lovibond & Lovibond, 1995; de Beurs, Van Dyck, Marquenie, Lange, & Blonk, 2001) at every time point, which contains a subscale for depressive, anxiety and stress symptoms (range of each subscale: 0-42). Furthermore, the Beck Depression Inventory – II (BDI-II; range: 0-63; Beck, Steer, & Brown, 1996; Van der Does, 2002) was administered, at BA and FU 6M. *Depressive rumination* was measured during every assessment, with the Ruminative Response Scale (RRS; Nolen-Hoeksema & Morrow, 1991; Treynor, Gonzalez, Nolen-Hoeksema, 2003), which reports rumination (range: 22-88), brooding (range: 5-20) and reflection (range: 5-20).

Secondary outcome measures. *Adaptive and maladaptive emotion regulation strategies* were measured with the Cognitive Emotion Regulation Questionnaire (CERQ; Garnefski, Kraaij, & Spinhoven, 2001). The CERQ contains several subscales, reflecting use of (mal)adaptive emotion regulation strategies. Adaptive strategies include acceptance, taking perspective, planning, positive reappraisal, and positive reflection. Maladaptive strategies contain catastrophizing, ruminating, blaming yourself and blaming others. In line with Hoorelbeke and Koster (2017), we will use compound scores for

adaptive and maladaptive emotion regulation strategies (range maladaptive compound score: 16-80; range adaptive compound score: 20-100). *Quality of life* was assessed using the Quality of Life in Depression Scale (QLDS; range: 0-34; Hunt & McKenna, 1992; Tuynman-Qua, de Jonghe, & McKenna, 1997). *Remission from depression* was measured with the Remission of Depression Questionnaire (RDQ; range: 0-82; Peeters, Nicolson, Wichers, & Hacker, 2013; Zimmerman et al., 2013). The RDQ contains seven subscales: depressive symptoms, other symptoms, coping, positive mental health, general functioning, life satisfaction, and sense of well-being and is a measure for residual symptomatology. *Resilience* was measured by the Connor-Davidson Resilience Scale (CDRS; range: 0-100; Connor & Davidson, 2003).

Other outcome measures. A behavioral measure for *cognitive control* was included as well, by means of a non-adaptive Paced Auditory Serial Addition Task (naPASAT; Gronwall, 1977). This task consisted of three blocks counting 60 trials each. Every block had a fixed intertrial interval (Block 1, 3000 ms; Block 2, 2000 ms; Block 3, 1500 ms), increasing difficulty with each block. Mean accuracy was used as a measure for cognitive control. Participants heard a continuous string of digits (1-9) and had to indicate the sum of the last two digits on a trial-by-trial basis. *Effortful control*, as measured by the subscale of the Adult Temperament Questionnaires (EC-ATQ; Rothbart, Ahadi, & Evans, 2000; Hartman & Rothbart, 2001) was assessed at BA and FU 6M. This scale counts three components (range of each component: 1-7): attentional control, activation control, and inhibitory control and acts as a subjective indicator of cognitive functioning.

Control variables. To control for motivational differences, the User Engagement Scale (UES) and Credibility and Expectancy Questionnaire (CEQ) were administered. *User engagement* was assessed using the UES (range: 31-155; O'Brien & Toms, 2010) at PA only. This questionnaire contains six components: aesthetics, endurability, focused attention, involvement, novelty and usability. The CEQ (Devilly & Borkovec, 2000) was administered at BA and PA. This questionnaire measures *credibility and expectancy* separately. *The occurrence of stressful life events* was monitored using the List of Threatening Experiences (LTE; Brugha & Cragg, 1990; Rosmalen, Bos, & de Jonghe, 2012), allowing to control for negative events during the study that might impact outcomes.

Procedure

Screening phase. As a first step, potential eligible participants completed a telephone screening. At this stage, participants received information regarding the study design. Upon confirming interest in participation, eligibility was assessed. (e.g., age, depressive history, current treatment plan, access to technological devices). In particular, we relied on the mood disorders module of the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998; Overbeek et al., 1999). Furthermore, screening questions were asked to exclude candidates with a history of substance abuse, psychosis and cognitive complaints after brain injury. When all criteria were met, an appointment for a second screening and subsequent BA was scheduled.

