Impaired Cognitive Control as a Causal Risk Factor for Intrusive Re-experiencing and Rumination in Posttraumatic Stress Disorder: Insights from Analogue and Clinical Samples

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Maria Voß

aus

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Referent/in: Prof. Dr. Thomas Ehring

Korreferent/in: Prof. Dr. Katja Bertsch

Drittes Mitglied der Prüfungskommission: Prof. Dr. Frank Padberg

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Abstract

Most individuals experience a traumatic event at least once in their life but only a minority develops persistent symptoms of Posttraumatic Stress Disorder (PTSD). Thus, pre-traumatic factors exist that increase vulnerability to PTSD. Identifying them is important to extend etiological models and to develop effective prevention programs. One pre-traumatic risk factor that has received particular attention in recent years is impaired cognitive control, defined as a decreased ability to maintain and regulate goal-directed behavior in the face of changing environmental demands. Although a considerable body of research reported associations between cognitive control impairments and PTSD, there is a lack of research investigating whether these impairments precede symptom development and whether manipulating them changes symptomatology. However, these conditions need to be met to label impaired cognitive control as a *causal* risk factor for PTSD. The major goal of this thesis is to fill this gap by examining temporal precedence as well as effects of manipulated cognitive control on PTSD symptoms in analogue and clinical samples. In particular, the studies presented in this thesis follow two different methodological approaches in influencing cognitive control—transcranial direct current stimulation (tDCS) and cognitive control training—and focus on posttraumatic intrusive re-experiencing as the main criterion. Additionally, they investigate the causal role of impaired cognitive control for posttraumatic rumination, a maladaptive processing style that maintains symptomatology.

Using the trauma film paradigm as an experimental equivalent, *study I* and *study II* aimed to manipulate cognitive control via tDCS over a brain region that is central to the cognitive control network—the left dorsolateral prefrontal cortex (dlPFC)—and to explore effects on film-related intrusive memories (*study I* & *II*) and rumination (*study I*) in healthy individuals. Furthermore, both studies examined whether impaired pre-stressor cognitive control was linked to increased post-stressor intrusive memories or rumination. *Study I* relied on the unity/diversity framework to operationalize cognitive control and focused on resistance to proactive interference—i.e. the inhibition of no-longer relevant information in working memory—as the relevant cognitive control function. N = 118 healthy women completed the modified California Verbal Learning Test assessing resistance to proactive interference twice—before and during 20-minutes tDCS (1mA; anodal, cathodal, or sham). Following tDCS, participants watched a trauma film and intrusive memories and rumination were measured after a 10-minutes resting period. There were no effects of tDCS on resistance to proactive interference and intrusive memories or rumination. Moreover, no significant correlations between these

measures emerged. *Study II* was designed to meet some methodological shortcomings of *study I*. This study used a similar design but relied on the dual mechanisms of control framework to define cognitive control. The dual mechanisms of control framework conceptualizes cognitive control as operating by two distinct modes: proactive control that is actively maintaining goal-relevant information to anticipate interferences, and reactive control that is goal reactivation only in response to interferences. To date, no study has tested whether deficits in proactive control are related to intrusive memories. N = 121 healthy men and women performed the AX-Continuous Performance Task—an established measure of proactive control—during 20-minutes tDCS (1 mA; anodal, cathodal, or sham), watched a trauma film, and reported intrusive memories after a 10-minutes filler task. There were no effects of tDCS on proactive control or intrusive memories. Moreover, decreased pre-stressor proactive control was not linked to increased post-stressor intrusive memories.

In contrast to the analogue designs in *study I* and *II*, *study III* focused on a clinical sample of N = 33 PTSD patients and investigated the effects of a 6-session cognitive control training on intrusive re-experiencing, rumination (repetitive negative thinking and brooding), and comorbid depressive symptoms. In this double-blind, randomized, controlled pilot study, participants were assigned to either a cognitive control training designed by Siegle et al. (2007) or a placebo training and tested at three time points (baseline, post, 1-month follow-up). The cognitive control training consisted of the adaptive Paced Auditory Serial Addition Task and Wells' Attention Training. All participants showed a significant reduction in intrusive re-experiencing, rumination defined as repetitive negative thinking, and comorbid depression after the training. However, training groups did not differ in these effects. Furthermore, only the placebo group reported a significant reduction in rumination defined as brooding. Additionally, there were no training effects on cognitive transfer tasks.

In sum, this thesis aimed to overcome the limitations of previous research by shedding light on causal associations between impaired cognitive control and intrusive re-experiencing as well as posttraumatic rumination. The study findings presented in this thesis question the role of deficient cognitive control for PTSD and thus contribute to our knowledge on risk factors that might influence the development of posttraumatic stress symptoms. Of course, methodological shortcomings, especially with regard to the manipulation of cognitive control, must be taken into account when interpreting the obtained results and are discussed. Moreover, implications for theoretical models and methodological approaches as well as directions for future research on cognitive control in PTSD are outlined.

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1. General Introduction

"Tell me, sweet lord, what is't that takes from thee
Thy stomach, pleasure and thy golden sleep?
Why dost thou bend thine eyes upon the earth,
And start so often when thou sit'st alone?
Why hast thou lost the fresh blood in thy cheeks;
And given my treasures and my rights of thee
To thick-eyed musing and cursed melancholy?
In thy faint slumbers I by thee have watch'd,
And heard thee murmur tales of iron wars;
Speak terms of manage to thy bounding steed;
Cry 'Courage! to the field!' And thou hast talk'd
Of sallies and retires, of trenches, tents,
Of palisadoes, frontiers, parapets,
Of basilisks, of cannon, culverin,
Of prisoners' ransom and of soldiers slain,
And all the currents of a heady fight.
Thy spirit within thee hath been so at war
And thus hath so bestirr'd thee in thy sleep,
That beads of sweat have stood upon thy brow
Like bubbles in a late-disturbed stream;
And in thy face strange motions have appear'd,
Such as we see when men restrain their breath
On some great sudden hest. O, what portents are these?(…)"

— Shakespeare: Henry IV, Part 1 (2.3.39-67) —

The observation that individuals suffer from serious emotional, behavioral, and cognitive disturbances after exposure to a life-threatening event is as old as mankind. From *The Iliad* by Homer to *All Quiet on the Western Front* by Remarque, classic literature offers numerous examples that illustrate the way in which traumatic experiences affect an individual's well-being (Weisaeth, 2014). Most impressively, in his history play *Henry IV, Part 1*, William Shakespeare (1598) lets Lady Percy bewail the condition of her husband after combat exposure, thereby providing one of the most accurate descriptions of posttraumatic stress

symptoms in the history of literature. Today, this symptom constellation is labeled Posttraumatic Stress Disorder (PTSD) and is defined in the most recent version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; APA, 2013, p. 271-272) by the following core criteria: persistent intrusive re-experiencing of the traumatic event (intrusive memories; nightmares; flashbacks; emotional distress in response to trauma reminders; physical reactivity to trauma reminders), avoidance of trauma-related internal or external reminders, alterations in mood and cognitions (deficits in recalling features of the traumatic event; negative assumptions about oneself or the world; exaggerated blame of self or others; negative affect; diminished interest in activities; feelings of isolation; diminished positive affect), and hyperarousal/reactivity (irritability or aggression; risky behavior; hypervigilance; heightened startle reaction; concentration disturbances; sleep disturbances).

Although posttraumatic stress symptoms have been well-known for many centuries, the acceptance of PTSD as an official diagnosis has been controversial. It has found its way into diagnostic systems not until 1980, being greatly influenced by the conditions of war veterans as well as women protests against institutional responses to rape victims (e.g., Friedman, Resick, & Keane, 2014). Part of this controversy came from the assumption that a strong mental reaction to life-threatening events is a natural coping mechanism, thereby questioning the legitimacy of disability claims (Weisaeth, 2014). Epidemiological research clearly disproved this assumption and demonstrated that trauma exposure is a necessary but not a sufficient condition for the development of PTSD: although experiencing traumatic events is part of human existence, most people do not suffer from posttraumatic stress symptoms in the direct aftermath of the event or they recover quickly within a few days or weeks (Friedman et al., 2014). For example, in Germany 24.2 % of individuals deal with a life-threatening event at least once in life, but 1-month prevalence rate of PTSD is only 2.3 % (Mearcker, Forstmeier, Wagner, Glaesmer, & Brähler, 2008). Thus, some individuals seem to be more vulnerable, more often fail to recover from the initial stress reaction, and experience more severe and persistent posttraumatic stress symptoms than others. As a consequence, identifying vulnerability factors has become an important focus in trauma research to better understand the origins of PTSD and extend etiological models but also to reduce individual and socioeconomical costs by developing prevention programs. A number of pre-traumatic, peri-traumatic, and post-traumatic factors that might influence PTSD were discussed in recent years. Especially the identification of pre-traumatic risk factors, defined as experiences or characteristics of the traumatized individual that existed prior to the traumatic event, is

challenging due to methodological and ethical restrictions. To date, female gender, young age, low socioeconomic status, and a history of mental disorders have been linked to more adverse trauma responses (Vogt, King, & King, 2014, for an overview). Additionally, the systematic investigation of cognitive impairments in war veterans with posttraumatic stress symptoms led to the conclusion that neurocognitive factors could also play a role in the development and maintenance of PTSD. Hence, in combination with the inclusion of neuroscientific methods into clinical psychology, trauma researchers are paying more and more attention to the neurocognitive underpinnings of PTSD, thereby translating basic cognitive models into clinical research approaches. In this context, one of the most studied but also most critically discussed factors that might be responsible for symptom variability in trauma survivors is impaired cognitive control, the main subject of this thesis.

