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**COGNITIVE CONTROL INTERVENTIONS FOR DEPRESSION:**

**A systematic review of findings from training studies**

Ernst H.W. Koster\*<sup>1</sup>, Kristof Hoorelbeke\*<sup>1</sup>, Thomas Onraedt<sup>1</sup>, Max Owens<sup>2</sup>, &  
Nazanin Derakshan<sup>3</sup>

1. Ghent University, BE
2. University of South Florida Saint Petersburg, USA
3. Birkbeck University College of London, UK

Note: Ernst H. W. Koster and Kristof Hoorelbeke contributed equally to the manuscript and share first authorship

\*Corresponding authors:

Ernst Koster  
Department of Experimental Clinical and Health Psychology  
Ghent University  
Henri Dunantlaan 2  
B-9000 Gent, Belgium  
e-mail: Ernst.Koster@UGent.be

Kristof Hoorelbeke  
Department of Experimental Clinical and Health Psychology  
Ghent University  
Henri Dunantlaan 2  
B-9000 Gent, Belgium  
e-mail: Kristof.Hoorelbeke@UGent.be

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## **Abstract**

There is a strong interest in cognitive control training as a new intervention for depression. Given the recent promising meta-analytical findings regarding the effects of cognitive training on cognitive functioning and depressive symptomatology, the current review provides an in-depth discussion of the role of cognitive control in depression. We consider the state-of-the-art research on how manipulation of cognitive control may influence cognitive and depression-related outcomes. Evidence for the effectiveness of cognitive control training procedures are discussed in relation to three stages of depression (at-risk, clinically depressed, remission) as well as the training approach that was deployed, after which the putative theoretical mechanisms are discussed. Finally, we provide ways in which cognitive control training can be utilized in future research.

## **Introduction**

Depression is the leading cause of disability worldwide, and is a major contributor to the global burden of disease (World Health Organization, 2012). Moreover, depression is one of the most common and debilitating psychiatric disorders with an estimated 8 to 20% of the population experiencing at least one depressive episode during their lifetime. Despite the availability of well-established psychological and pharmacological treatment options for depression, that have acceptable short-term effectiveness, various challenges in the treatment of depression remain. Major challenges are that relapse or recurrence rates after remission or recovery remain very high and tend to increase (up to 80%) with the number of episodes (Beshai, Dobson, Bockting, & Quigley, 2011). Moreover, there is a substantial proportion of patients who fail to respond to treatment (Thomas et al., 2013). Treatment-resistant and recurrent depressive episodes are strongly associated with poor psychosocial outcomes due to increasing social problems (e.g., elevated divorce rates) and financial problems (e.g., multiple sick leaves, unemployment).

A crucial idea is that current treatments insufficiently target key underlying vulnerability factors of depression, causing depression to remit insufficiently or, when remitted, to still act as a risk factor for new depressive episodes. Although cognitive impairments in concentration, memory, and attention were initially considered side effects of the affective problems, recent neurobiological as well as cognitive research indicates that diminished cognitive control over information in working memory may be a key psychological vulnerability factor (Joormann, Yoon, & Zetsche, 2007; Millan et al., 2012; Siegle, Ghinassi, & Thase, 2007). Information processing factors are thought to have proximal links with rumination, a key maladaptive emotion regulation strategy, that can in turn influence depressive symptoms (Joormann & D'Avanzato, 2010; Joormann &

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Vanderlind, 2014). Importantly, recent findings suggest that existing antidepressant treatments do not impact cognitive impairments in depression (Shilyansky et al., 2016).

Cognitive control involves executive processes that allow information processing and behavior to vary adaptively over time depending on current goals, rather than remain rigid and inflexible. These cognitive control processes include a broad class of mental operations including goal or context representation and maintenance, and strategic processes such as attention allocation and stimulus-response mapping. Miyake et al. (2000) have suggested that executive functions mapping cognitive control can be operationalized into three major, interrelated yet separable functions: mental set shifting (shifting), information updating and monitoring of working memory representations (updating), and inhibition of prepotent responses (inhibition). Joormann and colleagues (2007) have argued, based on the work of Hasher and Zacks (1979), that cognitive control processes play a crucial role in determining the content of working memory, conceptualized as a limited-capacity system for the temporary storage of information (Baddeley & Hitch, 1974; Jonides et al., 2008). Difficulties in exerting cognitive control over negative information operations could explain the proliferation of negative information in working memory (Joormann et al., 2007), directly linking cognitive control impairments to perseverative negative thinking (depressive rumination), a well-supported vulnerability factor for depression (Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008).

There is converging evidence from psychopathology and neurobiological research to indicate that depression is associated with broad impairments on cognitive control tasks (for a recent meta-analysis, see Snyder, 2013). Moreover, across a variety of different tasks individuals at-risk for depression have also been found to display reduced cognitive control. For instance, cognitive control deficits have been observed in participants showing heightened trait rumination (e.g., Beckwé, Deroost, Koster, De Lissnyder, & De Raedt, 2014) and

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subclinical levels of depressive symptomatology (dysphorics; e.g., Derakshan, Salt, & Koster, 2009; Joormann, 2004; Owens, Koster, & Derakshan, 2012). Similarly, cognitive control impairments have been observed in a vast amount of studies exploring cognitive functioning in depressive patients (e.g., Deveney & Deldin, 2006; Goeleven, De Raedt, Baert, & Koster, 2006; Harvey et al., 2004; Levens & Gotlib, 2010; Merriam, Thase, Haas, Keshavan, & Sweeney, 1999; Murphy et al., 1999), and remain evident following remission from depression (e.g., Demeyer, De Lissnyder, Koster, & De Raedt, 2012; Levens & Gotlib, 2015; Paelecke-Habermann, Pohl, & Leprow, 2005; Vanderhasselt & De Raedt, 2009). Importantly, impaired cognitive control is mainly observed in at-risk samples when individuals are processing emotionally negative information (e.g., angry faces or negative self-referring words), whereas the impairments appear to be more broadly present in individuals that meet clinical levels of depression (Snyder, 2013). Furthermore, several studies suggest that cognitive control deficits are most apparent when engaging in rumination (e.g., Philippot & Brutoux, 2008; Whitmer & Gotlib, 2012). Research indicates that these impairments are not merely correlates of depression, but predict future rumination and the development of new depressive symptoms in prospective studies in healthy (e.g., Pe, Brose, Gotlib, & Kuppens, 2016; Zetsche & Joormann, 2011) and at-risk samples (e.g., Demeyer et al., 2012).

At the neuropsychological level, fronto-limbic disruptions are thought to play a crucial role in cognitive impairments involved in emotion regulation (for reviews, see Pizzagalli, 2011; Roiser, Elliott, & Sahakian, 2012). Key findings from neuroimaging studies have shown that depression is associated with disrupted brain activity in the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) (Davidson, Pizzagalli, Nitschke, & Putman, 2002; Etkin, Gyurak, & O'Hara, 2013; Pizzagalli, 2011), with decreased activation in these prefrontal areas being related to reduced cognitive control (Collette & Van der Linden, 2002; Smith & Jonides, 1999). Depression-related increased and sustained amygdala activity

in response to negative information (Surguladze et al., 2005; Taylor & Fragopanagos, 2005) has also been related to impaired recruitment of frontal areas (Siegle, Thompson, Carter, Steinhauer, & Thase, 2007). These findings suggest that disrupted connectivity in the limbic-frontal circuitry could play a major role in explaining the hallmark features of depression such as problems in regulating mood and sustained negative affect (De Raedt & Koster, 2010; Joormann et al., 2007). Collectively, it is fair to conclude that improving cognitive control can have profound implications for ensuring better treatment outcomes in depression (Roiser et al., 2012; Siegle, Ghinassi, et al., 2007).

Building on the evidence implicating cognitive control in depression vulnerability (for excellent reviews providing in depth discussions of how cognitive control is related to maladaptive emotion regulation strategies, see Joormann & D'Avanzato, 2010; Joormann & Vanderlind, 2014; Mor & Daches, 2015), the current paper reviews the state-of-the-art research on the efficacy of cognitive control training targeting impaired emotion regulation and depressive symptomatology. Although in its infancy, this research domain is rapidly expanding with recent meta-analytic evidence suggesting beneficial effects of cognitive training on depression outcomes (Motter et al., 2016). However, existing studies strongly differ in training procedures deployed, intensity of training, comparison groups, outcomes, and quality of the research designs in general. Importantly, including studies with suboptimal designs in meta-analyses holds the risk of accumulating bias (Higgins & Green, 2011) allowing a very limited selection of the existing studies to be included in a meta-analysis, not fully representing the cognitive control training literature. Furthermore, including such heterogeneous studies in one meta-analysis – in absence of a sufficient amount of studies to conduct moderator analysis for type of intervention, intensity of training, phase of illness, etc. – is itself suboptimal as it may obscure genuine differences in training effects (Higgins & Green, 2011). As a result, based on the Cochrane recommendations for systematic reviews /

meta-analyses (Higgins & Green, 2011), the cognitive control training literature would benefit from a systematic review specifically focusing on current findings and challenges regarding the application of cognitive control training as a potential novel intervention tool throughout the different stages of depression. Hence, we provide an overview of methods used in training cognitive control as well as effects of cognitive control training on impaired emotion regulation and depressive complaints in at-risk, clinically depressed, and remitted depressed patient samples. Given that these studies often use a broad conceptual operationalization of cognitive control and show considerable overlap between executive functions, we will consistently refer to ‘cognitive control training’ while acknowledging the potential diversity in the specific components of interest.

### **Experimental manipulations of cognitive control**

Given the accumulating evidence that points towards the involvement of disrupted cognitive control in different stages of depression, it is imperative that research addresses the question of causality. For this purpose, existing cognitive paradigms can be modified to manipulate cognitive processes (e.g., Koster, Fox, & MacLeod, 2009; Koster & Hoorelbeke, 2015; MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002) to examine transfer related benefits of cognitive change on behavior. Several variations have been used in the broader field of cognitive transfer. That is, there is a long history of studies trying to establish transfer effects on cognitive tasks in non-clinical research with healthy populations. This has turned out to be a challenging endeavor (for a review, see Shipstead, Redick, & Engle, 2012). In this context, the distinction between (1) improvements on the specific training task, (2) *near transfer*, being improvements on tasks that are similar to the training tasks, and (3) *far transfer*, being improvements on tasks or other measures that are not of the same nature or appearance as the training task, is crucial (Shipstead, Redick, & Engle, 2010). Observing improvement on training and near transfer tasks is necessary to demonstrate the mechanism

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by which far transfer can occur. Critical to far transfer is the assumption that the training task and the outcome share a more general underlying component, and that training-induced plasticity will lead to benefits in daily life performance (Shipstead et al., 2010). In the context of cognitive control, a number of ‘cognitive control training’ (CCT) tasks have been developed to test the causal involvement of cognitive control in depression vulnerability.

Siegle, Ghinassi, et al. (2007) have adjusted the Paced Auditory Serial Addition Task (PASAT; Gronwall, 1977; for a review, see Tombaugh, 2006). During the adaptive PASAT, a series of digits is presented and participants continuously add the currently presented digit to the previously presented digit. They need to provide a response to the sum of the last two presented digits which generates interference with updating the last heard digits in working memory. Task difficulty is tailored to participant’s performance by changing the inter-stimulus interval between each digit, causing the digits to follow faster or slower. Doing so, it is assumed that cognitive control is being trained in a challenging task context. A second frequently used cognitive task to manipulate cognitive control is the dual n-back task. In the adaptive dual n-back task (Jaeggi, Buschkuhl, Jonides, & Perrig, 2008) combinations of visual (e.g., square position) and auditory (e.g., spoken letter) stimuli are presented simultaneously on each trial. On every presentation, participants have to respond if one or both of the currently presented stimuli matches a stimulus presented  $n$  steps before by pressing the respective response buttons. The difficulty of the task is adapted at the block-level, where based on participant’s performance the level of  $n$  of the subsequent block is changed according to the number of errors per session (Jaeggi et al., 2008). Another example is the modified Negative Affective Priming task. In the Negative Affective Priming (NAP) task (Joormann, 2006), a complete trial is comprised of two sequential trials: a prime trial and a probe trial. Both trials consist of a simultaneously presented distractor and target stimulus. In all trials, participants are required to respond to the target by categorizing it as negative or

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positive, while ignoring (inhibiting) the distractor. In order to train cognitive control, researchers have manipulated the ratio of negative and positive distractors and targets, training participants to either attend to negative words or to inhibit them (e.g., Daches & Mor, 2014). Other examples include modifications of the Flanker task in which participants train inhibition of irrelevant non-emotional information (distractor arrows flanking the target arrow) throughout a series of incongruent trials (e.g., Cohen et al., 2016).