The second, more elaborate screening took place in the lab, which contained the Dutch Mini-International Neuropsychiatric Interview screening version (Sheehan et al., 1998; Overbeek et al., 1999) for depression (again current and lifetime), suicidal risk,

mania, alcohol and substance dependence/abuse (modules A, C, D, J and K, respectively). Whenever a screening question received a positive response, the full corresponding module was administered. The module mood disorders was always administered completely. When all criteria were met, BA started.

Baseline assessment in the lab (BA). Written and oral psychoeducation was provided (as requested by the target population in Vervaeke et al., 2018) about the study in general and more specifically regarding the training platform. The following questionnaires were administered: DASS, BDI-II, RRS, CERQ, QLDS, RDQ, CDRS, LTE, CEQ and ATQ-EC. Furthermore, participants completed a naPASAT as a baseline assessment of cognitive functioning. Lastly, information regarding the following phases, including instructions when encountering issues, was offered, again in a written and oral manner.

Online training phase. For each condition, the training procedure consisted of ten sessions of 15 minutes each. Participants were instructed to complete all sessions within a period of 14 days and to complete no more than one session per day. The training phase was administered online and started within two weeks following the BA. This forms a deviation from Hoorelbeke & Koster (2017), where the training was to be completed within a period of two weeks following the BA. After each session, participants were asked to schedule in the next session and automated reminders via e-mail were sent accordingly.

Cognitive control task. An aPASAT was used as a CCT task. Participants heard digits (ranging from 1 to 9) and had to continuously indicate the sum of the most recently heard pair of digits (i.e., after each digit). By adapting the intertrial interval, the difficulty

of cognitive control training is adapted at an individual level. The intertrial interval decreased by 100 ms after four consecutive correct trials and increased by 100 ms after four consecutive incorrect or missed trials (as in Siegle et al., 2007; Hoorelbeke & Koster, 2017). In contrast to previous studies using the aPASAT training, the starting intertrial interval of each training session was based on the performance during the previous one. The ITI of the first session was based on performance on the naPASAT at baseline, offering a more individually tailored training approach.

Active control task. A speed-of-response training task was used as a low cognitive load variant of the aPASAT. Participants heard numbers (ranging from 1 to 18) and had to mark the corresponding response button with the same number on. The adaptive features of this task were identical to the CCT task. In addition, this task was visually identical to the CCT task and has repeatedly been used as an active control task (ACT) for CCT in previous studies (Hoorelbeke, Koster, Demeyer, Loeys, & Vanderhasselt, 2016; Hoorelbeke & Koster, 2017; Vervaeke, Hoorelbeke, Baeken, Van Looy, & Koster, 2020).

Online post-training assessment (PA). Participants were invited to complete an online post-training assessment within one week following completion of the final training session (as opposed to Hoorelbeke & Koster (2017), where this was the day following the last training session). The following questionnaires were administered: DASS, RRS, CERQ, QLDS, RDQ, CDRS, LTE, CEQ and UES. The naPASAT concluded this assessment.

Online follow-up assessment (FU 3M). Three months following completion of the last training session, participants were presented with another set of questionnaires

and the naPASAT. Questionnaires in this set were DASS, RRS, CERQ, QLDS, RDQ, CDRS, and LTE.

Final follow-up assessment in the lab (FU 6M). As a last step in this study, participants were invited back to the lab, six months after the final training session. This assessment started with these questionnaires: DASS, BDI-II, RRS, CERQ, QLDS, RDQ, CDRS, LTE, and ATQ-EC. Again, the naPASAT followed. Lastly, participants received a written and oral debriefing. Participants were thanked and monetary compensation was provided.

Data Analysis

Analyses were conducted using SPSS Statistics 25. We used mixed ANOVAs to model effects of CCT on primary, secondary, and other outcome measures. Significance was set at $\alpha \leq .05$. All available data was included and all means and performance data on tasks and questionnaires are displayed in Table 3.

Due to a technical error in a part of the questionnaire assessment, there was data loss for about 40% of the participants at FU 6M, for the questionnaires RRS, LTE and ATQ-EC, and questions regarding current treatment. This data loss was not limited to one condition and affected 25 subjects in total (12 from the CCT group and 13 from the ACT group), resulting in complete data of 38 participants for FU 6M (Figure 1). Missing data were handled with the Last Observation Carried Forward method and Intention-To-Treat analyses were conducted.