Cognitive control as a multiple-named, multifaceted construct

A man arrives at a train station early in the morning. While buying a train ticket, he chats with an old lady waiting next to him. Reaching for his purse, he finds a note with the number "25" written on it in this bag. Suddenly, he remembers that his colleagues had asked him to buy a bouquet of flowers for 25 euros today and to bring it to the office as a birthday present for their boss. Since there is no flower shop near his office, he has to buy it at the train station. Hurrying to the next flower shop, a man with an e-roller crosses his way. Luckily, he can stop in front of him and avoids a crash. In this moment, his colleague calls and tells him to spend only 15 euros for the flowers and to buy marguerites. Thus, the man walks into the next flower shop, briefly checks whether they are offering marguerites, orders a bouquet for 15 euros, and runs back to get the next train.

From coordinating behavior in response to changed goals to stopping automated actions to integrating new information—the described example illustrates that everyday situations require the constant, purposeful regulation of thoughts and actions. This ability is known as cognitive control and involves engaging in, maintaining, and regulating goal-directed behavior in the face of distracting information or changed situational demands (for overviews see Cohen, 2017; Goschke, 2014). Different names for this construct have been established, for example, "executive functions", "central executive", "attentional control", "supervisory attention system", or "frontal lobe mechanisms" (e.g., Baddeley, 1983; Miyake et al., 2000; Shallice, 1988; Unsworth & Engle, 2007). However, in this thesis, the term "cognitive control" will be used for the sake of simplicity. Although researchers across disciplines agree

that cognitive control is central to adaptive human functioning, there is still disagreement about its operationalization. Whereas some authors suggested cognitive control to be a unitary construct, relying on a single component, modern theories highlight the diversity of domain-specific cognitive control functions and propose different models to define the organization of these functions (Cohen, 2017). Two of these models are central to this thesis: the *unity/diversity framework* (Miyake et al., 2000) and the *dual mechanisms of control (DMC) framework* (Braver, 2012; Braver, Gray, & Burgess, 2007).

The unity/diversity framework

The unity/diversity framework is a descriptive model of the relation between three cognitive control functions: updating and monitoring of representations in working memory ("updating"), shifting between multiple tasks, goals, operations, or mental sets ("shifting"), and inhibition of automatic or dominant responses ("inhibition") (Miyake et al., 2000). For instance, in the example described above, organizing behavior for buying flowers and incorporating the new price information as well as which flowers to buy requires monitoring and updating of working memory. Buying a ticket while chatting with the old lady requires shifting and stopping in front of the e-roller to avoid a crash requires inhibition. However, in this example all three cognitive control functions seem to be intertwined. Indeed, using latent variable analyses, Miyake and colleagues (2000) found that updating, shifting, and inhibition are neither identical nor independent but best described as three separate but correlated factors. Thus, cognitive control is not seen as a unique construct but consists of three distinguishable functions (= diversity) that share an underlying similarity (= unity). Additionally, modifications of this model were proposed. First, by performing latent-variable analyses on inhibition-related tasks, Friedman and Miyake (2004) reported that inhibition of automatic or dominant responses is closely related to inhibition of interference from goal-irrelevant information (e.g., in the example, screening for marguerites between other flowers). Furthermore, both functions differ from inhibition of information that had been but is no longer relevant—known as resistance to proactive interference (e.g., ordering a bouquet for 15 instead of 25 euros). Hence, inhibition does also include diversity. Second, Miyake and Friedman (2012) suggested an alternative bifactor model. This bifactor model assumes each cognitive control function to consist of what is common across the three functions and of what is specific to this particular function. Interestingly, updating-specific components—reflecting controlled information gating or retrieval in working memory—and shifting-specific

components—reflecting cognitive flexibility—have been reported (Miyake & Friedman, 2012). However, the researchers could not find inhibition-specific components when including a common factor into the model. Thus, they described the common factor as the capability to maintain goal-relevant despite goal-irrelevant information, an ability that might also be central to inhibition. Importantly, the unity/diversity framework is not comprehensive, as other components of cognitive control might also exist, and should not be interpreted as the overall basics of cognition (Friedman & Miyake, 2017). Nevertheless, especially the original model has been established as a useful taxonomy of cognitive control functions to guide the examination of cognitive control in PTSD in recent years.

The dual mechanisms of control framework

In contrast to the unity/diversity framework, the DMC framework (Braver, 2012; Braver et al., 2007) is a theory-driven model based on cognitive and brain research. It highlights the temporal dynamics of cognitive control and describes performance in cognitive tasks as a result of task parameters and individual traits (Braver, 2012). In particular, the DMC framework postulates that cognitive control operates in two distinct modes: proactive and reactive. Whereas the proactive control mode involves active maintenance of goal representations to anticipate disturbances, the reactive control mode is transient and operates in response to interferences from the environment or salient trigger events. According to Braver (2012), a proactive control mode can be described as “early selection” and a reactive control mode as “late correction”. Adaptive cognitive functioning needs a mixture of both modes for a positive costs-benefits trade-off. In this regard, context plays an important role, defined as specific information that influence the selection of responses (Braver, 2012). Context representations in working memory bias attention towards goal-relevant information. For proactive control, these context representations have to be sustained over longer periods of time, but for reactive control, context representations only occur as needed. Thus, proactive control needs reliable contextual cues from the environment, is more resource-demanding, and not feasible in very long intervals between goal formation and realization (Braver et al., 2007). In contrast, reactive control is disadvantageous when failure has to be avoided as it depends on interfering events or salient triggers and when individuals are confronted with no-longer relevant goals or information (Braver et al., 2007). In the example described above, a reactive control mode would involve the representation of the goal to buy flowers only after it is formed, i.e. when his colleagues had asked him the evening before. Thus, it might not be

accessible when the man arrives at the train station and when he spends the last minutes before train departure chatting with the old lady. It is only retrieved by a salient trigger, for example, finding the note before boarding the train. In contrast, a proactive control mode would involve the continuous maintenance of the goal from the evening before to buying the flowers before train departure. Thus, behavior can be adjusted to meet the goal, for example, by arriving earlier at the train station to have enough time or by not chatting with the old lady. However, it has been found that individuals differ in their deployment of proactive and reactive control when performing highly demanding tasks (Braver, 2012). These differences are thought to result from selective impairments in one of both control modes and therefore from an imbalance in dual mechanisms (Braver, 2012). Interestingly, Friedman and Miyake (2017) assumed that the common factor within the bifactor model of the unity/diversity framework is similar to a proactive control mode. Moreover, performance in working memory tasks seems to rely on proactive control, since memory items have to be maintained and updated over a certain period of time (Braver, 2012). However, despite the conceptual clarity of the DMC framework and its link to the unity/diversity framework, the model has been applied less frequently in cognitive and clinical research and has not yet been investigated in the context of PTSD.

Brain regions associated with cognitive control

As important but also as controversial as the organization of cognitive control functions is their neuronal foundation. Based on lesions studies, neuroimaging, and computational modelling, cognitive control has mainly been associated with activation in the prefrontal cortex (PFC), but also with cingulate and parietal cortices (e.g., Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008; Miller & Cohen, 2001; Stuss, 2011). To converge information and to guide complex behavior, these regions interact with sensory and motor systems, as well as subcortical systems such as the basal ganglia and the limbic system (Miller & Cohen, 2001; Miyake & Friedman, 2012, for overviews). Especially the dorsolateral prefrontal cortex (dlPFC) and the anterior cingulate cortex (ACC) have been discussed to play the most critical roles in this network, providing top-down control for organizing, monitoring, and adapting goal-oriented actions and orchestrating cognitive control functions (e.g., Mansouri, Tanaka, & Buckley, 2009; Niendam et al., 2012; Robinson, Calamia, Gläscher, Bruss, & Tranel, 2014).

Within the unity/diversity framework, no specific assumptions on the involved brain regions have been made (Friedman & Miyake, 2017; Miyake & Friedman, 2012).

Empirically, manipulating information in working memory has frequently been linked to activation of the dlPFC and the ACC (e.g., Curtis & D'Esposito, 2003; Kim, Kroger, Calhoun, & Clark, 2015; MacDonald, Cohen, Stenger, & Carter, 2000). Activation in the dlPFC has also been related to performance in shifting tasks, besides activation in the inferior frontal gyrus, the parietal cortex, and the medial frontal cortex (e.g., Kim, Cilles, Johnson, & Gold, 2012; Sylvester et al., 2003). Additionally, performance in inhibition tasks has been associated with activation in the dlPFC, the ACC, and the inferior frontal gyrus as well as partly with ventrolateral, orbitofrontal, and parietal regions (e.g., Aron, Robbins, & Poldrack, 2004; Blasi et al., 2006; Fassbender et al., 2004; Nee, Wager, & Jonides, 2007; Warren et al., 2013). However, it must be noted that neuroscientific research on cognitive control is extensive and has also produced conflicting results. Thus, also less convincing evidence for the dlPFC's involvement in inhibition and shifting tasks exist (see also Aron et al., 2004; Wager, Jonides, & Reading, 2004). In contrast to the unity/diversity framework, the DMC framework makes predictions on the location and temporal dynamics of neural activity associated with proactive and reactive control (Braver, 2012; Chiew & Braver, 2017). Proactive control should be related to sustained activation of the lateral PFC as a top-down bias that maintains context representations. In contrast, reactive control should be linked to rapid, transient activation of the lateral PFC prior to responding but also to additional regions such as the ACC and the posterior cortical or medial temporal lobe areas. In particular, this transient activation should "reflect the bottom-up reactivation of task goals, mediated either via the detection of interference (…) or via associative and episodic associations" (Braver, 2012, p. 2).