Despite ongoing controversy over the effectiveness of cognitive control or working memory training transfer effects to cognitive performance (for critical reviews see Shipstead et al., 2012; Simons et al., 2016), there is extensive research indicating that sustained practice of specific cognitive operations can have reliable effects on cognitive performance on related tasks (near transfer) at behavioural and neural levels (Au et al., 2015; Klingberg, 2010). Furthermore, when exploring effects of cognitive control manipulations on outcome measures other than cognitive functioning (e.g., indicators of emotional well-being), lack of far cognitive transfer effects may warrant careful interpretation of experimental findings. However, this does not necessarily rule out transfer to emotional processes. In the following section we discuss how the systematic literature search was conducted, after which we review existing evidence for the clinical potential of CCT throughout the different stages of depression.

### **Effects of Cognitive Control Training for Depression**

#### **Method**

##### **Literature search**

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The search was conducted in accordance with the guidelines for transparent reporting of systematic reviews and meta-analyses (Moher, Liberati, Tetzlaff, Altman, & Prisma Group, 2009). During the first phase, Web of Science and PubMed – two central databases in the field of clinical psychology / psychiatry – were searched to identify CCT studies for potential inclusion in the systematic review. The last search was conducted on August 16, 2016. Given the diversity in applications of CCT in the context of (vulnerability for) depression (e.g., at-risk groups or outcomes, MDD and RMD samples), the search included key words specifying the type of intervention only. For this purpose, we used a broad range of terms that have often been used in the context of CCT for depression: *cognitive control therapy* OR *cognitive control training* OR *cognitive control task* OR *neurocognitive training* OR *cognitive training* OR *executive control training* OR *working memory training* OR *cognitive emotional training* OR *cognitive remediation* OR *neurobehavioral therapy* (all fields were entered at the level of record title).

Second, for each of the selected CCT manuscripts during the previous phase, Google Scholar profiles of the first authors were screened for additional CCT studies. Furthermore, we conducted an extra search for papers reporting results of protocols that were identified during the previous phase, and screened reference lists of identified theoretical papers, reviews, or meta-analyses regarding CCT for depression.

### **Inclusion criteria**

Studies were selected if they met the following inclusion criteria: (a) The study was a published manuscript written in English (to avoid file drawers, PhD theses were also considered); (b) Studies included an experimental manipulation of cognitive control using cognitive training methodology. Although this literature has often been linked to cognitive bias modification studies specifically aimed at manipulating the focus of information processing – for which a multitude of reviews exist as to date (e.g., Koster & Hoorelbeke,

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2015; Mor & Daches, 2015) – existing cross-sectional and prospective studies suggest specific impairments in cognitive control to be involved in depression vulnerability. Hence, we limit the scope of this review to interventions that aim to manipulate cognitive control processes directly. As a result, the training procedure should be targeting executive processes regulating working memory functioning (e.g., updating, inhibition, shifting; Miyake et al., 2000). For this purpose, studies strictly reporting effects of cognitive bias modification training or mere attention training were excluded. (c) Effects of CCT were evaluated in at-risk (e.g., showing subclinical levels of depressive symptomatology, elevated trait rumination scores, children of parents with MDD, etc.; excluding anxiety and/or psychotic disorders), clinically depressed (MDD, excluding bipolar disorder), or remitted depressed (RMD) samples. Additionally, convenience samples with a specific focus on factors associated with depression risk (e.g., maladaptive emotion regulation, depressive symptomatology, stress/emotional reactivity, affect, etc.) were also included as ‘at-risk studies’.

### **Study selection**

During the first phase of the search 5547 records were identified via Web of Science and PubMed (see Figure 1). A first screening took place based on title, after which the abstracts of the remaining 1160 records were screened. Prior to evaluation of the full-text articles, duplicates were removed. Full copies of 116 articles were read which resulted in the inclusion of 28 manuscripts reporting effects of CCT in the context of (vulnerability for) depression. Additionally, two records were identified as relevant protocols, along with 18 theoretical papers / reviews / meta-analyses. In a second phase, snowballing took place based on the Google Scholar profiles of the first authors of the selected CCT manuscripts (636 records). Moreover, reference lists of the theoretical papers / reviews / meta-analyses were screened for additional CCT studies (1448 records), and results of protocols were searched for online (two records). These records were again screened based on title and/or abstract, after

which duplicates were removed prior to conducting a full-text screening. Fifteen additional unique CCT full-text manuscripts were evaluated, resulting in the inclusion of five manuscripts reporting effects of CCT in the context of (vulnerability for) depression. After both phases 33 manuscripts were included in the systematic review, reporting findings of a total of 34 CCT experiments (cfr. Figure 1).

### **Coding procedure**

Each screening phase was conducted by two independent coders using a predefined strategy. Discrepancies between both coders were discussed with one of the first authors of this manuscript. During the full-text screening phase, both coders operated independently based on predefined coding strategies for exclusion and inclusion. Both coders were trained using a selection of the identified records. If coders opted for inclusion of the article, the article was categorized as ‘at-risk’, ‘MDD’ or ‘RMD’. Quality of the rating procedure was assessed using indicators of inter rater agreement. This yielded  $\kappa = .87$  and  $\kappa = .83$  for inter rater agreement on inclusion / exclusion and categorization of the to-be-included manuscripts respectively, suggesting excellent agreement (Orwin, 1994).

### **Results**

#### **Cognitive control training for at-risk samples**

*Single-session manipulations or extensive training procedures.* We identified 20 studies reporting effects of CCT on cognitive risk factors for depression (e.g., rumination, mood, depressive symptoms; see Figure 1; for a more detailed description of the research designs deployed in each at-risk study, see Supplemental material Table 1) in healthy or at-risk samples, from which six studies explored effects of a single-session manipulation. Critical review of these studies suggests that single-session manipulations are nonsufficient to yield reliable effects on (neurological indicators of) cognitive functioning (Calkins, Deveney,

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Weitzman, Hearon, & Siegle, 2011; Cohen et al., 2016; Daches, Mor, & Hertel, 2015), state rumination, or mood (Calkins et al., 2011; Daches et al., 2015; de Putter, Vanderhasselt, Baeken, De Raedt, & Koster, 2015). Interestingly, in absence of immediate effects on self-report measures for mood and state rumination, de Putter et al. (2015) observed beneficial effects of CCT on heart rate variability as a physiological indicator of stress reactivity during a rumination induction procedure. Furthermore, Cohen, Mor, and Henik (2015) found beneficial effects of a single-session cognitive control manipulation on susceptibility to a rumination induction procedure. Moreover, CCT seemed to buffer negative effects of trait brooding on mood during this induction procedure. In this context, it is interesting to note that Quinn, Keil, Utke, and Joormann (2014) found that individual differences in trait rumination predicted response to cognitive control manipulations in healthy participants. That is, only participants high in trait rumination showed beneficial effects of a single-session manipulation of cognitive control on cortisol response to a stress induction procedure. These findings suggest that given more extensive training, exerting cognitive control over (emotional) information may act to reduce cognitive vulnerability for depression.

Indeed, following-up on their initial promising effects (Cohen et al., 2015), Cohen et al. (2016) reported beneficial effects of an 18-session modified Flanker task training on amygdala activity and behavioral interference of aversive pictures in healthy participants. Moreover, Cohen and colleagues (2016) reported a tendency towards increased connectivity between the amygdala and prefrontal regions, two key structures in the context of vulnerability for depression. Importantly, change in amygdala activity was associated with reduced interference of aversive stimuli. Linking cognitive and emotional transfer measures to neurophysiological parameters, this innovative study provides insights in the mechanisms that may underlie beneficial effects of CCT. Furthermore, in contrast to the promising effects following 18 sessions of training, Cohen et al. (2016) found no beneficial effects following

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the first session, demonstrating the need for repeated practice. Moreover, extending findings of de Putter and colleagues (2015), Xiu, Zhou and Jiang (2016) reported beneficial effects of 20 days of adaptive Running memory task training on high-frequency heart rate variability during an emotion regulation task. Additionally, Gavelin, Boraxbekk, Stenlund, Järholm, and Neely (2015) explored effects of a multi-session and multi-training task approach on a wide variety of cognitive transfer measures in patients suffering from exhaustion disorder, showing beneficial effects on several near and far cognitive transfer tasks. Interestingly, patients in the combined CCT + TAU condition also reported less subjective cognitive complaints and showed a stronger decrease in burnout symptoms compared to a TAU control group. These findings demonstrate the need for repeated exposure to CCT tasks in order to accomplish cognitive and emotional transfer.

*Evidence from adaptive PASAT training studies.* Among multi-session CCT studies, the most widely adopted training approach is the adaptive PASAT. That is, from all studies identified as ‘cognitive control training’ studies using multiple sessions in this review, 12 manuscripts report effects of an adaptive PASAT manipulation. Here it is noteworthy that some studies combine the PASAT with an attention training developed by Wells (Wells, 2000). This is a selective attention training consisting of counting sounds accompanied by naturalistic sounds. Five of these have explored effects of this training approach on cognitive risk factors for depression in healthy or at-risk populations. In line with the above mentioned multi-session CCT studies of Cohen et al. (2016) and Gavelin et al. (2015), the adaptive PASAT trains cognitive control using non-emotional stimuli, which are believed to be presented in a stressful task context (Siegle, Ghinassi, et al., 2007). Initial studies have found mixed evidence for beneficial effects of this training on cognitive vulnerability for depression and depressive symptomatology. For instance, in a community sample with elevated depressive symptoms, Calkins, McMorran, Siegle, and Otto (2015) reported promising effects

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of a brief combined training procedure (three sessions of adaptive PASAT and Wells' attention training over two weeks) on self-reported mood and depressive symptomatology compared to an active control condition. Calkins and Otto (2013) also explored effects of a brief CCT procedure on mood and depressive symptomatology in a community sample characterized by heightened obsessive compulsive symptoms and low depressive symptomatology. Again, beneficial effects on mood were found. However, no differential effects on depressive symptomatology and a trend towards worsening of obsessive compulsive symptoms was reported. It is possible that the lack of effects on depressive symptoms in this study can be attributed to low levels of depressive symptomatology at baseline and the distinctive pattern of cognitive impairments that may underlie obsessive compulsive processes (e.g., Remijnse et al., 2013). Interestingly, using the same brief three-session training procedure, Moshier, Molokotos, Stein, and Otto (2015) could not replicate beneficial effects on depressive symptomatology in students or community adults with either euthymic or depressed mood.

Using a more extensive adaptive PASAT training procedure (10 sessions over two weeks), Hoorelbeke, Koster, Vanderhasselt, Callewaert, and Demeyer (2015) found beneficial effects on stress reactivity and brooding in a sample of high trait ruminators. That is, compared to an active control condition, the CCT group was less susceptible to a stress induction procedure in lab context in terms of momentary rumination and self-reported mood. Interestingly, participants from the CCT group also reported a decrease in brooding from baseline to four-week follow-up assessment, which took place during the examination period, a naturalistic stressor for students. Again, these findings suggest that at-risk groups may benefit from extensive training. Additionally, in line with previous findings suggesting that cognitive control impairments become more apparent when engaging in rumination (Philippot & Brutoux, 2008; Whitmer & Gotlib, 2012), these findings suggest that effects of CCT in at-

risk groups should be assessed in a challenging context. In following up on these initial promising results, Hoorelbeke, Koster, Demeyer, Loeys, and Vanderhasselt (2016) explored effects of CCT on the interplay between affect and emotion regulation in daily life using experience sampling. In a convenience sample of undergraduate students, they found that one of the mechanisms underlying the effects of adaptive PASAT on stress reactivity and trait rumination is that it allows individuals to engage less in ruminative thought processes when confronted with decreases in positive affect. However, next to demonstrating cognitive transfer on a dual n-back task, overall transfer effects on emotion regulation processes were limited in this healthy population.

*Evidence from n-back training approaches using neutral stimuli.* Dual n-back training forms a second widely adopted training approach. Following the initial promising findings of Jaeggi et al. (2008, 2010), Owens, Koster, and Derakshan (2013) explored whether eight sessions of adaptive dual n-back training could improve reduced working memory capacity and impaired filtering of irrelevant information in dysphoric participants, where filtering efficiency was measured by electroencephalographic recording of an event-related potential sensitive to the ratio of relevant to irrelevant information maintained in working memory. Dysphoric participants in the adaptive training group showed training-related gains in cognitive control that were accompanied by gains in working memory capacity and filtering efficiency compared to the non-adaptive control group. These results were among the first to provide promising findings in support of (adaptive) cognitive control training in improving cognitive as well as neural efficiency in dysphoric individuals. However, adopting a similar training approach using six sessions of dual n-back training over a period of one week in trait ruminators yielded no beneficial effects on working memory task performance in two CCT studies (Onraedt & Koster, 2014). Furthermore, no differential effects of training were found on self-reported rumination or depressive symptomatology over

time (Onraedt & Koster, 2014). Similarly, Owens and colleagues (2013) did not find beneficial effects on depressive symptomatology. Importantly, in one of both training studies conducted by Onraedt and Koster (2014), there was a tendency that improvement in CCT task performance predicted a decrease in depressive symptomatology over time, suggesting that more extensive training may be warranted.