Results

Sample Characteristics

Sample characteristics are displayed in Table 1. Among the 68 participants that entered the study, 10 participants met diagnostic criteria for bipolar disorder. Importantly, distribution of patients in remission from bipolar versus unipolar depression did not differ between both conditions (Table 1). Overall, there were no pre-existing differences between the two groups for most variables. They did, however, differ significantly in terms of age and number of depressive episodes. When adding these two variables (age and number of depressive episodes) as covariates in the analyses, similar findings were obtained for each of the outcome measures, with the exception of anxiety and residual symptomatology, for which adding these covariates impacted the Time x Condition interaction. As such, the main analyses reported below do not include these covariates. Instead, where age and number of depressive episodes impacted effects of CCT on the outcome measures, secondary analyses are presented taking into account age and number of depressive episodes. Furthermore, there were no differences in duration between groups, in terms of training phase or days between assessments (Table 1).

Training Progression

Due to the different nature of both training tasks, progress during training was analyzed separately for the two training conditions (as in Hoorelbeke et al., 2016; Hoorelbeke & Koster, 2017; Vervaeke et al., 2020). Two repeated measures ANOVAs showed that, as expected, median intertrial intervals (ITI) decreased, meaning that participants improved significantly, on both training tasks: $F(2.7, 88.2) = 73.62$; $p <$

0.001; $\eta_p^2 = 0.69$ for the CCT group and $F(1.9, 61.7) = 9.88$; $p < 0.001$; $\eta_p^2 = 0.23$ for the ACT group. The median intertrial intervals are displayed in Figure 2. Follow-up paired samples *t*-tests within the CCT condition suggest that aPASAT performance increased significantly with every consecutive session until completion of the sixth training session (all $ts \geq 2.10$). Following session six, training progress in terms of median ITI scores stalled: no significant improvement in aPASAT performance was observed from session six to session seven ($t(33) = 0.27$, $p = .79$). However, aPASAT performance further improved from session seven to session eight ($t(33) = 2.41$, $p = .02$; all other $ts < 1.09$).

Task-Specific Cognitive Transfer

Cognitive transfer effects were assessed using a 4 (time: BA, PA, FU 3M, FU 6M) by 2 (training: CCT, ACT) Mixed ANOVA on naPASAT accuracy. There was a significant transfer effect, indicated by a significant time x training interaction: $F(1.8, 121.9) = 43.27$; $p < 0.001$; $\eta_p^2 = 0.40$. Independent samples *t*-tests suggest a significant difference between groups in terms of cognitive task performance at PA, FU 3M and FU 6M. Thus, even after six months without training, task-specific cognitive transfer remained present. In addition, using paired samples *t*-tests, we observed an increase in task performance from BA to PA in the CCT condition. From PA to FU 3M, and from FU 3M to FU 6M, task performance slightly declined again. Similarly, participants in the ACT condition showed an increase from BA to PA. However, scores did not decrease but remained stable in this group. Scores and significance of follow-up *t*-tests are shown in Figure 3.

Primary Outcome Measures

In terms of *depressive symptomatology*, there was no main effect of time or training task on any of the DASS subscales. Importantly, there was a significant interaction of time by training for the depression subscale (Table 4). Follow-up independent samples *t*-tests showed no difference between groups at PA ($t(66) = 0.31$; $p = .760$; $d = 0.07$), yet there was a marginally significant difference at FU 3M ($t(51.9) = 1.89$; $p = .064$; $d = 0.46$) and FU 6M ($t(59.9) = 1.74$; $p = .088$; $d = 0.42$), where the CCT group reported a trend for less depressive symptomatology than the ACT group.