Linking cognitive control to PTSD: model suggestions

If cognitive control is indeed a factor that influences PTSD symptom development, there is a need for conceptual models specifying through which pathways this factor should operate. In a systematic review of neuropsychological studies, Aupperle, Melrose, Stein, and Paulus (2012) proposed such a model. They suggested that exposure to a traumatic event increases attention towards trauma-related internal or external stimuli in all individuals, but only individuals with pre-traumatic impaired cognitive control should experience difficulties in inhibiting attention and responses to these stimuli. As a result, these individuals should be constantly confronted with internal and external trauma reminders, a process that sustains re-experiencing and hyperarousal. To deal with this confrontation, coping strategies such as

avoidance are applied. Avoidance in turn reduces the engagement in rewarding or pleasurable activities, an effect that should foster emotional numbness or social isolation. Thus, this model provides an explanation of why individuals differ in posttraumatic stress symptoms by combining findings from attention and cognitive control research. Moreover, it explains the development of hallmark symptoms of PTSD. Nevertheless, the model follows a relative unspecific approach that is not integrated into established theories of PTSD or cognitive control, a limitation that also applies to most cognitive control literature on PTSD. To deal with this limitation, potential pathways by which cognitive control may influence symptom development with regard to two famous etiological models will be exemplified in the following. In particular, these suggestions will focus on intrusive memories as a key re-experiencing symptom of PTSD.

Example I: Ehlers and Clark's cognitive model of PTSD

Intrusive memories are brief, vivid, and recurring recollections of the traumatic experience, mostly occurring in the form of sensory fragments of the event (Marks, Franklin, & Zoellner, 2018, for an overview). A famous theory that explains the manifestation of intrusive memories in the aftermath of a trauma is *Ehlers and Clark's cognitive model of PTSD* (2000). This model assumes that intrusive memories develop when individuals process the traumatic experience in a way that elicits a continued sense of threat. This continued sense of threat results from individual differences in the appraisal of the traumatic event and/or its consequences as well as in the nature of the trauma memory and its integration into autobiographical memory. More specifically, Ehlers and Clark (2000, p. 325) suggested that the trauma memory is "poorly elaborated and inadequately integrated into its context in time, place, subsequent and previous information and other autobiographical memories". Thus, sensory-perceptual details about the traumatic event are encoded without context or conceptual organization, leading to a here-and-now threat experience when the memory is activated. Furthermore, due to strong stimulus-stimulus and stimulus-reaction associations, representations of the trauma memory can be easily and automatically triggered by a number of internal and external cues (Ehlers & Clark, 2000). Hence, pre-traumatic cognitive control functions that supervise contents of working memory might help individuals to ignore distracting cues and to stay focused on activated goals. In terms of the unity/diversity framework, the relevant cognitive control functions might be updating of working memory and inhibiting dominant responses or goal-irrelevant information and resisting to proactive

interference (see also Bomyea, Amir, & Lang, 2012). Moreover, Ehlers and Clark (2000) argued that maladaptive coping strategies such as avoidance should impede inhibitory learning, thereby aggravating intrusive re-experiencing (Ehlers, Hackmann, & Michael, 2004). If cognitive control supports individuals in dealing with trauma cues repeatedly and successfully, activation levels of trauma memory should decrease, resulting in increased inhibitory learning (see also Wessel, Huntjens, & Verwoerd, 2010) and decreased symptoms. In this way, cognitive control might contribute to a constant symptom reduction in the aftermath of a traumatic event. In contrast, deficient cognitive control might disturb this process, thereby increasing the likelihood that intrusive re-experiencing persists in the aftermath of the event. Additionally, the DMC framework has proposed that individuals with anxiety disorders who monitor their environment for external or internal cues of threat more often rely on a cost-efficient reactive instead of a proactive control mode (Chiew & Braver, 2017). It has also been demonstrated empirically that threat perception increases reactive control and impairs proactive control by occupying working memory capacity (e.g., Yang, Miskovich, & Larson, 2018). The continued sense of threat assumed by Ehlers and Clark's model might also reduce proactive control in trauma survivors. This imbalance in control modes might in turn decrease the maintenance of goal-relevant information and might enhance a shift of attention towards trauma-related distractors, therefore supporting persistent intrusive memories. However, individuals with pre-traumatic impairments in proactive control might be per se more sensitive to background monitoring and threat-relevant goal-incongruent features of the environment (Chiew & Braver, 2017), might have more difficulties in maintaining activated goals, and might also have less resources to attenuate the cognitive imbalance further elicited by threat perception, thereby being predisposed for symptom evolvement.

Example II: dual representation theory

Another theory that focuses on the development of intrusive memories is the *dual representation theory*, a model that connects established concepts of PTSD with results from cognitive neuroscience (Brewin, 2008; Brewin, Dalgleish, & Joseph, 1996; Brewin, Gregory, Lipton, & Burgess, 2010). Brewin and colleagues (2010) distinguished two separate but parallel-operating representational systems in memory: on the one hand, contextual memory representations (C-reps) that are contextually bound, deliberately retrieved, and can be integrated into semantic memory. They enable individuals to verbally communicate a

traumatic experience and to reappraise the event in a meaningful way. Moreover, at the neurological level, C-reps are associated with brain regions that are responsible for contextualizing memories such as the hippocampus and are controlled by top-down processes of the PFC. On the other hand, sensation-based memory representations (S-reps) cannot be deliberately retrieved but are low-level, isolated, and easily triggered by internal or external cues. S-reps involve emotional and autonomic components linked to the amygdala as well as brain regions that are directly related to perception rather than higher order prefrontal control. Brewin (2008) postulates that intense stress exposure during a traumatic event increases amygdala and decreases hippocampal activity. Therefore, it should lead to strong S-reps and weak C-reps. However, in traumatized but healthy individuals S-reps should be connected to C-reps of the traumatic event. Thus, the trauma memory can be integrated within an autobiographical context and is susceptible to top-down control of the PFC. In contrast, intrusive memories should result from the formation of a persistent S-rep that is poorly connected to a corresponding C-rep and therefore lacks contextualization and top-down control. Constant avoidance of trauma cues is thought to maintain this disintegration. Dual representation theory itself specifies the role of the PFC and of top-down cognitive control. When healthy individuals deliberately recall a traumatic event, visual imagery is activated via C-reps directed by PFC-related cognitive control mechanisms that support, for example, the inhibition of specific retrieval cues or the differentiation of contexts similar to the traumatic events (Brewin, 2008). However, individuals with decreased pre-traumatic activity in the PFC and diminished cognitive control functions such as inhibition (unity/diversity framework) or proactive control (DMC framework) might experience visual imagery to be more often activated bottom-up by S-reps and to be less successfully regulated. Moreover, this process might also increase avoidance and block integration, therefore further consolidating posttraumatic stress symptoms.

These model suggestions aimed to exemplify the pathways by which persistent intrusive memories might be causally influenced by pre-traumatic impaired cognitive control as defined within the unity/diversity framework, the DMC framework, or neuropsychological approaches. However, with the proposition of theoretical pathways, the question emerges whether empirical evidences support a causal relation between cognitive control deficits and PTSD symptomatology.

From theoretical models to empirical evaluation: constituting causality in cognitive control research on PTSD

PTSD is the only DSM-5 diagnosis that requires the identification of an etiological factor—the experience of a traumatic event—and is therefore outstanding in the conceptualization of mental disorders (APA, 2013). However, given the unpredictability of traumatic events, this requirement implies serious methodological and ethical challenges for research on causal relations between pre-traumatic cognitive control and PTSD symptoms. Nonetheless, clarifying causality is essential: Diminished cognitive control empirically observed in PTSD patients might be a cause or a consequence of posttraumatic stress symptoms or both might reinforce each other. For example, regarding the DMC framework, a proactive control mode consumes cognitive resources. Impaired proactive control possibly found in PTSD patients might also result from distress due to posttraumatic stress symptoms that reduce capacity for proactive control after the traumatic event. Moreover, reduced performance in cognitive control tasks might be a consequence of distracting posttraumatic symptoms. Additionally, impaired cognitive control prior to the trauma might interact with acquired disturbances after the trauma, with subtle pre-traumatic differences in cognitive control transforming into more severe impairments and leading to a vicious cycle of depleted cognitive resources and symptom reinforcement. Thus, causal relations need to be determined. To define what makes a potential risk factor a *causal* risk factor, Vogt and colleagues (2014) transferred the definition of causal risk factors by Kraemer and colleagues (1997) to trauma research. They stated that a causal risk factor in PTSD should meet the following criteria:

(1) It is associated with PTSD symptoms,
(2) temporally precedes PTSD symptoms as demonstrated by longitudinal or experimental designs,
(3) and can be manipulated and this manipulation induces symptom changes.

Even when these criteria are fulfilled, causality remains a probabilistic construct. Thus, the true causal mechanisms accounting for the effect of a risk factor can never be stated with absolute certainty (Vogt et al., 2014). Nevertheless, evaluating whether cognitive control deficits meet the criteria of a causal risk factor would clearly extend our understanding of the disorder and underpin the theoretical models postulated above. Hence, recent research as well as research gaps will be summarized in the following.