In this context, it is interesting to note that Takeuchi et al. (2013, 2014) adopted a training procedure in which a sample of healthy students had to complete 27 sessions of a multi-task training approach including the dual n-back task over a period of four weeks. Takeuchi et al. (2013) reported beneficial cognitive transfer effects on untrained verbal and visual working memory tasks. Interestingly, the CCT group also experienced beneficial effects on self-reported negative mood. Furthermore, during an implicit face-matching task intended to evoke negative affect, participants from the CCT group demonstrated reduced brain activity related to negative emotions in the left posterior insula and left frontoparietal area (Takeuchi et al., 2014). As suggested by Takeuchi and colleagues (2014, p. 11), this may reflect increased cognitive capacity allowing better management of emotional information. However, an important disadvantage of this study is that effects of CCT were compared to a no-training control condition.

***Training cognitive control over emotional information.*** In contrast to the dual n-back training studies that have tried to reduce cognitive vulnerability for depression by manipulating cognitive control over neutral information in at-risk populations, studies using affective modifications of this training paradigm have been more successful in demonstrating cognitive and emotional transfer. Note however that studies exploring effects of affective modifications of the dual n-back have also typically relied on more intensive training procedures. Schweizer, Hampshire, and Dalgleish (2011) were the first to extend the dual n-back training procedure to target the processing of emotional information in working

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memory. They modified the dual n-back task by changing the squares and spoken letters by pictures of faces and spoken words respectively. Schweizer et al. (2011) compared effects of the affective modification of the dual n-back with a neutral dual n-back training group, and an active control group over a training period of 20 days. Compared to the active control group, digit span and fluid intelligence scores improved significantly after dual n-back training for both the emotional and neutral training group. Furthermore, Schweizer et al. (2011) found that the emotional dual n-back training group showed greater transfer effects to emotional Stroop compared to the neutral training group, suggesting that affective modifications of CCT tasks may promote transfer to emotional outcome measures. Indeed, in a follow-up study, Schweizer, Grahn, Hampshire, Mobbs, and Dalgleish (2013) found that improved emotional dual n-back task performance over a 20-days training period was related to increased efficiency of the frontoparietal brain regions. Moreover, emotional CCT was associated with decreased reports of emotional distress after viewing distressing movie clips when instructed to regulate emotions, relative to movie clips during which participants did not have to regulate emotions. These findings indicate that emotional CCT improves emotion regulation. Finally, improvements in emotion regulation were associated with increased activation of the same frontoparietal regions involved in emotional dual n-back task progress.

Further elucidating the relation between cognitive control over emotional information and rumination, Daches and Mor (2014) found beneficial effects of a training to inhibit negative information (compared to a training to attend to negative information and a sham training). The inhibition training group was characterized by a non-significant trend towards increase in inhibition of irrelevant negative information on the NAP following training, whereas training participants to attend to negative information decreased inhibition to emotional stimuli over time. Moreover, only the inhibition training group showed a reduction

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in brooding over time. However, no beneficial effects were observed for depressive symptomatology.

***Interim conclusion.*** Taken together, these findings suggest that, given extensive repeated training, CCT holds potential as a preventive intervention for depression (see Supplemental material Table 1). That is, several studies have reported beneficial effects on behavioral and self-report measures of cognitive functioning, neurophysiological indicators of (affective) information processing and emotion regulation, and self-reported mood and emotion regulation. However, demonstrating both cognitive and emotional transfer has proven to be challenging with absence of effects often being reported in studies utilizing a limited amount of training sessions (independent of the CCT approach that was utilized; cfr. Supplemental material Table 1). Furthermore, limited effects on depressive symptomatology in healthy populations are to be expected given the nature of the population and the premise that CCT is only useful when there are cognitive control *deficits*, which may simply not be the case in healthy samples. Finally, there is a positive evolution in CCT-studies towards adoption of active control conditions (see Supplemental material Table 1). However, many studies have relied on relatively small samples, which may have yielded insufficient power to consistently detect training effects when analyzing between-group interactions. Nonetheless, given these mixed findings more research is necessary exploring the mechanisms underlying effects (or absence of effects) of CCT in at-risk populations.

### **Cognitive control training in MDD samples**

***Evidence from adaptive PASAT training studies.*** In the context of CCT for depression, one of the most influential studies was carried out by Siegle, Ghinassi, et al. (2007). Siegle, Ghinassi, et al. (2007; see Supplemental material Table 2 for a more detailed description of the research designs deployed in each MDD study) investigated the added

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benefit of CCT in clinically depressed patients receiving TAU (outpatient day-treatment in combination with psychotropic medication) compared to a control group only receiving TAU. They were the first to explore the clinical potential of CCT using a training protocol that was composed of two components known to activate the prefrontal cortex, being Wells' attention training and the adaptive PASAT. After two weeks of treatment, participants who received CCT showed significant improvements in non-adaptive PASAT performance compared to the control group. Furthermore, self-reported rumination and depressive symptomatology significantly decreased relative to the control group. Interestingly, a subset of the participants from the CCT condition also completed fMRI assessment, suggesting that disruptions in the amygdala and DLPFC related to depression normalized after CCT (Siegle, Ghinassi, et al., 2007).

In a follow-up report, Siegle and colleagues (2014) extended the data obtained in the previous study (Siegle, Ghinassi, et al., 2007). Beneficial effects of CCT on rumination remained and a general improvement in depressive symptomatology was observed. However, in contrast to rumination scores, no differential group effects were found for depressive symptomatology. Furthermore, pupil dilation indices during pre- and post PASAT administration were used as a physiological measure of cognitive load during task performance (see Beatty, 1982). Higher pupil dilation during pre-training PASAT performance and lower pupil reaction in rest were associated with a greater decrease in rumination scores after CCT, indicating training was most beneficial for those strongly engaging with training. Importantly, during a one year follow-up, Siegle et al. (2014) observed less intensive outpatient day-treatment visits in participants who performed at least one session of CCT compared to a group of service control patients. These findings indicate that changes in rumination following CCT precede changes in depressive symptoms (Siegle et

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al., 2014), suggesting that CCT is capable to contribute to stable changes in the underlying pathogenic mechanisms of depression.

Following-up on the initial findings of Siegle, Ghinassi, et al. (2007; Siegle et al., 2014) with TAU, researchers have explored whether combining CCT with alternative therapeutic interventions (other than antidepressants) may yield additional treatment effects. For instance, Moshier (2015) explored whether CCT consisting of the adaptive PASAT training and Wells' attention task may add to the effects of a brief behavior activation intervention for MDD. However, no additional effects of CCT were found compared to an active control condition undergoing the behavior activation intervention in combination with a sham training.

Interestingly, several studies have combined CCT with other forms of neurostimulation, such as transcranial Direct Current Stimulation (tDCS). For instance, Segrave et al. (2014) explored the antidepressant effects of simultaneous CCT (similar to the training reported by Siegle, Ghinassi, et al., 2007) and tDCS. Participants undergoing concurrent CCT and tDCS were characterized by heightened cognitive control over negative stimuli at follow-up. Interestingly, improved cognitive control over negative stimuli was associated with lower ratings of depression severity at follow-up. Furthermore, Segrave et al. (2014) reported a decrease in depression severity directly following five sessions of CCT (CCT and sham tDCS) or tDCS (sham training and tDCS). However, only the combination of CCT and tDCS provided sustained treatment effects at three weeks follow-up (Segrave et al., 2014). This indicates that stimulating cognitive control, using neurostimulation techniques or computerized training tasks, has a beneficial effect on depressive symptomatology directly following training, and that in the long term patients might even benefit from a combined approach.

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Also exploring combined effects of CCT and tDCS, Brunoni and colleagues (2014) used the adaptive PASAT in absence of the Wells' attention training. Depressed participants were randomly assigned to either 10 sessions of combined CCT and tDCS, or CCT and sham tDCS. Both training groups showed a significant decrease in depressive symptomatology directly following training, as well as at two weeks follow-up. Furthermore, increase in performance on the cognitive training task was associated with a greater reduction in depressive symptomatology. Interestingly, exploratory analyses seem to indicate that whereas both CCT groups showed a reduction in depressive symptomatology, older populations in particular might benefit from the combined administration of CCT and tDCS. Vanderhasselt et al. (2015) explored whether combined CCT and tDCS can be implemented to reduce depressive rumination. Results revealed a significant reduction in brooding in both CCT groups (i.e., CCT + tDCS, and CCT + sham tDCS). Moreover, increase in cognitive control during training was related to decrease in brooding over time. These findings confirm that CCT not only targets depressive symptomatology, but also important cognitive risk factors for depression, such as rumination. However, an additional sham training group would be necessary to check for placebo effects of undergoing a computerized training.

*Alternative training approaches using neutral stimuli.* Around the same time of the Siegle, Ghinassi, et al. (2007) report, Elgamal, McKinnon, Ramakrishnan, Joffe, and MacQueen (2007) reported effects of a cognitive remediation program containing multiple training tasks among which a training targeting executive functioning. Compared to a no-training MDD control condition and healthy control group, beneficial effects were reported for a multitude of cognitive transfer measures. However, no beneficial effects were found on depressive mood. Similar findings were reported by Trapp, Engel, Hajak, Lautenbacher, and Gallhofer (2016), where beneficial effects on neuropsychological indicators of working memory, memory, and executive functioning were reported in absence of significant

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differences between both conditions on change in depressive symptomatology. However, it should be noted that the latter finding may have been an artifact of modest sample size, since Trapp et al. (2016) reported moderate yet non-significant effects of CCT in favor of the training condition on depressive symptomatology (Cohen's  $d = .67$ ).

Interestingly, Alvarez, Sotres, León, Estrella, and Sosa (2008) explored effects of a multi-task non-emotional CCT and its interaction with antidepressant medication in students diagnosed with MDD. In addition to cognitive transfer effects, long-term beneficial effects on depressive symptomatology only remained in participants receiving CCT (independent of antidepressant intake). There was also a tendency for reduced self-reported trait anxiety in the CCT conditions. Furthermore, results suggested that effects of CCT in MDD may extend to self-reported attention problems and externalizing problems. However, early training studies typically lacked adequate control conditions, so the degree to which motivational effects influenced CCT was unclear. Moreover, intervention intensity in Alvarez et al. (2008) was dependent on CCT task performance, which is likely to induce bias when exploring treatment effects.

In contrast to its more frequent application in healthy and at-risk samples, only one study has evaluated the effects of a non-emotional adaptive n-back training approach in clinically depressed patients. Using a double-blind randomized controlled trial (RCT) design, Wanmaker, Geraerts, and Franken (2015) explored effects of 24 sessions of a combined non-emotional CCT in patients suffering from clinical depression and/or anxiety. However, with the exception of increased Reading span task performance following CCT, no beneficial effects were found for other cognitive transfer measures, self-reported rumination, depressive symptomatology, or anxiety (Wanmaker et al., 2015).

***Training cognitive control over emotional information.*** Although findings are mixed, in general the presented studies point to the potential of CCT for remediating cognitive impairments and (cognitive risk for) depression. However, an important question that remains unaddressed is whether CCT interventions for depression should focus on increasing general cognitive control, or directly target cognitive control in the context of emotional information processing. In a recent double-blind RCT study, Iacoviello et al. (2014) tested the superiority of an emotional CCT over a non-emotional CCT. At the end of four weeks of training, both training groups showed a similar increase in cognitive control, but only the emotional CCT group was characterized by a reduced memory bias for negative self-referent information. Concerning the clinical outcomes, both training groups showed a significant reduction in depression severity over time, but participants of the emotional CCT group reported marginally significant lower levels of depression severity following four weeks of training compared to participants of the non-emotional CCT group. However, in contrast to previous studies, Iacoviello et al. (2014) did not find significant effects of CCT on self-reported levels of rumination. Given the limited sample size (see Supplemental material Table 2), the lack of training effects on rumination might be due to limited power. For instance, the authors reported a medium-sized ( $d = 0.66$ ) yet non-significant reduction in rumination in the emotional CCT group, whereas in the non-emotional training group a small effect-size was reported ( $d = 0.39$ ). These preliminary findings indicate that using emotional stimuli may increase the efficacy of existing CCT methods in treating affective and cognitive characteristics of depression. However, sufficiently powered follow-up studies are necessary.

***Cognitive control training for treatment resistant depression.*** In a sample of treatment resistant MDD patients, Bowie and colleagues (2013) explored effects of cognitive remediation therapy – including intensive online cognitive training – on cognitive functioning. This revealed beneficial effects on a broad range of neuropsychological

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measures, among which indicators of attention / processing speed, verbal learning and memory. No significant effects were found for executive functioning and broader indicators of interpersonal competence and functioning. However, cognitive improvements were related to amount of completed training sessions, while cognitive training targeting executive functioning was only scheduled during the last two weeks of the ten week intervention. Furthermore, cognitive improvements were related to improvements in measures of interpersonal competence. Interestingly, Morimoto et al. (2014) explored the potential of CCT in an older clinical population suffering from treatment resistant geriatric depression which was due to non-response to antidepressant medication. Following four weeks of cognitive training, participants in the CCT condition showed *similar* treatment effects of 12 weeks of antidepressant treatment in a control group that was not selected to be treatment resistant. Furthermore, participants from the cognitive training group showed a greater increase in executive control, which was related to a reduction in depressive symptomatology. Importantly, the effects of four weeks of CCT remained stable at 12 weeks follow-up (Morimoto et al., 2014). This study illustrates that specific (treatment resistant) depressive subpopulations can benefit from CCT.