No interaction effects were found for the stress and anxiety scale of the DASS. However, after controlling for age and number of depressive episodes, we observed a marginal significant interaction effect for anxiety ($F(3, 192) = 2.49$, $p = .06$, $\eta_p^2 = 0.04$), which seems to be due to an increase in anxiety scores from PA to FU 3M in the ACT group ($t(33) = 2.81$, $p = .008$, $d_{av} = 0.29$; all other *t*s < 0.99), whereas anxiety scores remained stable in the CCT group (all *t*s < 0.43). However, both groups did not significantly differ in level of anxiety at any of the time points (all *t*s < 1.59). These effects were not corroborated on any of the other primary outcome measures. Modeling effects of CCT on the BDI-II, which was only assessed at BA and FU 6M, we did not find an effect of training task, time nor an interaction (Table 4).

In addition, *depressive rumination* decreased for both groups, as reported by a significant time effect on the total score of the RRS, and on the brooding and reflection subscale. However, there were no effects of training or significant interactions on the full scale or on either subscale (Table 4).

Secondary Outcome Measures

Except for a main effect of time for maladaptive emotion regulation, no significant main or interaction effects were observed for use of *(mal)adaptive emotion regulation strategies* (CERQ; Table 4). *Quality of life* scores (QLDS) were not impacted by time or training task and there was no significant interaction (Table 4). *Residual symptoms*, as reflected by the RDQ, did not show an effect of time, training task, nor an interaction (Table 4). In contrast to the other analyses, the outcome of this analysis was affected by the baseline differences in age and number of depressive episodes. That is, when adding age and number of depressive episodes as covariates in this analysis, the interaction became marginally significant ($F(3, 192) = 2.4$, $p = .070$, $\eta_p^2 = 0.36$) and a trend for a reduction of residual complaints from PA to FU 3M was observed for the CCT group, compared to an increase in the ACT condition. Visually, scores seemed different between conditions at 3M FU but this effect has disappeared at FU 6M. Given that Hoorelbeke & Koster (2017) analyzed residual symptomatology only at BA and at FU 3M, we conducted their exact analysis (2x2 Mixed ANOVA) as well in a post-hoc fashion, which showed a marginal significant interaction ($F(1, 66) = 3.28$, $p = .075$, $\eta_p^2 = 0.05$). When we controlled for age and number of depressive episodes, this interaction became significant ($F(1, 64) = 6.55$, $p = .013$, $\eta_p^2 = 0.09$), where participants showed a marginal significant decrease in RDQ from BA to FU 3M in the CCT condition ($t(33) = 1.72$, $p = .09$, $d_{av} = 0.29$), whereas RDQ scores remained stable from BA to FU 3M in the ACT condition ($t(33) = 0.91$, $p = .37$, $d_{av} = 0.16$). Neither time or training task affected the *resilience* scores (CDRS) and no interaction was found (Table 4).

Other Outcome Measures

Related to cognitive control, *effortful control* improved in both groups. Looking into each component of effortful control separately, activation and attentional control showed an increase over time, but inhibitory control did not. Additionally, a time by training interaction was found for the subscale activation control (Table 4). However, follow-up independent *t*-tests failed to show group differences for activation control at FU 6M ($t(66) = 0.45$, $p = .658$, $d = 0.11$). Follow-up paired samples *t*-tests suggested no change over time in activation control within the ACT group, meaning a stable score across time points for this group was observed ($t(33) = 0.44$, $p = 663$, $d_{av} = .03$). The CCT group on the other hand showed an increase in activation control from baseline to the final follow-up assessment ($t(33) = 2.77$; $p = .009$; $d_{av} = 0.25$).

Control measures

User engagement was assessed only once, making an intention-to-treat analysis impossible. Analysis of user engagement included data from 65 participants and consisted of a two-sided independent samples *t*-test. This showed no difference between the two groups, meaning that the two training tasks were rated equally engaging ($t(63) = 0.16$; $p = .877$; $d = 0.04$), allowing to control for motivational effects on training.

Credibility and expectancy scores did not differ across the two groups, or across time points. Thus, there did not seem to be motivational differences between the two training conditions (Table 4).

As important negative events can impact questionnaires scores, we assessed these as well. In the LTE, data cannot be handled with the Last Observation Carried Forward method. Therefore, we conducted a Mixed ANOVA on 37 participants who had complete data, which showed no differences between groups. Furthermore, independent samples *t*-

tests revealed no differences between the two training groups, at all assessments, when including all available data (which was $N = 68$; $N = 65$; $N = 62$; $N = 38$ for BA, PA, FU 3M and FU 6M, respectively).