(1) Cross-sectional research on cognitive control in PTSD

When reviewing the literature, it becomes evident that findings on cognitive control deficits in PTSD samples are inconsistent and differ between studies but also within studies. On the one hand, this lack of consistency might result from most studies not including a conceptual model of cognitive control or PTSD, thereby choosing specific cognitive control tasks only in terms of availability. On the other hand, differing outcomes might be explained by characteristics of specific cognitive control tasks or the explored trauma sample. Thus, meta-analyses that cumulate evidence across independent studies and take methodological variance into account should offer the best overview. Polak, Witteveen, Reitsma, and Olff (2012) pooled effects across 18 studies and found that PTSD patients perform significantly worse on measures of cognitive flexibility and working memory than trauma-exposed healthy controls and significantly worse on measures of cognitive flexibility and inhibition than trauma-unexposed healthy controls. However, subgroup characteristics influenced these results. Cognitive control deficits were more pronounced in individuals with war traumatization, male gender, higher age, and comorbid depression. Polak and colleagues (2012) suggested that severity of symptoms might explain these findings. For example, studies that included war combat patients reported higher symptom severity than studies with other trauma samples and men usually experienced more war traumatization. Importantly, this meta-analysis focused on a small subset of circumscribed cognitive control measures. For instance, only studies that assessed inhibition using the Stroop task or working memory updating using a simple digit span task had been included. In addition to Polak and colleagues (2012), Scott and colleagues (2015) applied meta-analytic techniques to investigate deficits associated with PTSD in nine broader neurocognitive domains across 60 studies. Besides attention/working memory and cognitive control, these domains also included verbal learning, verbal memory, visual learning, visual memory, language, speed of information processing, and visuospatial abilities. The researchers reported an overall medium effect size across domains, with also significant medium effect sizes for deficits in attention/working memory and cognitive control in PTSD patients. Specifically, these effect sizes were independent of trauma type, trauma exposure of the control group, symptom severity, age, or comorbidities. However, effect sizes were influenced by treatment seeking status of participants, comorbid attention-deficit/hyperactivity disorder, IQ, and male gender. Lastly, Woon, Farrer, Braman, Mabey, and Hedges (2017) recently evaluated whether PTSD symptom severity is a potential moderator of the link between PTSD and cognitive control in an analysis of 14 studies. In

accordance with previous research, PTSD patients showed mild-to-moderate impairments in cognitive control as compared to trauma-exposed and trauma-unexposed healthy controls. However, there was no moderating effect of PTSD symptom severity.

In conclusion, although inconsistencies exist (see also Danckwerts & Leathem, 2003, for an overview), meta-analyses on the current body of cognitive research indicate cognitive control deficits in PTSD patients as compared to healthy controls. These meta-analyses offer important insights into general cognitive control impairments associated with PTSD. However, they barely inform on specific cognitive control functions. Cognitive control was used as an unitary construct (Scott et al., 2015; Woon et al., 2017) or neurocognitive tasks were included that rely on a variety of cognitive control domains (Polak et al., 2012), making it difficult to draw general conclusions on single functions as defined within the unity/diversity framework. Moreover, to the best of our knowledge, no research has systematically investigated cognitive control deficits in light of the DMC framework.

(2) Longitudinal and experimental research on temporal precedence

A major issue of recent cognitive research in PTSD is that most findings are based on cross-sectional data. This approach answers the question whether cognitive control is indeed diminished in PTSD patients but it states nothing about temporal dynamics. Although longitudinal research is challenging and expensive, a few studies examined whether cognitive control deficits precede symptom evolvement. Nevertheless, the number of studies that focused on cognitive control instead of general intelligence and additionally excluded individuals with mild brain injuries is scarce. In a large epidemiological study on a community-based sample of young adults, Parslow and Jorm (2007) reported that individuals with lower scores in cognitive tasks that measured verbal recall, working memory, and visuomotoric speed prior to a natural disaster showed more intrusive re-experiencing afterwards. However, the results were not controlled for pre-traumatic PTSD symptom levels. Furthermore, Marx, Doron-Lamarca, Proctor, and Vasterling (2009) administered a neuropsychological test battery in a military sample and reported that diminished pre-deployment visual memory recall performance but not verbal memory, sustained attention, working memory, or response inhibition predicted PTSD symptoms after deployment. Interestingly, the effect was strongest in individuals with PTSD existing before deployment, a result that might support the assumption that cognitive impairments can be a risk factor but also a consequence of PTSD.

In addition to longitudinal research with PTSD samples, experimental research with healthy individuals also provides insights into temporal precedence. These approaches typically use paradigms that expose healthy individuals to laboratory stressors and assess subsequent intrusive memories. Especially the trauma film paradigm has been established as a useful prospective tool in recent years (e.g., Holmes & Bourne, 2008; James et al., 2016, for overviews). In this paradigm, healthy participants complete cognitive tasks, watch a film fragment that depicts stressful or traumatic events, and specify the number of intrusive memories either during a short period of time at the laboratory or via an intrusive memory diary. Research administering the trauma film paradigm indicated that post-film intrusive memories are related to pre-film deficits in resistance to proactive interference (Verwoerd, Wessel, de Jong, Nieuwenhuis, & Huntjens, 2011; Wessel, Overwijk, Verwoerd, & de Vrieze, 2008). Besides the trauma film paradigm, alternative approaches typically instruct participants to describe the most distressing experience of their life. Following this approach in the context of cognitive control, Verwoerd, Wessel, and de Jong (2009) showed that low resistance to proactive interference but no other inhibition-related measures predicted intrusive memories of the experience. Again, these findings can be integrated into the unity/diversity framework, but research on the DMC framework is missing.

In conclusion, prospective research on the link between cognitive control and posttraumatic stress symptoms is scarce. Whereas clinical research in different trauma samples has produced inconsistent findings, analogue research pointed towards the role of inhibition—especially resistance to proactive interference—and working memory updating for intrusive memories.

(3) New directions: manipulating cognitive control in the context of PTSD

The research findings described so far indicate that cognitive control deficits are not only associated with PTSD in general and intrusive memories in particular, but might also precede symptomatology. However, as stated by Kraemer and colleagues (1997), to determine whether a risk factor causally influences a target construct, it is necessary to demonstrate that a manipulation of the risk factor changes the target. To date, there is a lack of research addressing cognitive control manipulations in PTSD. Therefore, this thesis presents two methodological approaches that might help filling this gap.

First, a large body of research suggests that cognitive control can be manipulated by altering neuronal activity in related brain regions, for example via transcranial direct current stimulation (tDCS). TDCS is a well-established, safe, non-invasive, and effective method to modulate neuronal activity, cognition, and even behavior. Although the physiological effects of tDCS are complex and not entirely clear, tDCS is generally assumed to act by polarity-dependent hyper- or depolarization of resting membrane potentials (e.g., Nitsche & Paulus, 2001; Priori, 2003; Wassermann & Grafman, 2005). Importantly, tDCS does not trigger action potentials but rather changes membrane permeability and synaptic transmission by increasing/decreasing firing rate. More specifically, electric current flows from the positive anode to the negative cathode (Tremblay et al., 2014). Thus, anodal stimulation is assumed to cause increases in neuronal excitability and spontaneous firing rates by depolarizing resting membrane potentials, whereas cathodal stimulation leads to the opposite effect (Bestmann, de Berker, & Bonaiuto, 2015). These effects should persist for at least one hour, even after stimulation (Nitsche et al., 2008). In recent years, it has been shown that prefrontal cathodal tDCS has the ability to diminish cognitive control, and prefrontal anodal tDCS has the ability to enhance cognitive control in healthy individuals, especially in tasks measuring working memory updating and inhibition (e.g., Andrews, Hoy, Enticott, Daskalakis, & Fitzgerald, 2011; Brunoni & Vanderhasselt, 2014; Fregni et al., 2005; Hoy et al., 2013; Wolkenstein, Zeiller, Kanske, & Plewnia, 2014). In contrast, tDCS research on the DMC framework is limited (Gómez-Ariza, Martin, & Morales, 2017). However, no study has yet examined whether tDCS-induced alterations in cognitive control might also affect intrusive memories. This is surprising since previous research indicated structural and functional abnormalities associated with PTSD that parallel brain regions associated with cognitive control, for example, hypoactivation of the lateral PFC or the ACC (e.g., Aupperle et al., 2012; Hayes, VanElzakker, & Shin, 2012; Kühn & Gallinat, 2013; Patel, Spreng, Shin, & Girard, 2012; Pitman et al., 2012). Moreover, studies investigating the treatment effect of repetitive transcranial magnetic stimulation in PTSD patients demonstrated that neurostimulation of a brain region associated with cognitive control, the dlPFC, can influence re-experiencing (Boggio et al., 2010; Cohen et al., 2004; Watts, Landon, Groft, & Young-Xu, 2012). Thus, using prospective analogue designs that manipulate activation levels in prefrontal brain regions via tDCS and that test effects on cognitive control, intrusive memories, and their interactions would be a novel approach and extend our knowledge on causal relations.

Another approach to manipulate cognitive control is examining the effects of cognitive control trainings. There is converging evidence that training procedures can alter cognitive control and psychopathology across disorders (Koster, Hoorelbeke, Onraedt, Owens, & Derakshan, 2017; Siegle, Ghinassi, & Thase, 2007, for overviews). However, research in the context of PTSD is limited. Only a few studies have tested whether cognitive control trainings influence posttraumatic stress symptoms in healthy (Bomyea & Amir, 2011; Callinan, Johnson, & Wells, 2015; Nassif & Wells, 2014) or clinical (Bomyea, Stein, & Lang, 2015) samples. The general principle of these trainings is that performing multiple sessions of a computerized cognitive control paradigm should modulate cognitive control functions. These modulated functions should then translate into improvements in the specific cognitive control paradigm, into transfer effects on other cognitive paradigms, and into reductions in posttraumatic stress symptoms. Typically, the effects of a cognitive control training are compared to a placebo training not focusing on cognitive control. Although all of the existing training studies reported beneficial effects on posttraumatic stress symptoms such as intrusive re-experiencing, they differ in training targets. Based on results from analogue studies, some researchers explored a training that focused on resistance to proactive interference. Bomyea and Amir (2011) reported improvements in working memory updating as well as in intrusive memories during a thought suppression task after one session of this training in healthy individuals. Moreover, Bomyea and colleagues (2015) demonstrated beneficial effects on working memory updating and intrusive re-experiencing after eight sessions of this training in women diagnosed with PTSD. In both studies the training was compared to a less-intensive control training. Other researchers examined Wells's Attention Training, a cognitive paradigm that involves prefrontal activation and controlled selective attention despite automatic cognitions. Testing healthy individuals, Nassif and Wells (2014) and Callinan and colleagues (2015) reported significant effects of two sessions of this training (plus optional homework sessions) on intrusive memories in response to a recording of a distressing event, as compared to a placebo training consisting of a filler task. Although differing in training targets and assessments of intrusive memories, both approaches focused on training tasks that included neutral stimuli. In contrast, Schweizer and colleagues (2017) showed that performing twenty sessions of a working memory training with standardized trauma-related words and pictures of negatively valenced faces increased response inhibition and decreased posttraumatic stress symptoms in adolescents with PTSD. However, approaches with trauma-related material do not inform about the role of more basic cognitive control functions.