***Interim conclusion.*** In sum, although some studies have failed to find effects of CCT on rumination and depressive symptomatology in MDD samples, most CCT studies have yielded promising effects in MDD samples in terms of reducing cognitive vulnerability for depression (see Supplemental material Table 2). This is in line with recent meta-analytical findings confirming the beneficial effects of cognitive training on working memory functioning, symptom severity, and daily functioning in depression (Motter et al., 2016), with effects on these outcome measures ranging from small to moderate. Although such results suggest that effects of CCT may complement effects of antidepressant treatments and TAU, no additional effects were found when combining CCT with a brief behavior activation

protocol. This may indicate that the mechanisms targeted via behavior activation do not rely on cognitive control. Interestingly, first findings seem to indicate that effects of CCT can be increased by specifically targeting emotional information processing. However, given that only one study has compared effects of an affective CCT with a training fostering general cognitive control, replication of these findings is warranted. Preliminary evidence suggests there are specific predictors of response to CCT (e.g., pupil dilation, task performance). Furthermore, recent studies suggest that specific subgroups of MDD patients may benefit from combining CCT with additional neurostimulation techniques. However, caution is warranted given that many of the above presented findings are based on potentially underpowered analyses that were mostly not preregistered. Furthermore, in contrast to CCT studies in healthy and at-risk populations, CCT studies using MDD samples are typically based on less stringent designs, often lacking an adequate control condition for the cognitive training condition.

### **Cognitive control training for RMD samples**

As to our knowledge, only one study has directly addressed the question whether CCT can have beneficial effects on cognitive vulnerability for depression in RMD patients (see Supplemental material Table 3). In a double-blind RCT study, Hoorelbeke and Koster (2017; Hoorelbeke, Faelens, Behiels, & Koster, 2015) explored the effects of a two-week multi-session CCT. Effects were assessed immediately following training and at three months follow-up. After having established near cognitive transfer, using intention-to-treat analysis, Hoorelbeke and Koster (2017) found immediate and stable effects on brooding and (residual) depressive symptomatology. Moreover, similar effects were found when using alternative measures of maladaptive emotion regulation and residual symptomatology. Furthermore, effects were not limited to reducing maladaptive processes, but also transferred to resilience and completers reported reduced cognitive complaints and increased functioning at three-

months follow-up. Interestingly, mediation analysis provided evidence for the proposed mechanism underlying CCT for depression (Siegler et al., 2014; Siegler, Ghinassi, et al., 2007). That is, beneficial effects of increased cognitive control during training on depressive symptomatology at three-months follow-up, were partially mediated by immediate training effects on brooding (Hoorelbeke & Koster, 2017).

In sum, this study provided first evidence for the effectiveness of CCT in reducing cognitive vulnerability for recurrent depression in a RMD sample. Although these first findings are encouraging and in line with previous findings in MDD samples, these effects clearly need replication.

### **Critical appraisal of the evidence**

CCT is considered a promising intervention since it targets specific risk factors for depression. Despite a decade of research our review cannot unambiguously answer the question whether CCT is an effective intervention for depressive complaints given the mixed findings and the strong variability in research quality. After initial promising findings in studies using more intensive CCT procedures (e.g., Alvarez et al., 2008; Siegler et al., 2014; Siegler, Ghinassi, et al., 2007), a number of studies have tried to extend training effects (a) using a more limited amount of training sessions (e.g., Calkins et al., 2015; Calkins & Otto, 2013; Moshier, 2015; Moshier et al., 2015), and (b) in a wide variety of populations ranging from healthy to clinical samples, a combination which has yielded inconsistent findings. Furthermore, with the exception of some studies that have shown to be adequately powered for the presented analyses, a substantial amount of CCT studies have relied on limited sample sizes, which has resulted in not being able to consistently detect moderate effects of CCT on rumination (e.g.,  $d = 0.66$ ; Iacoviello et al., 2014) and depressive symptomatology (e.g.,  $d = 0.67$ ; Trapp et al., 2016). These factors may have led to an underestimation of training effects

in the latter studies. However, it is also important to note that early training studies have typically relied on suboptimal designs (e.g., lack of active control conditions), which do not control for the motivational effects of undergoing CCT. This, in its turn, may have led to an initial overestimation of training effects, although more recent studies comparing training procedures of similar intensity with adequate control conditions have observed similar effect-sizes in at-risk and patient samples (e.g., Hoorelbeke & Koster, 2017; Hoorelbeke, Koster, Vanderhasselt, Callewaert, & Demeyer, 2015). Importantly, this is in line with recent meta-analytical findings regarding effects of general cognitive training in depression (Motter et al., 2016). Another factor that seems to be important in observing transfer is task engagement / motivation (e.g., Siegle et al., 2014), where studies may benefit from explicitly framing training procedures (and active control trainings) as interventions (e.g., using psycho-education).

Overall, a number of studies obtained promising findings but it is clear that strides need to be made before CCT can be considered an evidence-based intervention. Progress in CCT research will require a detailed understanding of the precise cognitive mechanisms that are altered through training and identification of sequential pathways through which CCT alters depressive symptoms, identifying the mediating mechanism(s). A fine-grained analysis of moderating factors as detailed in our paper is crucial to advance answering these main questions. Therefore, we will now discuss the state-of-the-art with regard to these questions and provide a number of recommendations for future research in this area (see Supplemental material, Table 4).

### **Transfer effects of CCT**

As stated, in healthy individuals there has been quite extensive research using training paradigms that have been modified for clinical purposes. For instance, Olesen et al. (2004)

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reported increased prefrontal and parietal activity following five weeks of CCT, suggesting training related plasticity in the neural systems that underlie working memory functioning. One of the paradigms that has generated extensive research on near and far transfer is the dual n-back task where initially research has indicated that extensive training on the dual n-back but also the single n-back can show far transfer to key cognitive variables such as fluid intelligence (e.g., Jaeggi et al., 2008, 2010, 2011). Yet, a recent well-controlled dual n-back training study could not replicate these findings (Redick et al., 2013). Furthermore, other studies using a broad battery of tasks targeting working memory capacity and executive functions (e.g., multiple adaptive single- and complex working memory span tasks) failed to observe transfer to fluid intelligence after demonstrating near transfer (e.g., Harrison et al., 2013). However, recent meta-analytical findings confirm that dual n-back training can improve fluid intelligence (Au et al., 2015). These mixed findings indicate the need for multiple measures of both near and far transfer (for reviews see Klingberg, 2010; Shipstead et al., 2012; Simons et al., 2016).

It is clear from our review of the current data that there are also mixed findings as well as important limitations to the current literature of clinical CCT studies. That is, in more clinical studies it is typically feasible to only administer a small number of transfer tasks where in most research only close cognitive transfer is assessed with tasks highly similar to the training procedures. As a result, there is a likelihood that strategy learning can explain training-related improvements without broader improvement of executive functions. Furthermore, with the exception of a few studies included in this systematic review that have explored effects of CCT on a wide variety of neuropsychological / cognitive measures in MDD patients (e.g., Bowie et al., 2013; Trapp et al., 2016), the majority of studies consider examining cognitive transfer a manipulation check without trying to precisely identify the cognitive effects of training in a comprehensive way.

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Here, it is crucial that in order to determine causal effects of cognitive control on depressive symptoms, which is possible using CCT, establishing that there is change in cognitive control which is (a) due to training (compared with placebo) and (b) related to the magnitude of change in depressive symptoms is required for strong *causal* conclusions. Thus based on the pattern of findings, researchers need to be careful in their interpretations. That is, some studies obtained effects on depressive symptoms without measuring or observing cognitive change which, because of the experimental manipulation of CCT, may be interpreted as evidence that cognitive control is causally involved. Yet, such conclusions need to be tempered because other variables cannot be fully excluded and the key mechanisms influencing depressive symptoms do not necessarily have to be cognitive control. Alternatively, other CCT studies where cognitive control changed in function of training but depressive outcomes did not change could be taken as evidence for the absence of a causal relationship between cognitive control and depression. Indeed, such studies should be given equal weight as studies where significant changes in depressive outcomes are obtained as they may help to quantify the causal relationship. Obviously, such studies do need to be carefully examined taking into account statistical power and methodological qualities. For instance, with regard to the latter notion, if depressive outcomes are measured directly after one week of training, absence of any effects on depressive outcomes could be due to insufficient training or too limited time for CCT to have an influence on depressive symptoms that are typically assessed in relation to the past two weeks (for instance in the BDI-II). Furthermore, extending the analytical procedures used in CCT studies may also further enhance our understanding of training effects, where (especially) studies presenting null-findings would benefit from statistical analyses that allow to accumulate evidence in favor of the null-hypothesis of no training effect (e.g., Bayes factor).

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In relation to the issue of inconsistent transfer effects in clinical CCT studies we think the following desiderata are useful for future research: CCT studies should (a) contain multiple training sessions; That is, the current literature indicates that single-session manipulations and low intensity training procedures fail in altering cognitive functions underlying depression vulnerability. However, the current literature does not allow for clear-cut indications of the amount of training sessions necessary to establish stable transfer effects. For instance, training approaches such as the adaptive PASAT have shown relatively long-term beneficial effects following 10 sessions of CCT or in some cases even less in at-risk and clinical populations, whereas in other cases no effects were found using other intensive training procedures targeting cognitive control (e.g., following 24 sessions). To answer this question requires adjusted designs and analyses taking into account variability in the degree of training session adherence. Furthermore, previous studies suggest that cognitive deficits are most apparent in an affective context or in the context of depressive rumination. As such, (b) cognitive control training should be targeting cognitive functioning in a task context that may elicit cognitive processes directly involved in repetitive negative thinking. One possibility could be using emotional stimuli or training cognitive control using neutral stimuli in a stressful / frustrating task context. Currently, it is unclear to what extent training approaches differ in this. Directly related to this, (c) (cognitive) transfer effects would ideally be assessed in a similar emotional task context, rather than exploring effects on more general indicators of cognitive functioning and far transfer measures. In this context, recent training studies exploring effects on underlying neurological mechanisms have yielded promising findings (e.g., Cohen et al., 2016). Furthermore CCT studies should ideally: (d) contain multiple measures of cognitive transfer (e.g., Schwarb, Nail, & Schumacher, 2016) *or* should use training paradigms where such transfer has already been demonstrated convincingly; (e) whenever feasible explore the relationship between cognitive and emotional transfer (but see

Moreau, Kirk, & Waldie, 2016), integrating indicators of neurophysiological mechanisms of depression vulnerability on multiple levels (e.g., HPA axis activation, neural filtering, functional connectivity). For instance, future research may benefit from exploring associations between changed brain connectivity (e.g., Cohen et al., 2016) and changes in behavioral outcomes as a function of training; (f) extensively report analyses examining change in cognitive control as well as associations between change in cognitive control and change in depressive symptoms, even when not significant. Furthermore, in order to allow effects of CCT on emotional outcomes to occur, designs should ideally (g) contain follow-up assessments and (h) samples that allow sufficient improvement in and heterogeneity regarding the emotional outcomes (e.g., clinical populations). These simple desiderata will reduce file drawer problems in future (meta-)analyses of causal effects of CCT where the criteria of Hill (1965) with regard to determining causal effects could provide a useful tool to systematically analyze the literature on cognitive control and depression in a systematic way (see for instance Van Bockstaele et al., 2014).

### **Sequential pathways through which CCT alters depressive symptoms**

How does CCT alter depressive outcomes? At the moment there are different ideas why CCT influences depressive outcomes. Most views provide pathways that include various mediating factors in their explanation (e.g., stress-reactivity, rumination, cognitive biases), indicating the need to carefully map the sequence of effects obtained with CCT. One influential theory proposed by Siegle, Ghinassi, et al. (2007) suggests that CCT specifically targets the neurocircuitry that has been identified in relation to depression. This theory builds on observations of reduced frontal activity (predominantly at the level of the DLPFC) and sustained amygdala activity (e.g., Sheline et al., 2001; Siegle, Thompson, et al., 2007) which has been related to cognitive risk factors such as rumination and sustained negative affect. The key notion here is that in depressed individuals in emotionally challenging situations, the

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DLPFC – which is a central region involved in the application of cognitive control (Cohen, 2001; Miller & Cohen, 2001; Ridderinkhof, Van Den Wildenberg, Segalowitz, & Carter, 2004) – is less actively recruited to dampen activity of the amygdala. In empirical studies this has been related to reduced functional connectivity between the anterior cingulate cortex (signaling cognitive conflict) and frontal regions (Holmes & Pizzagalli, 2007). In relation to CCT, it is thought that in order to successfully perform the PASAT one needs to recruit the DLPFC (e.g., Lazeron, Rombouts, deSonneville, Barkhof, & Scheltens, 2003) while downplaying interference from limbic pathways which become activated since the adaptive PASAT is highly challenging and by design evokes frequent errors (Siegle, Ghinassi, et al., 2007; Tombaugh, 2006). Similarly, meta-analytical findings suggest n-back task performance heavily relies on DLPFC activity (Owen, McMillan, Laird, & Bullmore, 2005).