Discussion

In the current study, we aimed to replicate and extend the findings of Hoorelbeke and Koster (2017) using our new cognitive control training (CCT) platform. We randomly assigned remitted depressed individuals to either the CCT or an active control condition. Assessments were conducted at baseline, immediately following training, and three and six months after training. We hypothesized to find beneficial effects of CCT on indicators of objective (task-specific cognitive transfer) and subjective cognitive functioning (effortful control). In addition, we expected to find beneficial effects on primary outcome measures depressive symptomatology and rumination, in addition to observing beneficial effects on secondary outcome measures residual symptomatology, maladaptive emotion regulation, and resilience. Based on previous research, no effects were expected for quality of life or indicators of adaptive emotion regulation.

The current study provides a partial replication of the previously observed effects (Hoorelbeke & Koster, 2017). That is, we observed stable task-specific cognitive transfer, beneficial effects of CCT on activation control as an indicator of subjective cognitive functioning, but unexpectedly not on indicators of attention- or inhibitory control, and a tendency for improvements in depressive symptomatology as assessed with the DASS. In addition, after controlling for baseline group differences in age and number of depressive episodes, we also observed a marginal significant interaction for level of anxiety-

(DASS) and residual symptomatology (RDQ). At the same time, however, we failed to observe beneficial effects of CCT on many other primary and secondary outcome measures, including alternative measures for depressive symptomatology (BDI), indicators of maladaptive emotion regulation (RRS, CERQ), and resilience (CDRS). In line with our expectations, no beneficial effects were observed for adaptive emotion regulation or quality of life. We will discuss these findings in more detail below.

Importantly, we observed task-specific cognitive transfer. That is, following training participants in the CCT condition outperformed participants in the ACT condition on a cognitive transfer task. This effect remained present until FU 6M. This is in line with recent studies suggesting long-term task-specific cognitive transfer effects following aPASAT training (e.g., one year; Hoorelbeke, Van den Bergh, De Raedt, Wichers, & Koster, 2021). Interestingly, analysis of training progress suggests that improvements in training task performance most strongly occurred between the first and the sixth training session, after which the speed of training progress reduced. For instance, no significant increase in training task performance was detected between the sixth and seventh training session, yet training task performance further improved from session seven to session eight. In this context, previous studies have typically used six or ten aPASAT sessions to train cognitive control (e.g., Siegle et al., 2007; Hoorelbeke et al., 2015; for a review, see Koster et al., 2017). However, as to date it remains to be investigated which training dosage would result in optimal cognitive and emotional transfer. In addition, individual differences are likely to influence training progress.

In addition to task-specific cognitive transfer, we also observed beneficial effects of training on self-reported effortful control, an indicator of subjective cognitive functioning. In particular, compared to the ACT condition in which level of activation control remained stable over time, we observed an increase in activation control in the CCT group. These findings are important provided that depression has been linked to lower scores on the effortful control scale. For instance, Kanske and Kotz (2012) showed opposite correlational patterns for depression and effortful control in a range of experiments on conflict processing. While higher depression scores were correlated with slower conflict processing, higher effortful control was associated with faster conflict processing. However, they did not investigate the correlation between depression and effortful control directly. Furthermore, Moriya & Tanno (2008) found a negative association between the activation control component and depression, as measured by Zung's Self-rating Depression Scale (1965) which has a strong correlation with the DASS Depression scale (Pearson's r = .78; Dunstan, Scott, & Todd, 2017). These findings are in line with our data, where we observed a decrease in depressive symptomatology and an increase in activation control in the CCT group.

However, the time by condition interaction on activation control needs to be interpreted with caution. The increase in activation control scores for the CCT group might reflect a regression to the mean. Interestingly, using an alternative indicator of cognitive functioning (self-reported working memory complaints), Hoorelbeke and Koster (2017) observed a marginally significant effect of CCT (completers-only). There, the CCT group also seemed to improve while the scores of the ACT group remained

stable. This pattern of results resembles our findings with the activation control scale of the ATQ-EC, although the current time frame was extended.