Taken together, both—tDCS and cognitive trainings—are important avenues for experimentally manipulating cognitive control and help to further shed light on causality in posttraumatic stress symptomatology. Thus, both approaches will be followed in the studies presented in this thesis.

Rumination as an additional target of cognitive control manipulations

As mentioned above, intrusive memories include the short, involuntary, sensory reliving of the traumatic event itself. Equally aversive but phenomenologically and functionally distinct is rumination, defined as uncontrollable, repetitive, verbal thinking about the causes and consequences of the traumatic event for a longer period of time (Michael, Halligan, Clark, & Ehlers, 2007). Rumination typically appears in the form of "why" and "what if" questions, for example about how the event could have been prevented or whether something similar could happen again (Ehlers & Clark, 2000). Thus, it also differs from intrusive memories in the type of cognition, as rumination does not include recollections but evaluative thoughts (Ehring & Watkins, 2008). Importantly, rumination is not a key symptom of PTSD but a maladaptive cognitive processing style that maintains symptomatology. According to the cognitive model by Ehlers and Clark (2000), trauma survivors might ruminate to gain control over the perception of current threat and the experience of distressing symptoms and to escape intrusive memories by focusing on the traumatic event in a more abstract way. However, Ehlers and Clark (2000) assume that this is counterproductive as rumination might directly produce further posttraumatic stress symptoms by inducing negative affective states and providing internal cues for intrusive memories. Moreover, rumination might prevent change in posttraumatic stress symptomatology by further strengthening negative appraisals and by interfering with the completion of the fragmented trauma memory as it does not include recapitulating the details of what actually happened (Ehlers & Cark, 2000). Additionally, rumination has been identified as a core risk factor for depression (e.g., Spasojević & Alloy, 2001). Therefore, it might also contribute to the development of comorbid depressive symptoms.

In general, there is accumulating evidence that rumination is cross-sectionally associated with PTSD (e.g., Ehring, Frank, & Ehlers, 2008; Michael et al., 2007; Razik, Ehring, & Emmelkamp, 2013) and represents a powerful predictor of posttraumatic stress symptoms such as intrusive re-experiencing in the aftermath of a traumatic event (e.g., Ehring & Ehlers, 2014; Ehring et al., 2008; Michael et al., 2007; Murray, Ehlers, & Mayou, 2002; Wild et al.,

2016). For example, in a recent meta-analysis, Szabo, Warnecke, Newton, and Valentine (2017) reported a moderate, positive relationship between rumination and posttraumatic stress symptoms in trauma-exposed individuals, with effects being strongest for intrusive re-experiencing. Additionally, analogue research in healthy samples showed that experimentally manipulating rumination results in more intrusive memories (Ball & Brewin, 2012; Ehring, Fuchs, & Kläsener, 2009; Zetsche, Ehring, & Ehlers, 2009). However, given the significance of rumination as a maintaining factor for PTSD, the question is what drives trauma survivors to engage in rumination despite its negative effect? As mentioned above, Ehlers and Clark (2000) assumed rumination to be a consequence of problematic appraisals, in contrast to intrusive memories that mainly result from specific characteristics of the trauma memory. However, research from other clinical domains such as depression or emotion regulation also suggested that reduced cognitive control makes individuals more susceptible to ruminative thinking. Thus, cognitive control impairments might also causally influence rumination in trauma survivors and therefore further sustain persistent posttraumatic stress symptoms.

In recent years, different theories were proposed that link impaired cognitive control to rumination (e.g., Vălenaş & Szentágotai-Tătar, 2017, for an overview). For example, Linville (1996) suggested that deficient inhibition might increase the risk that thoughts become repetitive by failing to guard working memory against information or thoughts that are irrelevant to currently pursued goals. Moreover, reduced inhibition might make it more difficult to remove activated information that is no-longer relevant from working memory. Furthermore, according to the impaired disengagement hypothesis postulated by Koster, De Lissnyder, Derakshan, and De Raedt (2011), rumination might be a normal phenomenon but becomes pathological if it persists over a longer period of time. Especially decreased cognitive control might hinder the disengagement of attention from cued negative or self-referring thoughts and the inhibition of negative, goal-irrelevant information, thereby prolonging the processing of activated negative or self-referent material. Although referring to rumination in healthy or depressed individuals, these approaches can be transferred to rumination associated with PTSD. As described above, impaired cognitive control might make it more difficult for trauma survivors to ignore distracting trauma-related cues, to stay focused on activated goals, and to control contents of working memory, thereby facilitating persistent intrusive memories. In a similar way, deficient cognitive control might influence the control of stimuli that trigger rumination such as external stressors or negative affect. Additionally, cognitive control deficits might also be the reason why individuals get stuck in

recurrent ruminative thinking. Rumination does not consist of the short, sensory reliving of the trauma but is a type of thinking that persists over a longer period of time. In contrast to intrusive memories, reduced cognitive control might especially hinder individuals to stop ruminative thoughts once they have emerged by gaining control over contents of working memory, inhibiting trauma-related, self-referring thoughts, or shifting to alternative contents or evaluations. Thus, in terms of the unity/diversity framework, updating of working memory, inhibition, and shifting might be relevant for rumination.

Indeed, rumination has been empirically associated with impairments in cognitive control (e.g., Bernstein, Heeren, & McNally, 2017; De Lissnyder, Koster, & De Raedt, 2012; Pe et al., 2012; Whitmer & Gotlib, 2013; Zetsche, D'Avanzato, & Joormann, 2012; Zetsche & Joormann, 2011). Three meta-analyses investigated the role of particular cognitive control functions. Yang, Cao, Shields, Teng, and Liu (2016) as well as Vălenaş and Szentágotai-Tătar (2017) reported significant relations between rumination and deficits in inhibition as well as shifting but no associations with working memory. Moreover, Zetsche, Bürkner, and Schulze (2018) demonstrated that individuals who frequently engage in rumination show particular deficits in removing no-longer relevant information from working memory. However, previous research did not focus on rumination in PTSD. Furthermore, causality must be clarified. According to the resource depletion account, ruminative thinking might also occupy cognitive resources, reduce capabilities for exerting cognitive control, and decrease performance in cognitive control tasks (Philippot & Brutoux, 2008; Watkins & Brown, 2002). Hence, impaired cognitive control might also be a consequence but not a cause of frequent ruminative thinking. Fortunately, in contrast to cognitive research on posttraumatic stress symptoms, the examination of causal directions in the context of rumination has been extensively followed in recent years. For instance, tDCS was shown to influence ruminative thinking by targeting the dlPFC (De Raedt, Remue, Loeys, Hooley, & Baeken, 2017; Vanderhasselt, Brunoni, Loeys, Boggio, & De Raedt, 2013) and cognitive control trainings were proven to be effective for altering rumination (Koster et al., 2017; Mor & Daches, 2015, for overviews). Nevertheless, all of these results stem from healthy or depressed samples, not examining the causal link between rumination and cognitive control in the context of PTSD.

In conclusion, as rumination is a maintaining factor for posttraumatic stress symptoms and has been linked to impaired cognitive control, exploring whether modulating cognitive control does also affect posttraumatic rumination would clearly extend etiological models of PTSD.

Thus, although the main focus on this thesis is to further examine causal associations between impaired cognitive control and intrusive re-experiencing as a key symptom of PTSD, additional measures of rumination will be integrated in some of the studies presented in this thesis.

Aim of the present thesis

The major goal of this thesis is to investigate the *causal* association between impairments in cognitive control and posttraumatic stress symptoms. In particular, this thesis addresses the questions whether a modulation of cognitive control influences intrusive re-experiencing and whether poor cognitive control precedes symptom development. Additionally, this thesis also focuses on the role of cognitive control for rumination, an important maintaining factor of PTSD symptomatology. Three studies are presented; two analogue studies with healthy samples exploring the effects of tDCS and one clinical study with a PTSD sample exploring the effects of a cognitive control training.

Study I and *study II* combine the trauma film paradigm with the tDCS approach. Both studies aim to manipulate a brain region that is related to cognitive control and to assess its effects on cognitive control as well as the development of intrusive memories after a trauma film. Furthermore, *study I* also measures post-film rumination. In both studies, the left dlPFC is chosen as the target brain region given its significance for cognitive control and its susceptibility to neuromodulation. A between-group design is used to compare the effects of anodal and cathodal tDCS with a sham stimulation group. Additionally, correlations between pre-stressor cognitive control and post-stressor intrusive memories or rumination are explored. The major difference between both studies is the theoretical framework to define cognitive control. *Study I* follows the unity/diversity framework and, based on recent analogue research, focuses on resistance to proactive interference as a specific cognitive control function. This study investigates whether tDCS on the left dlPFC influences resistance to proactive interference and film-related intrusive memories or rumination in a sample of 118 women. Moreover, this study aims to replicate the well-established correlations between resistance to proactive interference and intrusive memories or rumination. In contrast, *study II* follows the DMC framework and focuses on proactive and reactive control as cognitive control functions. More specifically, effects of tDCS over the left dlPFC on proactive control and film-related intrusive memories as well as associations between both are examined in 121 men and women. These studies extend earlier research by exploring relations between

activation in the left dlPFC, two different conceptualizations of cognitive control, and intrusive memories/rumination in healthy individuals. The idea of combining tDCS with the trauma film paradigm is novel and has not been studied before. Furthermore, to date no study has tested the DMC framework in the context of intrusive memories.