There are some initial data supporting this view. For instance, Siegle, Ghinassi, et al. (2007) explored effects of CCT on DLPFC and amygdala activity in a subsample of MDD patients. Following treatment, these patients demonstrated decreased disruptions in DLPFC and amygdala activity while performing a cognitive and emotional task. Moreover, other pieces of evidence stem from CCT research where pupil dilation was measured. Pupil dilation is considered a psychophysiological marker of cognitive effort linked to DLPFC activity. In recent CCT studies, beneficial effects of CCT on rumination were mostly obtained in participants with higher levels of pupil dilation suggesting that beneficial effects of CCT are limited to individuals who are able to recruit sufficient DLPFC activity while training (Siegle et al., 2014). Finally, an important recent study provided 18 sessions of a modified Flanker training to healthy participants, which resulted in reduced amygdala activity and behavioral interference of aversive stimuli (Cohen et al., 2016). Furthermore, Cohen and colleagues (2016) observed increased amygdala – prefrontal region connectivity following CCT. Additionally, researchers have also reported associations between neural indicators of

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increased cognitive task performance and observed improvements in emotion regulation following CCT (e.g., Schweizer et al., 2013). However, despite these encouraging data, the neural underpinnings of CCT remain to be investigated further.

Based on our review of the CCT studies many of the studies consider emotion regulation as an important mediating factor of CCT. This is in line with theoretical models of emotion regulation in depression (Joormann & Vanderlind, 2014). However, to our knowledge only one study has directly examined the sequential effect of CCT on rumination and subsequent depressive symptoms. In a sample of RMD patients, Hoorelbeke and Koster (2017) have tested whether cognitive transfer effects of a two-week cognitive control manipulation predicts depressive symptomatology at three months follow-up via depressive rumination (brooding) immediately following training. While controlling for baseline depressive symptomatology and brooding, increase in cognitive control task performance predicted lower depressive rumination immediately following training, which partially mediated effects on depressive symptomatology at three months follow-up. It is noteworthy that these effects were small and suggest partial mediation, indicating that effects of CCT may be due to other, to be identified cognitive mechanisms. Interestingly, one could think that CCT could augment adaptive emotion regulation strategies. However, this idea was not supported in multiple studies (Hoorelbeke & Koster, 2017; Hoorelbeke et al., 2016).

Another complementary option is that CCT influences cognitive vulnerability for depression by targeting different cognitive biases. There is extensive research showing that multiple cognitive biases at the level of attention, interpretation and memory influence depressive symptoms through their influence on stress reactivity (for reviews, see Everaert, Koster, & Derakshan, 2012; Farb, Irving, Anderson, & Segal, 2015; Gotlib & Joormann, 2010). Interestingly, recent work has shown that cognitive control over emotional information is linked to a host of these information-processing biases (Everaert, Grahek, & Koster, 2016),

where the specific interplay between such biases has also been linked to rumination and depressive symptoms (Everaert, Grahek, Van den Bergh, et al., 2016). Unfortunately, currently there are no studies using more extensive training procedures mapping such influences of CCT.

It is clear that there are a number of interesting proposals on the pathways through which CCT influences depressive symptoms. This area of research is in its infancy but nevertheless of key relevance for progressing our understanding and improving the efficacy of CCT for depression. In order to be able to map sequential effects related to CCT we make the following recommendations, CCT studies should: (a) include measures of potential mediating variables; (b) include multiple time points in order to examine mediation; and (c) compare CCT with active control conditions to ensure that mechanisms can be linked to cognitive control. One promising way forward is to combine CCT with experience sampling methodology (ESM; see for instance Hoorelbeke et al., 2016) in order to be able to measure changes in relevant variables before, during, as well as following CCT to obtain a clear picture on the temporal effects elicited through CCT. Moreover, an ESM approach allows to map changes in the dynamic between affect and emotion regulation processes, which could be more informative than merely focusing on mean levels of mood and emotion regulation. Here, it is important that studies on CCT move away from simplistic notions of considering some emotion regulation strategies as adaptive and others as maladaptive. Emotion research suggests that the effects of different emotion regulation strategies depend on their context and the flexibility of their application (Aldao, 2013; Aldao, Sheppes, & Gross, 2015; Bonanno, Papa, Lalande, Westphal, & Coifman, 2004), where ESM allows to do justice to more fine-grained approaches to emotion regulation.

### **Analysis of moderating factors**

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Depression is a highly heterogeneous construct where there is large variability in the symptoms expressed by patients. Moreover, when considering the practical application of CCT for prevention and/or treatment of depression, there are many variables that could have an impact on the efficacy of CCT. Examples of such variables are the timing of the CCT intervention, the length of the intervention, the use of other therapies or interventions, etc. Examining for whom CCT is efficacious is an important endeavor for clinical purposes and could simultaneously provide useful insights into the working mechanisms of CCT. It is therefore not surprising that the question of moderating factors has already received some attention in the literature. For instance, Quinn and colleagues (2014) successfully tested the assumption that trait rumination moderates training effects in healthy participants.

In several studies it has been shown that there is individual variability in the engagement with CCT and improvement throughout the training sessions (e.g., Bowie et al., 2013). As described earlier, Siegle et al. (2014) found that higher levels of engagement on a cognitive transfer measure (non-adaptive PASAT) through pupil dilation forms a predictor of stronger benefits of training with regard to improvements in rumination. Importantly, whether this variable was associated with effects of CCT on other depressive outcomes is not reported. In other studies, progress during training has been associated with the efficacy of training. For instance, the slope of training progress has been associated with lower post-training brooding levels in a MDD sample (Vanderhasselt et al., 2015). Furthermore, several studies have reported associations between increased CCT or cognitive transfer task performance and depressive outcomes or broader indicators of functioning in at-risk (e.g., Hoorelbeke, Koster, et al., 2015) and clinically depressed samples (e.g., Bowie et al., 2013; Brunoni et al., 2014; Segrave et al., 2014). However, it is noteworthy that engagement with and progress in training or on cognitive transfer measures are not consistently linked to the depressive outcomes of CCT since some studies failed to find such associations (e.g., Calkins et al., 2015; Daches &

Mor, 2014; Onraedt & Koster, 2014; Takeuchi et al., 2014) and many studies do not report such analyses.

Other moderating variables that have occasionally been reported in studies are age (e.g., Brunoni et al., 2014). However, the recent meta-analysis by Motter et al. (2016) indicated decreased effects of CCT with increasing age. Furthermore, Motter et al. (2016) found no moderating effects of gender or medication status. Clearly, the latter finding that cognitive training is equally effective regardless of medication use is promising since this suggests that CCT can be combined with other evidence-based treatments.

Interestingly, one plausible candidate moderator has received very scarce support so far. That is, one might expect that the level of cognitive impairments at the start of training is a moderator of treatment effects. Yet, this variable is not consistently associated with outcome in current reports (e.g., Moshier, 2015) or is not reported. Since this is a null finding, several explanations are possible. It could be that there is a restriction of range phenomenon in depressed samples or there might be a non-linear relation between cognitive control impairments and CCT related improvements. Alternatively, it could also be that CCT is effective only in the group that has some but not too extensive impairments in cognitive control. Especially in the population of severely depressed patients CCT might not be sufficient to improve cognitive control (potentially through limited task engagement). Future research should investigate the usefulness of sequential treatment strategies to remediate cognitive impairments in severe populations where for instance neuromodulation techniques (e.g., repetitive transcranial magnetic stimulation) could precede CCT (see De Raedt, Vanderhasselt, & Baeken, 2015).

Identifying moderators of the efficacy of CCT on depressive symptoms is an area of large clinical and theoretical interest. To date, current research has identified a number of

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moderators related to training as well as client characteristics that influence the efficacy of CCT. In order to improve upon the current state-of-the-art we propose the following recommendations: there is a strong need for (a) confirmatory research to replicate the moderators that have been observed; (b) CCT studies containing larger sample sizes, which would allow researchers to identify potential moderators; and (c) targeted research on specific clinical moderators that have a high likelihood of influencing CCT efficacy (e.g., severity, etc.). Basic research on the presence of cognitive control impairments has shown cognitive control impairments mainly at group levels (Snyder, 2013). However, there is quite substantial heterogeneity in the presence of cognitive control impairments. Here it is important that the basic research needs to get a better handle on the role of cognitive control impairments at the individual level which will likely be highly informative on generating more specific hypotheses on potential moderating roles of such variables in the efficacy of CCT.

### **Discussion**

The current review aimed to provide a state-of-the-art on cognitive control training in depression. One of the clear benefits of this intervention is that it targets a specific, well-established cognitive risk factor that is associated with maladaptive emotion regulation and depression risk. Moreover, there is research showing that traditional interventions such as antidepressant medication do not remediate this risk factor (Shilyansky et al., 2016). Importantly, an initial meta-analysis recently indicated that training cognitive functioning yields moderate to large effects on near and far cognitive transfer measures in MDD samples (e.g., attention, working memory, intelligence). Furthermore, Hedges'  $g$  effect-sizes of .43 and .72 were reported for symptom severity and daily life functioning respectively, suggesting that effects of cognitive training on depression-related outcomes are in the range of small to moderate (Motter et al., 2016). Therefore, we sought to describe this emerging research area

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with regard to the current empirical research, the theoretical underpinnings, and the potential clinical application of cognitive control training in relation to the prevention and treatment of depression.

In our systematic review it is clear that there is quite substantial heterogeneity between different studies. Beneficial effects of CCT are mainly observed in populations with clear impairments at the onset of training when training is rather extensive. Within training it seems key that individuals are engaged with training that demands activating frontal areas such as the DLPFC which are implicated in attentional control, while ignoring task-unrelated stressful thoughts. As such it seems plausible that CCT firstly impacts repetitive negative thinking (rumination) to subsequently reduce depression levels. However, at the same time our review clearly shows that research will need to further establish the working mechanism in a more detailed manner since empirical evidence on this is only in its infancy.

CCT has several features that make it attractive clinically. It can be easily disseminated online, is low cost intensive, and may target mechanisms that are otherwise not changed through traditional interventions. Interestingly, the research shows that the engagement with training is key to obtain transfer effects in interaction with the levels of cognitive impairment at the onset of training. This suggests that not everyone with depression risk or complaints will benefit from training because (a) their working memory functioning is not impaired (for instance, Owens et al., 2012 showed individuals with high depression levels frequently have intact working memory capacity); and (b) they are insufficiently able to engage in training because of several reasons (e.g., lack of motivation). Clinically, we may need to apply CCT in a more tailored intervention based on participant status and working memory baseline measures. Moreover, monitoring training progress can provide an indication of task engagement to show the increments in training are met with increments in behavioral

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change. Looking at the learning curve of depressed participants across training is key to understanding how and when we can expect transfer and benefits from training.

In sum, research on CCT is an exciting area where there are promising clinical benefits to training. There is a clear need for larger scale, confirmatory research as well as innovative ways to tailor this treatment, track changes within training, and optimize effect sizes.