The findings regarding depressive- and residual symptomatology also warrant discussion. In line with previous studies (e.g., Brunoni et al., 2014; Calkins et al., 2015; Hoorelbeke & Koster, 2017; Segrave et al., 2015; Siegle et al., 2007), our findings pertaining to the DASS depression scale suggest beneficial effects of aPASAT training on depressive symptomatology. Follow-up analyses suggest that this is mostly due to delayed effects of CCT on depressive symptomatology. For instance, in the current study a marginal significant difference in mean depression levels was observed between the CCT and ACT condition at three and six months following training, whereas no immediate effects were observed post training. In line with this, Hoorelbeke and Koster (2017) also observed effects of CCT on depressive symptomatology in RMD patients to be stronger at three months follow-up compared to immediately following training. Moreover, recent time-to-event analyses suggest a similar delay in effects of CCT on risk for recurrent depression in RMD patients (Hoorelbeke et al., 2021).

Interestingly, we also observed a marginal significant interaction effect between time and training on the RDQ, an indicator of broader residual symptomatology and functioning. This interaction was present only when adding the covariates age and number of depressive episodes, which differed between conditions at baseline. In this interaction, residual symptomatology seemed to decrease in the CCT group and increase in the ACT group, from PA to FU 3M. However, follow-up *t*-tests (without covariates) failed to show group differences and these trend for effects disappeared again at FU 6M.

As the RDQ in the original study of Hoorelbeke and Koster (2017) was only measured at BA and FU 3M, we analyzed data post-hoc in this manner. This yielded a marginal interaction, and this interaction reached significance when controlling for age and number of depressive episodes. Replicating the original effect found by Hoorelbeke and Koster (2017), we observed a tendency for residual symptomatology to decrease in the CCT condition from BA to FU 3M, whereas this was not the case for the ACT condition. This finding seems to suggest that the CCT led to a small and temporary decrease in residual symptomatology. Although this finding suggests that previously observed effects of CCT on the RDQ are replicable (3M FU), the effects are small and need to be interpreted cautiously. In particular, the effect seems to be limited in time, suggesting no lasting beneficial effects six months following training. Similarly, while controlling for age and number of previous depressive episodes we observed a marginal significant interaction effect for anxiety. Previous studies suggest that aPASAT training may have beneficial effects on anxiety (Vervaeke et al., 2020), albeit that in the current study this finding was mostly due to a worsening of anxiety symptoms from PA to FU 3M in the ACT condition, which was not the case in the CCT condition.

Noteworthy, however, several effects were not replicated. First, we did not find any effects on primary outcome measure depressive symptomatology as measured with the BDI-II. We believe that this might be due to the fact that the BDI-II was only re-assessed at FU 6M. Fluctuation of scores in-between these time points could be obscured if these effects are temporary and thus, no longer observable at final assessment. In line with this claim, the DASS Depression scale shows smaller effects at FU 6M than at FU 3M. Similarly, effects of CCT on the RDQ did not last until FU 6M. Second, primary

outcome measure rumination (RRS and its subscales) did not show any effects apart from a decrease over time, for both conditions. The original study of Hoorelbeke and Koster (2017) reported decreasing scores over time for both groups, but this decrease was greater for the CCT group, which we could not replicate. Noted, given that we lacked a substantial amount of data on this measure, our power was substantially decreased due to data loss, increasing difficulty of finding effects. Third, we were unable to replicate findings on some secondary outcome measures as well. Hoorelbeke and Koster (2017) found clear effects on maladaptive emotion regulation strategies and resilience, but we did not. Moreover, we could not find any effects regarding quality of life, while the original study showed some mixed evidence here. Lastly, we replicated the null findings regarding adaptive emotion regulation strategies.

Even though the method was highly similar, we were only able to replicate some of the previously observed beneficial effects of CCT. The reason for this is unclear. In the following part, we aim to describe the most prominent differences between studies. A first difference was our selected sample as we applied less strict inclusion criteria. It sufficed when participants were in remission for at least three months (instead of six months). At BA, eight participants were in remission for a period between three and six months and all eight, through randomization, were assigned to the ACT group. However, there were no baseline differences between this subset of eight participants, and the remainder of the sample (all *t*s < 1.56). Follow-up analyses suggest that exclusion of participants who were in remission for less than six months does not impact the pattern of findings presented above (see supplemental materials). Furthermore, we also included participants that had suffered from bipolar depression (instead of only unipolar). Ten