Study III follows the training approach and examines whether a cognitive control training including neutral material influences intrusive re-experiencing, rumination, and comorbid depressive symptoms in 33 PTSD patients. In this double-blind, randomized, controlled pilot study patients are assigned to either a 2-week cognitive control training designed by Siegle and colleagues (2007) or a placebo training and tested at baseline, post training, and a 1-month follow-up. The training consists of Wells's Attention Training and the adaptive Paced Auditory Serial Addition Task, tasks that already demonstrated to influence cognitive control, intrusive memories, and rumination in healthy and depressed individuals. *Study III* is the first investigation that transfers the established training by Siegle and colleagues (2007) to a PTSD sample. Despite answering the question whether modulating cognitive control affects posttraumatic intrusive re-experiencing and rumination, this study also aims to explore the suitability of the training as a short and easy-to-administer cognitive intervention in patients waiting for psychological treatment.

2. Study I

Does Transcranial Direct Current Stimulation Affect Post-stressor Intrusive Memories and Rumination? An Experimental Analogue Study

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Abstract

Deficits in cognitive control have been linked to intrusive memories after traumatic life events as well as rumination. However, causal relations are still unclear. Causality can be investigated by directly influencing a brain region associated with cognitive control via transcranial direct current stimulation (tDCS). In this study, we investigated the effects of tDCS over the left dorsolateral prefrontal cortex (dlPFC) on one aspect of cognitive control—resistance to proactive interference (PI)—as well as on intrusive memories and rumination. Using a between-subject design, we expected active tDCS to affect intrusive memories and rumination by influencing resistance to PI. N = 118 healthy individuals completed the modified California Verbal Learning Test twice, once without stimulation and once during 20-minutes tDCS (anodal, cathodal, or sham). Following tDCS, participants watched a trauma film; afterwards, intrusive memories and rumination were assessed. TDCS neither affected resistance to PI nor film-related intrusive memories or rumination. Furthermore, individuals with low resistance to PI did not experience more intrusive memories or rumination. These results question the role of the left dlPFC as well as the well-established link between resistance to PI and intrusive memories. Future studies are needed to replicate these findings and to address possible methodological shortcomings of this study.

Introduction

Natural disasters, armed conflicts, accidents, or interpersonal violence: Many individuals experience a life-threatening event at least once in their life. However, only a minority develops persistent symptoms of posttraumatic stress disorder (PTSD), including trauma-related intrusive memories and rumination (Kilpatrick et al., 2013). Intrusive memories are unwanted recurring memories of the traumatic event that often take the form of sensory fragments of the experience (APA, 2013). In contrast, rumination is a maladaptive processing style that is experienced as uncontrollable repetitive verbal thinking about the trauma, its causes, and consequences (Ehlers & Clark, 2000; Ehring et al., 2008). Both phenomena include difficulties in controlling unwanted memories and/or thoughts that grab an individual's attention and affect current behavior. There is growing evidence that these difficulties are linked to individual differences in cognitive control as a basic cognitive mechanism (Aupperle et al., 2012; Joormann, Yoon, & Siemer, 2010; Polak et al., 2012; Whitmer & Gotlib, 2013).

Cognitive control comprises meta-level functions that are associated with working memory and keep thoughts or actions focused on goals despite goal-irrelevant interferences (e.g., Miyake et al., 2000). Since traumatic representations in long-term memory are easily activated by internal or external cues, cognitive control is needed to prevent them from intruding into consciousness and from interfering with goal-directed behavior (Wessel et al., 2008). Thus, individuals with limited cognitive control might be unable to ignore those cues and therefore experience persistent intrusive memories. Furthermore, persistent rumination might be maintained by a limited capacity to update cued negative representations in working memory and to inhibit currently irrelevant information (e.g., Brinker, Campisi, Gibbs, & Izzard, 2013; De Lissnyder et al., 2012; Vanderhasselt et al., 2013; Zetsche et al., 2012). Indeed, associations of intrusive memories and rumination with deficits in cognitive control have been empirically demonstrated across clinical and healthy samples (e.g., Beckwé, Deroost, Koster, De Lissnyder, & De Raedt, 2014; Brewin & Beaton, 2002; Brewin & Smart, 2005; Joormann & Gotlib, 2008; Klein & Boals, 2001; Polak et al., 2012). However, causality remains unclear: pre-trauma deficits in cognitive control might be a risk factor for intrusive memories and rumination, but intrusive memories and rumination might also induce stress levels that in turn reduce performance in cognitive control tasks.

Establishing causality in the context of post-trauma symptomatology is difficult. It requires the manipulation of relevant processes either pre- or shortly post-trauma, a procedure that posits serious practical and ethical challenges. Therefore, the trauma film paradigm if often used as a laboratory analogue, whereby healthy individuals are confronted with a film depicting traumatic situations. In doing so, stressor-related intrusive memories and rumination can be assessed, and their modulation by experimental manipulations of key processes can be tested (Holmes & Bourne, 2008). Earlier studies have used the trauma film paradigm to investigate the relationship between cognitive control and the development of intrusive memories (e.g., Verwoerd et al., 2011; Wessel et al., 2008). These studies have focused on resistance to proactive interference (PI), a specific aspect of cognitive control that describes the inhibition of information that is no-longer relevant in working memory (Friedman & Miyake, 2004). For example, Verwoerd and colleagues (2011) showed that a poor ability to resist PI, as measured by a modified California Verbal Learning Test (CVLT), is linked to more intrusive memories one week after watching a trauma film in a healthy sample. Thus, first evidence suggests that low ability to overcome PI might be a vulnerability factor for intrusive memories after a stressful event. Nevertheless, due to the design of previous studies, it cannot be ruled out that both, PI and intrusive memories, are affected by a third variable and thus do not causally influence each other.

Therefore, the present study aimed at modulating activation in a brain region that is associated with cognitive control and, in particular, resistance to PI to investigate causal effects on intrusive memories and rumination. A well-established method to induce such a modulation is transcranial direct current stimulation (tDCS). This safe, non-invasive, and effective method manipulates cortical excitability in a specific brain area by hyper- or depolarization of resting membrane potentials (Nitsche & Paulus, 2001; Priori, 2003; Wassermann & Grafman, 2005). Whereas cathodal stimulation decreases cortical excitability, anodal stimulation increases cortical excitability. When applied for several minutes, these tDCS-induced changes persist for at least one hour (Nitsche et al., 2008). We proposed the left dorsolateral prefrontal cortex (dlPFC) to be a promising target brain area for such a modulation, for a number of reasons.

Firstly, cognitive control in general but also interference resolution in particular are linked to frontal cortices, with the dlPFC being an important component of this network (e.g., Blasi et al., 2006; Bunge, Ochsner, Desmond, Glover, & Gabrieli, 2001; Curtis & D'Esposito, 2003; Dulas & Duarte, 2016; Nee et al., 2007; Postle, Berger, Goldstein,

Curtis & D'Esposito, 2001; Postle, Brush, & Nick, 2004; Wolf, Walter, & Vasic, 2010). For example, Wolf and colleagues (2010) used a PI task with varying contextual demands and investigated corresponding activity in different brain regions. They proposed that increased cognitive control exerted by the left dlPFC is relevant for decreasing susceptibility to PI. Secondly, the dlPFC has been associated with controlling unwanted memories and thoughts as well as with symptoms of PTSD (e.g., Anderson et al., 2004; Arnsten, Raskind, Taylor, & Connor, 2015; Clark et al., 2003). For instance, in a suppressing versus recalling task of memory contents, healthy individuals showed greatest dlPFC activation when intrusive memories needed to be controlled and individuals with negative coupling between dlPFC and hippocampus during early suppression attempts experienced fewer intrusive memories later on (Benoit, Hulbert, Huddleston, & Anderson, 2014). Thirdly, beneficial effects of anodal tDCS and detrimental effects of cathodal tDCS over the left dlPFC on cognitive control have been documented in previous research (Andrews et al., 2011; Fregni et al., 2005; Wolkenstein & Plewnia, 2013; Wolkenstein et al., 2014; Zaehle, Sandmann, Thorne, Jancke, & Herrmann, 2011). Moreover, it has been shown that the effect of anodal tDCS over the left dlPFC on state rumination, as measured several minutes after stimulation termination, is mediated by an enhancement of cognitive control in healthy individuals (Vanderhasselt et al., 2013). In sum, in the current study we focus on the left dlPFC as there is consistent evidence that it plays a major role in cognitive control, including resistance to PI. However, it should of course be noted that resistance to PI and the control of intrusive memories and rumination can be expected to be supported by a complex inhibitory network, involving different brain regions that might also be promising targets for tDCS in future research (e.g., Anderson, Bunce, & Barbas, 2015; Badre & Wagner, 2005; Blasi et al., 2006; Caplan, McIntosh, & De Rosa, 2007; D'Esposito, Postle, Jonides, & Smith, 1999; Feredoes, Tononi, & Postle, 2006; Johnson, Saykin, Flashman, McAllister, & Sparling, 2001; Kühn, Vanderhasselt, De Raedt, & Gallinat, 2012; Nee, Jonides, & Berman, 2007).

Overall, the major goal of this randomized, sham-controlled, double-blind analogue study was to identify causal relations between cognitive control and intrusive memories/rumination in a healthy sample. To achieve this goal, we manipulated the activity of the left dlPFC via anodal and cathodal tDCS and explored the impact of this manipulation on resistance to PI as an indicator of cognitive control. We hypothesized cathodal tDCS to decrease and anodal tDCS to increase resistance to PI, compared to sham stimulation (H1). Furthermore, we examined offline effects of tDCS on intrusive

memories and rumination after a trauma film to further clarify the role of pre-stressor differences in cognitive control for re-experiencing. As mentioned above, tDCS effects last for at least one hour (e.g., Nitsche et al., 2008) and offline designs have been used successfully in former studies (e.g., Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016a; Hill, Fitzgerald, & Hoy, 2016; Vanderhasselt et al., 2013; Wolkenstein et al., 2014). We predicted cathodal tDCS to increase and anodal tDCS to decrease intrusive memories (H2) and rumination (H3) after a trauma film, compared to sham stimulation. Finally, we assumed that higher resistance to PI is associated with less intrusive memories (H4) and less rumination (H5) after the trauma film.