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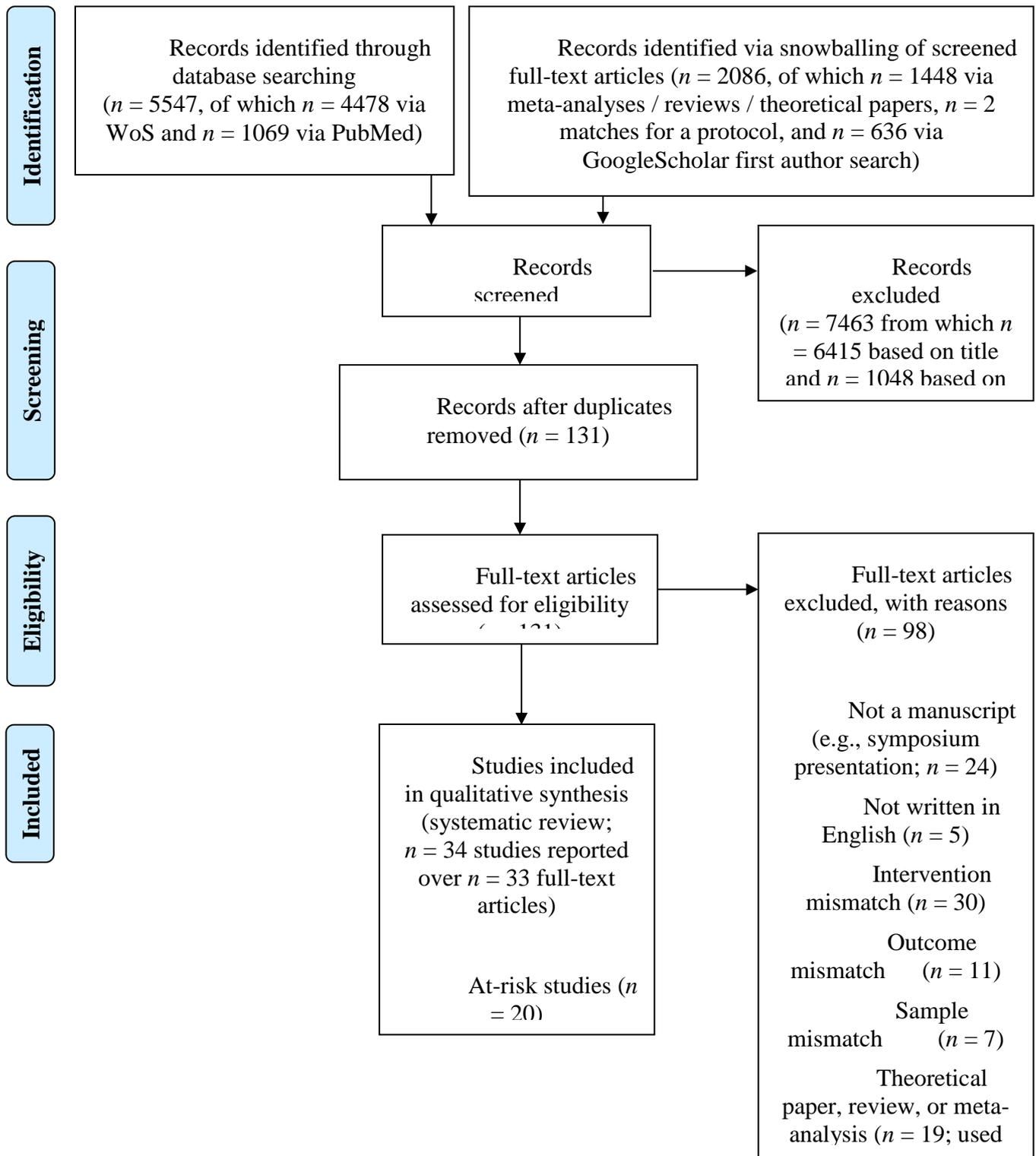


Figure 1. PRISMA flow chart

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Supplemental Table 1. Overview of effects of CCT on cognitive and depressive vulnerability outcomes in healthy- or at-risk samples

<b>Study</b>	<b>Sample</b>	<b>Stimulus material</b>	<b>Training conditions [amount of training sessions, training period]</b>	<b>Training effects</b>	<b>Within-group effects (CCT condition)</b>
Calkins, Deveney, Weitzman, Hearon, & Siegle (2011)	Healthy community sample ( $n = 59$ )	Neutral (numbers, tones)	Adaptive PASAT and Wells' attention training (CCT, $n = 27$ ) vs. peripheral vision task ( $n = 31$ )  [Single-session manipulation]	Effects of a mood induction were stronger following exposure to the CCT tasks compared to the peripheral vision task (significant: PANAS state positive affect; trend level: PANAS state negative affect)  No differential effects were found on emotional reactivity towards images (ERRT) or attentional bias towards threatening stimuli (dot probe task)	-Adaptive PASAT performance was unrelated to self-reported affect throughout the mood induction procedure and bias towards threatening stimuli -Adaptive PASAT performance was related to increased positive experience of pleasant images and reduced negative experience of unpleasant images (ERRT)
Calkins, McMorran, Siegle, & Otto (2015)	Community sample with elevated depressive symptoms ( $n = 48$ )	Neutral (numbers, tones)	Adaptive PASAT and Wells' attention training (CCT, $n = 24$ ) vs. adaptive peripheral vision task ( $n = 24$ )  [3 sessions, 2 weeks]	Beneficial effects on depressive symptomatology (BDI-II)  Trend towards lower negative affect post-training (PANAS state)	-Increased adaptive PASAT performance was related to increased positive affect (PANAS state, VAS relaxed/tense) -This was unrelated to negative affect (PANAS state, VAS) or depressive symptomatology (BDI-II)
Calkins & Otto (2013)	Community sample	Neutral (numbers,	Adaptive PASAT and Wells' attention	Cognitive transfer: -No differential effects on goal	-Increased adaptive PASAT performance was related to

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	showing elevated obsessive compulsive symptoms and low depressive symptoms ( $n = 48$ )	tones)	training (CCT, $n = 24$ ) vs. adaptive peripheral vision task ( $n = 24$ )  [3 sessions, 2 weeks]	disengagement (Anagram task)  Beneficial effects of CCT on trait negative affect and marginal effects on trait positive affect (PANAS trait)  Trend towards worsening of obsessive compulsive symptoms (OCI-R) compared to the active control condition  No differential effects on depressive symptomatology (BDI-II)	reduced obsessive compulsive symptoms (OCI-R) and increased positive affect (PANAS) -This was unrelated to negative affect (PANAS). -Higher mean adaptive PASAT performance was (marginally) related to more time spent on (un)solvable anagrams
Cohen et al. (2016)	Healthy participants ( $n = 26$ )	Neutral (orientation of arrows)	High-frequent Executive Control training (Modified Flanker task with 80% incongruent trials, CCT; $n = 13$ ) vs. Low-frequent Executive Control training (20% incongruent trials; $n = 13$ )  [(1) Single-session manipulation, (2) followed by 18 sessions of training over 6 days]	Cognitive transfer effects: -Increased task performance on incongruent trials compared to the control group -Reduced amygdala activity and behavioral interference of aversive pictures following multiple-session CCT, but not following the single-session manipulation -Tendency towards increased amygdala – prefrontal region connectivity	-Change in amygdala activity was associated with reduced interference of aversive stimuli -Increased amygdala – prefrontal region connectivity
Cohen, Mor, & Henik (2015)	Convenience sample ( $n =$	Paired neutral	Modified Flanker task (pairing of	Increased resilience to state rumination (VAS) following a	-The CCT group was characterized by a reduction

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	68)	training stimuli (orientation of arrows) with emotional information (pictures)	incongruent trials and negative emotional stimuli; CCT, $n = 37$ ) vs. sham training (pairing of congruent trials and negative emotional information; $n = 31$ )  [Single-session manipulation]	rumination induction procedure  No immediate effects of training on change in mood (VAS) throughout a rumination induction procedure  However, compared to the sham training, CCT buffered negative effects of trait brooding (RRS) on sad mood (VAS) during a rumination induction procedure	of emotional interference of negative pictures on a discrimination task
Daches & Mor (2014)	Trait ruminators (brooders; $n = 85$ )	Emotional (words)	Inhibition of negative content (modified NAP task, CCT; $n = 31$ ) vs. Attend to negative (modified NAP task; $n = 25$ ) vs. sham training ( $n = 29$ )  [4 sessions, 2 weeks]	Cognitive transfer: -Following training the CCT group showed higher levels of inhibition bias compared to the attend to negative information control group  Although a Time x Group interaction for brooding (RRS) was significant, follow-up between group comparisons indicated that groups did not significantly differ in brooding following training  No beneficial effects on depressive symptomatology (BDI-II) were found	-Change in inhibition in the CCT group was non-significant -The CCT group reported a decrease in brooding levels from baseline to post-training -Change in inhibition bias was unrelated to the reduction in brooding
Daches, Mor, & Hertel (2015)	Convenience sample (compares high and low trait	Emotional (words)	Inhibition of negative content (modified NAP task, CCT; $n = 68$ ) vs. Attend to negative	Cognitive transfer: -High ruminators show training incongruent effects on inhibition -No interaction of training on inhibition over time in low	-Rumination moderated effects of CCT on inhibition and interpretation bias -High ruminators show negative effects of training

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	ruminators based on median split; $n = 140$ )		(modified NAP task; $n = 72$ )  [Single-session manipulation]	ruminators -No differential effects of training on interpretation bias in high ruminators, and a tendency in low ruminators  No beneficial effects on state rumination (MRSI) or mood (VAS)	on inhibition, no beneficial effects on inhibition were found in low ruminators -High ruminators demonstrated a stronger interpretation bias than low ruminators following training
de Putter, Vanderhasselt, Baeken, De Raedt, & Koster (2015)	Healthy participants ( $n = 57$ )	Neutral (letters & locations)	tDCS + Dual n-back ( $n = 19$ ) vs. tDCS + Single 1-back ( $n = 19$ ) vs. sham tDCS + Dual n-back ( $n = 19$ )  [Single-session manipulation]	Cognitive transfer: -There were no differential effects on working memory task performance (R-Span task) -The sham tDCS + Dual n-back condition showed slower task switching than the groups including tDCS (IST)  No differential effects on mood were found (POMS) throughout the experiment  Groups did not differ in their ruminative response to a rumination induction procedure (MRSI) However, conditions including the dual n-back training component responded to the rumination induction procedure with increased heart rate variability, suggesting beneficial effects of CCT on emotion regulation processes	

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Gavelin, Boraxbekk, Stenlund, Järholm, & Neely (2015)	Exhaustion disorder ( $n = 59$ )	Neutral (letters, words, numbers, geometric shapes)	6 cognitive tasks + TAU (Updating: Letter memory running span task, Keep track task; Shifting: Alternating runs with digits, Unpredictable task cueing paradigm; Visuospatial short-term memory: Visuospatial span task; Episodic memory: Three-word-associates task; TAU: stress rehabilitation program; $n = 27$ ) vs. TAU ( $n = 32$ )  [36 sessions, 12 weeks]	Cognitive transfer: -Beneficial effects on Letter memory running span task performance -Overall beneficial effects of training on cognitive functioning (driven by near transfer effects on 3-back task performance and Recall of concrete nouns; far transfer effects: Raven's matrices) -No differential effects were found for Inhibition cost, Shift cost, Digit span forwards, Digit span backwards, Letter-number sequencing (near transfer), and Digit symbol task (far transfer)  Beneficial effects on self-reported cognitive complaints (6-QEMP; but no differential effects on PRMQ Prospective and Retrospective)  Beneficial effects on self-reported burnout complaints (SMBQ)
Hoorelbeke, Koster, Demeyer, Loeys, & Vanderhasselt (2016)	Convenience sample ( $n = 61$ )	Neutral (numbers)	Adaptive PASAT (CCT, $n = 29$ ) vs. low cognitive load / attention training ( $n = 32$ )  [10 sessions, 2 weeks]	Cognitive transfer effects: -Marginal beneficial effects on cognitive control task performance (dual n-back)  No differential effects on reappraisal ability in lab context  CCT condition showed a tendency to

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				respond with less rumination to reductions of positive affect in daily life (ESM)	
				No differential effects on deployment of positive appraisal and efficacy of emotion regulation in daily life (ESM)	
Hoorelbeke, Koster, Vanderhasselt, Callewaert, & Demeyer (2015)	Trait ruminators ( <i>n</i> = 47)	Neutral (numbers)	Adaptive PASAT (CCT, <i>n</i> = 25) vs. adaptive Visual Search task ( <i>n</i> = 22)  [10 sessions, 2 weeks]  *Analyses of training effects on rumination in response to a naturalistic stressor are based on <i>n</i> = 37 (CCT: <i>n</i> = 20, control: <i>n</i> = 17)	Cognitive transfer effects: -No differential effects on working memory task performance (O-Span)  Beneficial effects of CCT on stress reactivity in lab context (VAS negative affect; thought intrusions – breathing focus task)  Beneficial effects of CCT on brooding (RRS) in response to a naturalistic stressor (examinations) at 4 weeks follow-up  No additional beneficial effects on depressive symptomatology (BDI-II, MASQ-D30), anxiety (MASQ-30), worrying (PSWQ), resilience (RS), attentional control (ACS), and affect (PANAS)	-Increased performance on cognitive transfer measure (O-Span) following CCT predicted a reduction in brooding and increased self-reported resilience (this was not the case for the active control condition) -Effects of CCT on stress reactivity (VAS) and thought intrusions (breathing focus task) immediately following two weeks of training marginally predicted effects on brooding in response to the naturalistic stressor at 4 weeks follow-up
Moshier, Molokotos, Stein, & Otto (2015)	Student- and community sample with euthymic ( <i>n</i>	Neutral (numbers, tones)	Euthymic mood / Adaptive PASAT and Wells' Attention Training (CCT, <i>n</i> =	Comparison of training effects on depressive symptomatology (BDI-II) in the depressed mood group yielded no significant effects	