participants had suffered from at least one (hypo)manic episode in the past, with six of them being assigned to the CCT group. Of these ten, two participants did not complete training, one in each condition. Checking for baseline differences showed a difference on the ATQ-EC, with the unipolar group having higher scores for inhibitory control (MDD: $M = 4.70$, $SD = 0.99$; Bipolar: $M = 3.70$, $SD = 1.28$; $t(66) = 2.81$, $p = .007$; all other ts < 1.49). However, follow-up analyses in a subsample consisting of patients with a history of MDD ($N = 58$) suggest that the inclusion of patients with a history of bipolar disorder did not impact our findings. That is, in line with the findings presented in this manuscript we only observed beneficial effects of CCT on naPASAT performance, depressive symptomatology (DASS), and activation control (ATQ-EC) in the MDD sample, in absence of beneficial effects of CCT on anxiety and stress symptoms, indicators of emotion regulation, quality of life, and resilience (for a more detailed discussion of these findings, see supplemental materials). In addition, there was a difference between conditions at baseline for age and number of depressive episodes, which both are predictors for relapse. Controlling for these differences did not impact results (except for findings regarding the RDQ and DASS anxiety scores). Overall, although we used broader criteria, the samples were similar.

A second difference was the response button layout and surrounding software. This layout was based on input from remitted depressed individuals during development (Vervaeke et al., 2018), that disliked the original task layout used by Hoorelbeke & Koster (2017). Therefore, we changed this to a layout that diminished the distance between response buttons. However, we do not believe that this has an impact, given that previous studies, such as Siegle et al. (2007; 2014) use yet another response button

pattern (in a diamond shape). Furthermore, the task was still identical, even though certain parameters might be deviating slightly, so participants should have recruited the same brain regions and this should have had a comparable effect.

A third difference related to dosage of training. While every training session in Hoorelbeke & Koster (2017) consisted of 400 trials, we implemented a fixed training duration of 15 minutes, resulting in a varying number of trials per person and per session. Given that limited training fails to impact cognitive functioning (Koster et al., 2017), this is an important issue. Even though we found a strong cognitive transfer effect and progress during training, we examined the number of trials in our training to ensure adequate training dosage. There were seven participants in the CCT group with less than 400 trials on average. For all but one, at least one session contained more than 400 trials. All other participants had on average over 400 trials per session. Therefore, we state that our training dosage was in line with Hoorelbeke & Koster (2017). However, what amount of training dosage is adequate in this context remains an important research question.

There are a number of limitations to our current study that warrant mentioning. First, one could argue that the naPASAT is not the most adequate measure to examine transfer effects. This task is highly similar to the training task where ideally more distinct cognitive control tasks are also implemented to examine transfer effects. Previous studies have been mixed with regard to the amount of transfer observed (see Koster et al., 2017). In the current study, this limitation is mitigated by the use of a self-report measure of effortful control where improvements in the CCT condition were found for activation control in absence of changes in activation control in the ACT condition. Second, due to a

programming error there was quite substantial data loss on some of the measures administered at 6 month follow-up, specifically the RRS, LTE, and the ATQ-EC. Although most of these measures were not part of the primary outcomes, this limits the number of participants in order to examine long-term effects on rumination.

In conclusion, even though there were some deviations in methodology from the original study, we believe none of them can explain the difference in findings between the original and the replication study. Moreover, there was a lot of variability in our data with relation to clinical outcomes and cognitive functioning. An interesting avenue for further research would be to investigate moderators of effectiveness of CCT, which might explain the differences found between our study and the one we tried to replicate, and other CCT studies. By confirming already observed moderators and identifying new moderator variables, effects of CCT might become clearer and insights on underlying mechanisms can be gained, ensuring more consistent results and precisely targeted implementation of this training as a preventive intervention for certain subgroups of (remitted) depressed individuals.

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Compliance with Ethical Standards

Disclosure of Potential Conflicts of Interest

Jasmien Vervaeke, Kristof Hoorelbeke, Chris Baeken and Ernst H.W. Koster declare that they have no conflict of interest.

Informed Consent

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

Statement on the Welfare of Animals

This article does not contain any studies with animals performed by any of the authors.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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