Methods

Design, randomization, and blinding

This randomized, double-blind, sham-controlled analogue study followed a between-subject design with the between-factor stimulation condition (anodal vs. cathodal vs. sham). For resistance to PI, time point was an additional within-subject factor (pre vs. post tDCS). Allocation to stimulation condition was randomized via automated randomization software (randomizer.org). For blinding, all participants were informed that they would be randomly assigned to one of three stimulation conditions. These conditions would include 20 minutes of stimulation but vary in electrode placement and stimulation intensity. The application of predefined codes to start the stimulator further allowed for a computerized double-blind assignment to the sham or verum condition.

Sample

N = 120 healthy women between 18 and 40 years were recruited via advertisements at LMU Munich. Two participants were excluded due to violations to the study protocol. The final sample consisted of 118 women with a mean age of 23.32 (SD = 4.46). Exclusion criteria were diseases of the central nervous system; cardiovascular, respiratory and neuroendocrine diseases; seizures; first-degree relatives suffering from epilepsy; a history of traumatic brain injury; metallic particles around the head; a cardiac and cerebral pacemaker, cochlea implants and hearing aid devices; strong allergic reactions to sensing electrodes; current pregnancy; left-handedness as assessed by a version of the Edinburgh Handedness Inventory (EHI; Oldfield, 1971); psychotropic medication; a substance use disorder with less than 2 years of abstinence; a history of psychiatric disorders as assessed

by the M.I.N.I. International Neuropsychiatric Interview for DSM-IV (Ackenheil, Stotz-Ingenlath, Dietz-Bauer, & Vossen, 1999) and the PTSD Checklist for DSM-5 (PCL-5; Krüger-Gottschalk et al., 2017); and a history of psychological treatment. Inclusion criteria were an educational qualification of university entrance diploma or higher and sufficient knowledge of the German language. We solely included females to preclude effects of gender. The administered stressful film fragment depicted the rape of a woman and thus might be differently processed by male compared to female participants. All participants signed informed consent and were reimbursed with 30 Euros or course credit. The study was approved by the local ethics committee and was conducted in accordance with the provisions of the World Medical Association Declaration of Helsinki.

TDCS

A direct current of 1 mA was delivered via a battery-driven stimulator (NeuroConn GmbH, Ilmenau, Germany) and a pair of 0.9 % NaCL-soaked sponge electrodes (35cm2 surface). One electrode was placed on the scalp over F3 according to the international 10-20 system of electrode placement. The reference electrode was placed on the right deltoid muscle. The current was applied for 20 minutes plus a 5 second fade-in and fade-out phase. The sham stimulation also lasted 20 minutes with the current being applied only for the first 30 seconds and then ramped down. Thus, a temporary tingling experience comparable to that induced by verum stimulation was elicited. Active tDCS was only applied during the assessment of resistance to PI and not during the film or the assessment of intrusive memories and rumination.

Stressful film fragment

Participants watched a 14-minutes fragment from "Irréversible" by Gaspar Noé depicting an extreme sexual and physical abuse of a woman. This fragment has been frequently used in trauma film research (Arnaudova & Hagenaars, 2017, for an overview). All participants were explicitly informed in the study advertisement and in the informed consent that they would be exposed to a film with violent content. The film was presented on an 18-inch screen in a darkened room.

Outcome measures

Resistance to PI. We used a modified version of the CVLT (Delis, Kramer, Kaplan, & Ober, 1987) as used by Verwoerd and colleagues (2011) to assess resistance to PI. This task was applied with identical parameters on both time points. The test contained two word lists. List 1 consisted of ten names of vegetables, ten names of animals and ten names of flowers. List 2 consisted of ten new names of vegetables, ten new names of animals and ten names of musical instruments. Hence, the two lists shared the categories vegetables and animals. Both lists were matched on word frequency. The order of the two lists was counterbalanced between participants. First, participants were presented the words of List 1 in a randomized order on the computer screen for 1000 ms each, with a 1000 ms inter-stimulus interval. They were instructed to learn the words to the best of their ability. This phase was followed by a 4 minute free-recall phase in which participants had to speak out loud all words they could remember. The examiner documented the responses. Second, learning and free recall of List 1 were repeated, with participants being instructed to learn and recall more words than during the first trial. Third, participants again completed the procedure of the first trial but with List 2. Following Verwoerd and colleagues (2011), we computed a PI index as a measure of resistance to PI. We multiplied the total number of words recalled on Trial 1 with the total number of shared category words that were recalled on Trials 1 and 2. Next we divided this outcome by the total number of words recalled on Trials 1 and 2 and finally subtracted the number of shared words recalled from List 2 (PI = ((total recall Trial 1 × (recall shared words Trial 1 + Trial 2))/ (total recall Trial 1 + total recall Trial 2)) - recall shared words List 2). Higher values on this index indicate poorer resistance to PI.

Post-film intrusive memories. We assessed the occurrence of intrusive memories after the film by a 6-item questionnaire based on Weidmann and Papsdorf (2010). The questionnaire began with a short definition of intrusive memories. Subsequently, participants were asked to indicate how often they had experienced intrusive memories during the resting period. They also indicated the percentage of time (from 0 to 100) they had experienced intrusive memories and the predominant quality of them (“thought”, “image”, “short film scene”, “feeling”, “sound”, “something else”, “I do not know”, “I did not have intrusive memories”). Additionally, level of distress caused by the intrusive memories, level of vividness of the intrusive memories and level of control were rated on a 6-point Likert-scale (1 = “not at all” to 6 = “very”).

Post-film rumination. Rumination after the film was assessed by a modified version of the Perseverative Thinking Questionnaire (PTQ; Ehring et al., 2011). Six items from the original version of the PTQ were excluded because they referred to thoughts unlikely to occur after watching films. The remaining nine items captured the core characteristics of rumination (repetitiveness, intrusiveness, difficulties to disengage), were adapted for measuring film-related rumination (e.g., "I could not stop thinking about the film")[1] and rated on a 5-point scale (1 = “never” to 5 = “almost always”). Internal consistency of the questionnaire was excellent (Cronbach's α = .946).

Control measures

Trait rumination. The habitual use of rumination was measured by the German version of the 10-item Response Styles Questionnaire (RSQ-10D; Huffziger & Kühner, 2012). Participants indicated their thoughts and actions in response to sad or depressed feelings (e.g., "I think ‘Why do I always react this way?’ “) on a 4-point scale, ranging from 1 = “almost never” to 4 = “almost always”.

Trait film-related intrusive memories and rumination. The trait tendency to experience intrusive memories and rumination in response to stressful films was measured by modified versions of the questionnaires for post-film intrusive memories and post-film rumination. This time the participants had to rate their typical responses to films that trigger negative emotions in general. For the frequency of intrusive memories, answers were given on a 5-point scale (1 = “never” to 5 = “always”).

Neuropsychological control measures. We assessed visual-motor conceptual screening and cognitive flexibility by use of the Trail Making Test (TMT A/B; Reitan, 1992) and short-term and working memory capacity by use of a digit span test forward and backward (a version similar to the Wechsler Adult Intelligence Scale; Petermann, 2012). These measures were only used to rule out group differences in cognitive functioning prior to tDCS. They were not used as covariates.

Mood and arousal. To assess possible effects of tDCS and the film scene on participants’ mood and arousal, we administered two Self-Assessment-Manikins (SAM; Bradley & Lang, 1994) at several time points (see procedure). In the SAMs, participants had to indicate how they felt (1 = “very negative” to 9 = “very positive”) and how aroused they were (1 = “very calm” to 9 = “very high arousal”).

[1] All items used in this study can be obtained upon request.

Film-related emotion regulation. To check whether groups differed in their emotional processing and responding to the film, we assessed participants' spontaneous use of reappraisal and suppression to regulate emotions during film presentation and resting period. Specifically, reappraisal and suppression during the presentation of stressful stimuli have been found to influence emotional distress and posttraumatic symptoms afterwards (e.g., Cavanagh, Fitzgerald, & Urry, 2014; Dunn, Billotti, Murphy, & Dalgleish, 2009). For reappraisal, we used four adapted and slightly rephrased items (e.g., "I changed my thoughts about the film in a way that made me experience less negative emotions") from Ehring, Tuschen-Caffier, Schnülle, Fischer, and Gross (2010) as well as from the Emotion Regulation Questionnaire (ERQ; Gross & John, 2003). For suppression, we used four adapted items (e.g., "Whenever possible, I avoided realizing my feelings") from the Heidelberg Form for Emotion Regulation Strategies (HFERST; Izadpanah, Barnow, Neubauer, & Holl, 2017). Participants rated the extent to which the statements applied to them in the period during and after film presentation on a 5-point scale (1 = "does not apply" to 5 = "does apply").

Film exposure and distress. Participants estimated the amount of time they had looked away from the screen during the film on a 5-point scale (1 = "never" to 5 = "almost always"). For measuring subjective distress during the film, participants also indicated their mood (1= "very negative" to 9 = "very positive") and arousal (1 = "very calm" to 9 = "very high arousal") during film presentation retrospectively on two SAMs. To assess how attentively participants had followed the film, they completed 22 self-generated single choice, multiple choice and open-ended questions about the film (e.g., "What was the color of the victim's handbag?"). We calculated a sum score for correct answers. Moreover, we assessed whether participants had seen the film before and whether they watched similar films frequently.