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	= 37) or depressed mood ( $n = 32$ )		16) vs. Depressive mood / Adaptive PASAT and Wells' Attention Training (CCT, $n = 20$ ) vs. Euthymic mood / Peripheral Vision Task ( $n = 16$ ) vs. Depressive mood / Peripheral Vision Task ( $n = 17$ )	No differential effects of depressive mood group and cognitive training condition on meta-memory and memory accuracy (in the context of a repeated knob-checking task, cfr. OCD induction)	
			[3 sessions, 2 weeks]		
Onraedt & Koster (2014) – Study 1	Trait ruminators ( $n = 72$ )	Neutral (letters & locations)	Adaptive dual n-back (CCT, $n = 21$ ) vs. single 1-back ( $n = 25$ ) vs. no training ( $n = 26$ )	Cognitive transfer effects: -No differential effects on working memory capacity (R-Span task) -No differential effects on emotional and non-emotional shift cost (IST-task)	-Improved performance on CCT task, which was marginal significantly related to a decrease in depressive symptomatology over time -Improved CCT task performance was unrelated to difference scores for cognitive transfer tasks and rumination
			[6 sessions, 1 week]	No differential effects on rumination, brooding (RRS), or depressive symptomatology (BDI-II) following training and at 2-weeks follow-up	
Onraedt & Koster (2014) – Study 2	Trait ruminators ( $n = 45$ )	Neutral (letters & locations)	Dual n-back (CCT, $n = 21$ ) vs. Single 1-back ( $n = 24$ )	Cognitive transfer effects: -No differential effects on cognitive transfer tasks (R-Span task, O-Span task, emotional 2-back task)	-Improved performance on CCT task, which was marginal significantly related to increased working memory capacity (O-Span) -Improved CCT task performance was unrelated
			[6 sessions, 1 week]	No differential effects on rumination, brooding, reflection (RRS), or	

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				depressive symptomatology (BDI-II) following training and at 2-weeks follow-up	to difference scores for other cognitive transfer tasks, depressive symptomatology and rumination
				No moderation of metacognitions regarding rumination (NBRS, PBRS)	
Owens, Koster, & Derakshan (2013)	Dysphorics ( $n = 22$ )	Neutral (letters & locations)	Adaptive dual n-back (CCT, $n = 11$ ) vs. dual 1-back ( $n = 11$ )  [8 sessions, 2 weeks]	Cognitive transfer effects: -Improved working memory capacity scores (change detection task performance) -Improved filtering efficiency (ERP component for Contralateral Delay Activity)	
				No differential immediate effects of training on depressive symptomatology (BDI-II)	
Quinn, Keil, Utke, & Joormann (2014)	Students ( $n = 69$ )	Neutral (words) & emotional (words)	Affective n-back (affective CCT; $n = 23$ ) vs. Neutral n-back (neutral CCT; $n = 23$ ) ) vs. Control condition (affective control task; $n = 23$ )  [Single-session manipulation]	No differential effects of training condition on self-reported anxiety (VAS) or cortisol response to a stress induction procedure  No moderating effect of trait rumination to self-reported anxiety following a stress induction procedure  Trait rumination moderates the relation between training condition and effect of stress induction on cortisol: no differential cortisol response in low trait ruminators,	

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				whereas high trait ruminators benefited from CCT compared to the control group. Affective and neutral n-back conditions did not differ.	
Schweizer, Hampshire, & Dalgleish (2011)	Convenience sample ( $n = 45$ )	Emotional (words & faces) and neutral (letters & locations)	Affective dual n-back (affective CCT, $n = 15$ ) vs. Neutral dual n-back (neutral CCT, $n = 14$ ) vs. Feature match task (active control, $n = 16$ ) [20 sessions, 4 weeks]	Cognitive transfer: -The neutral and affective CCTs showed beneficial effects on working memory functioning (Digit span) and Gf (Raven's Progressive Matrices)  The affective CCT provided additional beneficial effects on an affective transfer measure (Emotional Stroop)	-Trend for increased training task performance to be related with Gf
Schweizer, Grahn, Hampshire, Mobbs, & Dalgleish (2013)	Convenience sample ( $n = 32$ )	Emotional (words & faces)	Affective dual n-back (affective CCT; $n = 17$ ) vs. Feature match task (active control, $n = 15$ ) [20 sessions, 4 weeks]	Cognitive transfer: -Beneficial effects of CCT on behavioral and neurological indicators of cognitive functioning (non-adaptive affective dual n-back task performance; frontoparietal demand network) -Beneficial effects of CCT on emotion regulation (regulate vs. attend to induction procedure)	-Cognitive task improvements were associated with increased efficiency of the frontoparietal brain regions -Improvements in emotion regulation were associated with increased activation of the same frontoparietal regions involved in emotional dual n-back task progress
Takeuchi et al. (2014)	Convenience sample ( $n = 61$ )	Neutral	4 cognitive tasks (visuospatial WM task, auditory backward operation span task, dual WM)	Cognitive transfer: -Beneficial effects of CCT on untrained verbal and visual working memory tasks [reported in Takeuchi et al. (2013)]	-Improved performance on CCT task was unrelated to emotional state change and change in functional activity parameters

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			task, dual n-back task; CCT; $n = 41$ ) vs. no training ( $n = 20$ )  [27 sessions, 4 weeks]	Beneficial effects on self-reported negative mood: anger/hostility, depression/dejection, fatigue/inertia (POMS) and state anger (STAXI) (But no beneficial effects on self-reported tension/anxiety, vigor/activity, and confusion/bewilderment; POMS)  Beneficial effects on negative emotion-related activity (left posterior insula, left frontoparietal area) during tasks evoking negative emotions
Xiu, Zhou, & Jiang (2016)	Healthy students ( $n = 40$ )	Neutral (letters, animals, or locations)	CCT (3 variants of the Running Working Memory task: Letter Running Working Memory task + Animal Running Working Memory task + Location Running Working Memory task; $n = 20$ ) vs. no training ( $n = 20$ )  [20 sessions, 3 weeks]	Cognitive transfer effects: -Beneficial effects on RT-indices of working memory ability (2-back task), but no differential effects on accuracy scores.  No differential effects of training condition on subjective emotion ratings during an emotion regulation task  Beneficial effects of training on high-frequency heart rate variability (HF-HRV) during an emotion regulation task (cognitive down-regulation of negative film clips) as an indicator of emotion regulation

ability

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*Note:* All studies have been selected based on (a) inclusion of a CCT procedure, in combination with (b) the sample characteristics (at-risk for depression; e.g., rumination, dysphoria), *or* (c) inclusion of outcome measures which allow evaluation of effects of CCT on cognitive vulnerability for depression (e.g., mood, rumination, depressive symptomatology). Additional within-group effects are only reported in case of absence of reported between group analyses or when they provide additional information relating to effects of CCT on cognitive vulnerability for depression.

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Supplemental Table 2. Overview of effects of CCT in MDD samples

<b>Study</b>	<b>Sample</b>	<b>Stimulus material</b>	<b>Training conditions [amount of training sessions, training period]</b>	<b>Training effects</b>	<b>Within-group effects (CCT condition)</b>
Alvarez, Sotres, León, Estrella, & Sosa (2008)	MDD students ( $n = 31$ )	Neutral (numbers & letters)	Alcor ('Series game' and 'Goose game', CCT; $n = 10$ ) vs. Alcor + antidepressant medication (combined CCT treatment, $n = 10$ ) vs. antidepressant medication ( $n = 11$ )  [2 times per week, length of treatment was depending on task performance, until participants reached level 60 for 'Series Game' and level 70 for 'Goose game']	Cognitive transfer: -beneficial effects on Intelligence Quotient (WAIS)  Beneficial effects on depressive symptomatology (BDI) and trait anxiety (tendency, STAI) at conclusion of CCT No significant Time x Group interaction for state anxiety (STAI)  Beneficial effects on externalized problems (EPA) and attention problems (APAS)	
Bowie et al. (2013)	Treatment resistant MDD ( $n = 33$ )	Unspecified	Online cognitive training (Scientific Brain Training Pro package, containing processing speed and attention training as	Cognitive transfer: -beneficial effects on attention and processing speed (compound of Symbol Coding Task, Continuous Performance Test-Identical Pairs Version, Controlled Oral Word	-Cognitive improvements were related to perceived competence with computerized cognitive remediation and amount of online training sessions

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			<p>well as working memory, delayed memory and executive functions training) + cognitive remediation group therapy (computer-based exercises, strategic self-monitoring and discussing applications of learned techniques in daily life) (<math>n = 17</math>) vs. waiting list condition (<math>n = 16</math>)</p> <p>[online training: 2 sessions of 20 minutes daily; group session: 90 minutes per week; 10 weeks]</p> <p>*Completers only analysis is based on <math>n = 11</math> (CCT) and <math>n = 10</math> (waiting list)</p>	<p>Association Test and Animal Naming tests, Trail Making Test part A)</p> <p>-beneficial effects on verbal learning and memory (Hopkins Verbal Learning Test)</p> <p>-no differential effects on executive functioning (Letter Number Sequencing Test, Trail Making Test part B, Stroop color-word test). <i>Note: these cognitive functions were only targeted during the last two weeks of online training</i></p> <p>No differential effects on functioning and competence (Social Skills Performance interpersonal competence Assessment and Advanced Finances task) nor on the Interview-based assessment of Real-world functioning (Longitudinal Interval Follow-up Evaluation Range of Impaired Functioning Tool)</p>	<p>completed</p> <p>-Cognitive improvements were related to improvements on ratings for impaired real-world behavior, but not significantly related to improvements in objective measures of interpersonal or adaptive competence.</p> <p>-Severity of depression was related to higher completion rates for the online training. Such associations were not found for perceived competence, intrinsic motivation, or anxiety severity</p>
Brunoni et al. (2014)	MDD patients ( $n = 37$ )	Neutral (numbers)	<p>Active tDCS + CCT (adaptive PASAT; <math>n = 20</math>) vs. sham tDCS + CCT (adaptive PASAT; <math>n = 17</math>)</p>	<p>-Decrease in depressive symptomatology throughout CCT (HAM-D-21, BDI-II)</p> <p>-Older age predicted greater enhancement of tDCS on CCT</p>	

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			[10 sessions, 2 weeks]		-Greater PASAT improvement predicted increased beneficial effects on depressive symptomatology
Elgamal, McKinnon, Ramakrishnan, Joffe, & MacQueen (2007)	Non-acute recurrent MDD patients ( $n = 24$ ) and healthy controls ( $n = 22$ )	Neutral (see Chen et al., 1997)	PSSCogReHab cognitive remediation software program (training of attention, verbal memory, psychomotor speed and executive functions; CCT, $n = 12$ ) vs. no training MDD controls ( $n = 12$ ) vs. no training healthy controls ( $n = 22$ )  [On average 2 weekly sessions, 10 weeks]	Cognitive transfer: -Beneficial effects of CCT on general episodic verbal learning and memory compared to both control conditions (Total CVLT performance; beneficial effects on Short-delay free recall, Short-delay cued recall, and Long-delay free recall, but no differential effects on interference List B Learning or recognition hits) -Beneficial effects of CCT on total speed on the measure for visual selective attention (Ruff's 2 & 7 Selective Attention test) -Beneficial effects on Digit Span Forwards task performance, but no differential effects on Digit Span Backwards task performance -Beneficial effects on Trail Making Test A performance, but no differential effects on Trail Making B performance -No differential effects on abstract verbal reasoning (WAIS-R Similarities subtest) or verbal association fluency	

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				(COWAT)	
				No differential effects on depressive mood (HAMD)	
Iacoviello et al. (2014)	MDD patients ( <i>n</i> = 21)	Emotional (faces) vs. neutral (geometric shapes)	Adaptive emotional Faces Memory task (adaptive emotional n-back, emotional CCT; <i>n</i> = 11) vs. Adaptive neutral n-back task (neutral CCT; <i>n</i> = 10)  [8 sessions, 4 weeks]	Cognitive transfer: No differential effects of neutral and emotional CCT on cognitive task performance (composite score for attention span and working memory: Digit Span Forward, Digit Span Backward, Letter Number Sequencing)  Differential effects of training on depressive symptomatology (HAM-D). The emotional CCT group showed a tendency for lower depressive symptomatology immediately following training compared to the neutral CCT. 6:11 participants in the emotional CCT group showed a reduction in HAM-D of $\geq 50\%$ vs. 1:10 in the neutral CCT group	-Small to medium sized though non-significant reduction in rumination (RRS) -The emotional CCT group showed a significant reduction in short-term memory for negative self-referential information (SRIP task) -Tendency for increased cognitive functioning (composite score attention span and working memory: Digit Span Forwards, Digit Span Backwards, Letter Number Sequencing). No significant increase in the neutral CCT group.
Morimoto et al. (2014)	Treatment resistant geriatric depressed patients (failed at least one adequate	Neutral (among others: geometric shapes, colors, words)	3 bottom-up training tasks (auditory tone sweep, phonemic discrimination, visual discrimination) + 2 top-down training tasks (Catch the ball, Semantic Strategy) +	Cognitive transfer: -Beneficial effects on executive functioning (Trails B + tendency for Stroop Color-Word)  Beneficial effects on depressive symptomatology (MADRS)	-Improved cognitive control: Stroop Color-Word task performance, Trails B performance, design fluency switching (D-KEFS) -Trend for improved semantic clustering (DRS I/P)

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	antidepressant trial; $n = 43$ )		continuation of intake of antidepressants to which participants previously demonstrated no response (CCT, $n = 10$ ) vs. TAU (escitalopram, $n = 33$ )*  [30 hours, 4 weeks; vs. escitalopram, 12 weeks]  *Participants in the CCT condition were preselected treatment resistant patients, whereas this was not the case in the TAU control group	Cognitive training was equally effective in treatment resistant patients as escitalopram treatment in patients <i>unselected</i> on being treatment resistant Furthermore, training effects emerged faster in the cognitive training group (following 4 weeks compared to 12 weeks)	-No improvement in working memory (WAIS-IV digits backwards) or verbal memory (CVLT-ii long delay recall) functioning -Increased Trails B task performance was related to a reduction in depressive symptomatology -Beneficial treatment effects were sustained at 3-months follow-up -9 CCT patients met criteria for response to treatment at the end of the 4-week training (8 met criteria for remission), 6 CCT patients met criteria for response to treatment at 3-month follow-up (all 6 met criteria for remission)
Moshier (dissertation, 2015)	MDD patients ( $n = 34$ )	Neutral (numbers, tones)	Adaptive PASAT + Wells' attention training + brief behavior activation intervention (CCT, $n = 21$ ) vs. peripheral vision task + brief behavior activation intervention (active control, $n =$	Cognitive transfer: -No beneficial effects on inhibition of emotional processing (NAP) or attentional shifting (IST)  CCT had no added effects to behavior activation therapy concerning depressive symptomatology (BDI-II, MADRS), rumination, brooding (RRS),	-Stronger initial cognitive control (adaptive PASAT ISI) was related to better improvement in depressive symptoms and less improvement in brooding (Note: $r = -.51$ ; MADRS, $r = -.36$ , BDI-II; $r = .32$ , RRS; n.s. due to $n = 12$ ). Not replicated in hierarchical

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			13) [4 sessions, 4 weeks]  *Analyses of cognitive transfer effects relied on $n = 26$ (CCT: $n = 14$ , active control: $n = 12$ )	environmental reward (RPI), and anxiety (BAI)	regression model after controlling for baseline symptom level -High levels of baseline inhibitory control of negative emotional material predicted lower depressive symptomatology (MADRS, tendency) at follow-up
Segrave, Arnold, Hoy, & Fitzgerald (2014)	MDD patients ( $n = 26$ )	Neutral (numbers, tones/bird sounds)	tDCS + CCT (Adaptive PASAT and Wells' attention training; $n = 8$ ) vs. sham tDCS + CCT (Adaptive PASAT and Wells' attention training; $n = 9$ ) vs. tDCS + sham training (adaptive Peripheral Vision Task; $n = 9$ )  [5 sessions, 5 days]	Cognitive transfer: -tDCS + CCT group showed the strongest increase in negative 2-back functioning -No differential effects on positive and neutral 2-back task accuracy. No differential effects on positive, negative, and neutral 2-back RT data  Beneficial effects of tDCS and CCT on depressive symptomatology (MADRS) immediately following training. Depressive symptomatology only further decreased at 3-week follow-up in the tDCS + CCT condition  Trend for difference in response rates immediately following training: only responders in the two CCT groups (33 – 44%) vs. no responders in the tDCS + sham training condition	-Increased negative 2-back task accuracy was associated with lower depression severity at 3-week follow-up

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				Differential effects on response rate at 3-week follow-up: beneficial effect of added tDCS to CCT	
				Immediate effects of CCT and tDCS on alternative outcome measure for depressive symptomatology (BDI-II). Only effects at 3-week follow-up in CCT + tDCS and sham training + tDCS condition	
Siegle, Ghinassi, & Thase (2007)	MDD patients ( $n = 23$ )	Neutral (numbers, tones/bird sounds)	Adaptive PASAT and Wells' attention training (CCT) + TAU ( $n = 15$ ) vs. TAU ( $n = 8$ )  [6 sessions, 2 weeks]	Cognitive transfer effects -Beneficial effects on cognitive control (non-adaptive PASAT) -No transfer on the Digit Sorting task (ceiling effect prior to training)  Beneficial effects on depressive symptomatology (BDI-II) and rumination (RSQ)	-fMRI data on a subsample ( $n = 6$ ) suggests decreased disruptions in DLPFC and amygdala activity during a cognitive (digit sorting task) and emotional (personal relevance rating) task respectively following CCT
Siegle et al. (2014)  [extended sample from Siegle et al., 2007]	MDD patients ( $n = 43$ )	Neutral (numbers, tones/bird sounds)	Adaptive PASAT and Wells' attention training (CCT) + TAU ( $n = 23$ ) vs. TAU ( $n = 20$ )*  [6 sessions, 2 weeks]  *For service	Cognitive transfer: -Increased non-adaptive PASAT performance compared to healthy controls -Increased task-related processing (on-task power) compared to TAU -No differential effects on non-task-related processing (off-task power)	-Less increased task-related processing (on-task power) was related to more decreased rumination -Change in rumination (RSQ) and depression (BDI-II) levels were unrelated -Decreased rumination was predicted by higher initial

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			<p>utilization analyses Siegle et al. (2014) compared participants of the CCT condition and participants of the TAU group who after completing the training also performed at least one session of CCT (<math>n = 43</math>) with a group of service control patients (<math>n = 57</math>)</p> <p>*Non-adaptive PASAT performance was compared with a healthy control sample from Jones, Siegle, Muelly, Haggerty, &amp; Ghinassi (2010; <math>n = 19</math>)</p>	<p>Beneficial effects of CCT on rumination and brooding (RSQ), no effects on reflection</p> <p>No differential effects on depressive symptomatology (BDI-II)</p> <p>Participants who performed at least one CCT session had fewer intensive outpatient day-treatment visits in the year following treatment than a control group</p> <p>No such effects were found for medication management visits or regular outpatient therapy</p>	<p>task-related processing (on-task power, non-adaptive PASAT) and lower non-task-related processing (off-task power), and the related unfocus index</p> <p>-Decreased pupil dilation following the intervention</p> <p>-Decrease in pre- versus post-CCT intensive outpatient day-treatment visits</p> <p>-Amount of completed CCT sessions was unrelated to post year service utilization</p>
Trapp, Engel, Hajak, Lautenbacher, & Gallhofer (2016)	MDD patients ( $n = 46$ )	Unspecified	<p>Cognitive remediation + TAU (10 cognitive training tasks targeting executive functioning, visuomotor functioning, and memory functioning; CCT condition, <math>n = 23</math>)</p>	<p>Cognitive transfer:</p> <p>-beneficial effects after four weeks of training on working memory functioning (Wechsler Memory Scale: significant effects for spatial span backward and logical memory immediate recall; a tendency for digit span backward and visual reproduction immediate recall; no effects for digit span forward and</p>	

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			vs. TAU (control group, $n = 23$ )  [12 sessions, 4 weeks]	<p>spatial span forward) -beneficial effects on memory (Wechsler Memory Scale: significant effects on visual reproduction delayed recall and logical memory delayed recall) -beneficial effects on executive functioning (significant effects on the Trail Making Test part B and delta score Trail Making Test part B minus part A; a tendency for performance on the Wisconsin Card Sorting Test) -no differential effects on attention (degraded Continuous Performance Test &amp; Trail Making Test part A)</p> <p>No immediate beneficial effects on depressive symptomatology (BDI and HAMD). <i>Note: possibly due to limited power as Cohen's <math>d = .67</math> in favor of the CCT condition</i></p>	
Vanderhasselt et al. (2015)  [additional analyses for Brunoni et al., 2014]	MDD patients ( $n = 33$ )	Neutral (numbers)	Active tDCS + CCT (adaptive PASAT; $n = 19$ )  vs. sham tDCS + CCT (adaptive PASAT; $n = 14$ )  [10 sessions, 2 weeks]	<p>-Increased performance on the CCT task with no differential effect of tDCS (absence of an interaction effect) -However, the slope of improvement in CCT task performance (adaptive PASAT ISI slope) tended to be steeper in the sham tDCS</p>	

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					+ CCT condition compared to the active tDCS + CCT group -CCT reduced brooding (no differential effects of tDCS) -The greater the improvement in working memory functioning throughout training, the larger the decrease in brooding
Wanmaker, Geraerts, & Franken (2015)	Patients with clinical anxiety and/or MDD ( $n = 75$ )	Neutral (letters & locations, geometrical shapes)	Adaptive Dual n-back task + Symmetry span (CCT, $n = 36$ ) vs. 0-back task + Non-adaptive Symmetry span ( $n = 39$ )*  [24 sessions, 4 weeks]  *91% of patients have been in therapy and/or are currently in another form of therapy	Cognitive transfer: -Beneficial effects of CCT on inhibition (Reading Span) -No differential effects on shifting (IST) and training incongruent effects on updating (backwards Digit Span)  No differential effects on rumination or its subtypes brooding and reflection (RRS), trait and state anxiety (STAI), or depressive symptomatology (BDI-II) No effects at 2-months follow-up	

*Note:* Studies have been selected based on (a) inclusion of a CCT procedure, and (b) the sample characteristics (MDD patients). Additional within-group effects are only reported in case of absence of reported between-group analyses, when they provide additional information relating to effects of CCT on depressive outcomes. In case all comparison groups contain the same CCT procedure (e.g., when the between-group manipulation is tDCS), effects are reported in this table on within-CCT group level instead of at between-group level.

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Supplemental Table 3. Overview of effects of CCT in RMD samples

Study	Sample	Stimulus material	Training conditions [amount of training sessions, training period]	Training effects	Within-group effects
Hoorelbeke & Koster (2017)  [Protocol: Hoorelbeke, Faelens, Behiels, & Koster, 2015]	Remitted depressed patients ( $n = 68$ )	Neutral (numbers)	Adaptive PASAT (CCT, $n = 34$ ) vs. low cognitive load / attention training ( $n = 34$ )  [10 sessions, 2 weeks]  *Completers-only analysis at 3-months follow-up is based on $n = 57$ (CCT: $n = 28$ , control: $n = 29$ )	Cognitive transfer: -Beneficial effects on cognitive task performance (non-adaptive PASAT) immediately following training and at 3-months follow-up -Completers show a tendency to report reduced cognitive complaints  Beneficial effects on brooding (RRS) and depressive symptomatology (BDI-II) immediately following training and at 3-months follow-up  Beneficial effects on general maladaptive emotion regulation (CERQ), residual symptomatology (RDQ). Completers reported increased functioning in daily life at 3-months follow-up (WHODAS 2.0)  No beneficial effects were found for adaptive emotion regulation (CERQ) and quality of life (QLDS)	-Over all participants, the effect of gains in cognitive control on depressive symptomatology (BDI-II) at follow-up, were partially mediated by immediate training effects on brooding (post-training; RRS), while controlling for baseline depressive symptomatology and brooding

*Note:* Studies have been selected based on (a) inclusion of a CCT procedure, and (b) the sample characteristics (RMD patients).

Supplemental Table 4. Recommendations for future research

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*Increasing understanding of transfer effects*

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1. Pre-register efforts to establish transfer effects
2. Use a sample size that allows to at least detect changes of moderate magnitude on the primary outcome measure(s)
3. Use multiple training sessions
4. Foster task engagement (e.g., using psycho-education)
5. Training should be targeting cognitive functioning in a task context that may elicit cognitive processes directly involved in repetitive negative thinking (e.g., frustrating task context)
6. Transfer effects should be assessed in a similar task context relevant to the cognitive mechanisms involved in the emotional outcome(s)
7. Use training paradigms for which cognitive transfer has already been demonstrated or include multiple measures of transfer
8. Explore the relation between cognitive and emotional transfer
9. Integrate indicators of neurophysiological mechanisms of depression vulnerability on multiple levels
10. Examine how change in cognitive control is related to change in the emotional outcome measure(s)
11. Use follow-up assessments to pick up training effects and to explore stability of transfer effects
12. Train samples that allow sufficient improvement in cognitive control and show sufficient heterogeneity regarding the emotional outcome(s)
13. For different training procedures and populations, taking into account potential moderators, set-up designs allowing to determine the number of sessions needed to establish transfer on cognitive and emotional outcomes

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*Increasing understanding of underlying mechanisms*

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14. Include measures of potential mediating variables
15. Include multiple time points in order to examine mediation
16. Compare training effects using an adequate comparator condition (e.g., active control) to ensure mechanisms can be linked to cognitive control

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*Increasing understanding of moderators of training effects*

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17. Conduct confirmatory research to replicate the moderators that have been observed
18. Moderator analysis requires sufficient data (cfr. sample size)
19. Explore the influence of specific clinical moderators that have a high likelihood of influencing efficacy of training
20. Assess cognitive impairments on multiple levels

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