Procedure

Each participant performed two sessions at the lab with an average inter-session-interval of 7.22 days (*SD* = 0.85). First, sociodemographic and health data were assessed and M.I.N.I. and PCL-5 were administered to check exclusion criteria. Furthermore, participants completed TMT A/B and digit span test, a baseline measurement of the modified CVLT via E-prime, and a set of questionnaires (EHI, RSQ-10D, trait film-related intrusive memories/rumination) via Unipark (EFS Survey, Questback GmbH). At session 2, partici-

pants were screened for changes in exclusion criteria and tDCS was applied for 20 minutes. The modified CVLT started 5 minutes after the onset of stimulation to reach maximum effects and took 15 minutes. After that, the room was darkened and the experimenter left the room while the participants watched the film scene. After the film scene, participants were asked to lean back for a moment and do nothing until the experiment would continue after 10 minutes. Thus, there were no environmental demands that could trigger intrusive memories or rumination (see also Vanderhasselt et al., 2013). Finally, participants completed questionnaires for post-film intrusive memories, post-film rumination, emotion regulation and film exposure and distress via Unipark (EFS Survey, Questback GmbH). SAMs were administered at baseline, after 5 minutes of tDCS and after resting period. Heart rate and respiration rate were recorded via a respiration belt and three electrodes on the upper body and additional emotional measures were assessed during session 2. However, the obtained data was not subject to this paper.

Data analyses

Data were analyzed by use of SPSS® Version 24.0. First, we examined whether tDCS groups significantly differed in any of the baseline control measures assessed on t1 to check comparability of groups. Furthermore, we examined group differences for control variables assessed after film presentation, i.e. film-related emotion regulation, film-elicited distress, time looked away and film-related attentiveness. All analyses were performed by use of Analyses of Variance (ANOVAs) and Kruskal–Wallis tests. Additionally, changes in SAM mood and arousal ratings over the course of the experiment were analyzed by use of two separate mixed ANOVAs with the between-subject factor stimulation condition (sham vs. anodal vs. cathodal) and the within-subject factor time point (baseline vs. after tDCS start vs. after resting period). For main analyses, a mixed ANOVA with the between-subject factor stimulation condition (sham vs. anodal vs. cathodal) and the within-subject factor time point (session 1 vs. session 2) was performed on the index of resistance to PI (H1). Effects of tDCS on intrusive memories (H2) and rumination (H3) were analyzed by use of a Multivariate Analysis of Variance (MANOVA) with the number of post-film intrusive memories, the percent of time they have been experienced and post-film rumination as dependent variables. For all subjects who reported intrusive memories, an exploratory MANOVA was conducted to investigate effects of tDCS on level of distress, vividness and control. Next, correlational analyses were performed to test associations

between resistance to PI and the intrusive memories measures (H4) as well as rumination (H5). Lastly, in exploratory post-hoc analyses, we examined whether resistance to PI, rumination and number of intrusive memories significantly correlated with any of the control measures and we analyzed the result patterns for CVLT performance in shared and non-shared trials by use of mixed ANOVAs. Moreover, we calculated Bayes Factors to quantitate the relative strength of evidence for our main findings. For all correlation analyses, the *p*-values were Bonferroni-Holm-corrected and Greenhouse-Geisser corrected tests are reported when the assumption of sphericity was violated in mixed ANOVAs.

We determined sample size by use of G*power (version 3.1, University of Duesseldorf, Germany), assuming a statistical power of .80 and an alpha level of .05. For resistance to PI, we calculated a total sample of 42 participants for the interaction between tDCS condition and time point ($f = 0.25$). For the global effect of tDCS on number of post-film intrusive memories, the percent of time they have been experienced and post-film rumination, we calculated a total sample of 114 participants ($f^2(V) = 0.0625$). Lastly, for correlational analyses, a total sample of 84 ($r = 0.3$) participants was determined.

Results

The data reported in this study is openly accessible in the associated OSF repository (https://osf.io/bcq6y/).

Descriptive statistics and group differences in control measures

Descriptive statistics and group comparisons for control variables are presented in Table 1.1. 6.8 % of participants already knew the film fragment and 32.2 % of participants reported having watched similar films before. The amount of time participants had looked away during film presentation was low. Regarding film-related distress, participants reported to have experienced negative mood and to have felt aroused during film presentation. The stimulation groups did not differ in any of the control measures except for their arousal during film presentation, $H(2) = 6.88$, $p < .05$, with a mean rank of 55.92 for the sham group, 70.47 for the anodal group and 51.71 for the cathodal group. However, we also compared valence and arousal ratings over time (baseline vs. after tDCS start vs. after resting period). For valence there was a significant main effect of time, $F(1.88, 216.26) = 227.67$, $p < .001$, $\eta^2 = .66$, with mood worsening from baseline ($M = 6.84$, $SD = 1.25$) to tDCS start ($M = 6.14$, $SD = 1.60$) and from tDCS start to resting period

(M = 3.67, SD = 1.62). For arousal there was also a significant main effect of time, F(1.75, 200.99) = 107.24, p < .001, η^2 = .48, with all participants feeling less aroused from baseline (M = 3.78, SD = 1.98) to tDCS start (M = 3.11, SD = 1.87) and more aroused from tDCS start to resting period (M = 5.97, SD = 1.84). However, there was neither a main effect of group nor a group x time interaction (all ps > .10).

Resistance to PI

Descriptive statistics for the dependent variables are presented in Table 1.2. In contrast to H1, the tDCS conditions did not differentially affect resistance to PI as indicated by a non-significant time x group interaction, F(2, 115) = 0.41, p = .66, η^2 = .01. Unexpectedly, all individuals showed more PI at t2 (M = 2.74, SD = 2.65) compared to t1 (M = 0.05, SD = 2.58), F(1, 115) = 94.92, p < .001, η^2 = .45.

Post-film intrusive memories and post-film rumination

Overall, 22.9 % of participants reported intrusive memories during resting period in form of thoughts, 12.7 % in form of images, 30.5 % in form of a short film scene, 8.5 % in form of feelings and 1.7 % in form of sounds. 19.5 % of participants did not experience any intrusive memories. 1.7 % experienced a mix of different modalities and the remaining 2.5 % included one participant who did not specify the modality of the intrusive memories, one participant who indicated “some kind of paranoia” and one participant who reflected about the quality of the movie. Removing these individuals from analyses did not change the main results. We applied square-root transformations for both intrusive memories measures to improve normality of the data distribution and reduce the impact of one extreme value. Using Pillai’s trace, the three tDCS groups neither differed in post-film rumination nor in the two intrusive memories measures, V = 0.02, F(6, 228) = 0.45, p = .84, η^2 = .01. These results are in contrast to H2 and H3. Exploratory analyses of effects of tDCS on intrusion-related level of distress, level of vividness and level of control for those individuals who had experienced intrusive memories did also not reveal significant group differences, all ps > .10.

Table 1.1

Descriptive Statistics and Group Differences of the Control Variables

		Sham (n = 40)	Anodal (n = 40)	Cathodal (n = 38)	
	Min - Max	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*p*
Age	18.00 - 40.00	22.58 (4.50)	24.30 (5.13)	23.08 (3.51)	*ns*
Inter-session Interval	6.00 - 10.00	7.10 (0.90)	7.40 (0.93)	7.16 (0.68)	*ns*
TMT-A t1	10.50 - 50.00	26.73 (9.54)	22.81 (6.31)	23.31 (7.60)	*ns*
TMT-B t1	21.70 - 120.00	54.04 (19.00)	49.45 (15.63)	52.78 (15.17)	*ns*
Digit Span forward t1	5.00 - 12.00	9.00 (1.93)	9.53 (1.28)	9.11 (1.45)	*ns*
Digit Span backward t1	4.00 - 12.00	7.85 (2.07)	7.83 (2.18)	7.87 (2.11)	*ns*
Trait Rumination t1	10.00 - 33.00	19.95 (4.55)	20.25 (4.60)	21.47 (5.10)	*ns*
Trait Film-Related Rumination t1	9.00 - 36.00	16.70 (5.44)	17.10 (6.08)	17.92 (5.95)	*ns*
Trait Film-Related IM t1	1.00 - 5.00	1.95 (0.71)	2.05 (0.90)	2.21 (1.02)	*ns*
Trait Distress of IM t1	1.00 - 5.00	2.03 (0.85)	2.24 (1.00)	2.50 (1.07)	*ns*
Trait Vividness of IM t1	1.00 - 6.00	2.67 (1.06)	2.59 (1.05)	2.82 (1.31)	*ns*
Trait Control of IM t1	1.00 - 6.00	4.60 (1.35)	4.14 (1.27)	3.93 (1.61)	*ns*
Film-Related Suppression t2	4.00 - 20.00	9.75 (3.83)	10.35 (3.82)	9.87 (3.74)	*ns*
Film-Related Reappraisal t2	4.00 - 20.00	11.58 (3.86)	11.50 (4.62)	11.00 (4.10)	*ns*
Time looked away t2	1.00 - 5.00	1.48 (0.88)	1.68 (0.86)	1.74 (0.98)	*ns*
SAM Valence during Film t2	1.00 - 5.00	2.05 (0.88)	2.03 (1.07)	2.29 (1.25)	*ns*
SAM Arousal during Film t2	1.00 - 9.00	7.03 (1.48)	7.60 (1.39)	6.66 (1.92)	*.03*
Film-Related Attentiveness t2	9.00 - 20.00	13.58 (2.71)	14.69 (2.82)	13.53 (2.77)	*ns*

Notes. TMT = Trail Making Test, IM = Intrusive Memories, SAM = Self-Assessment Manikin; Analyses for Distress, Control and Vividness of Intrusive Memories were performed only for individuals who reported to experience Intrusive Memories at least seldom (sham n = 30, anodal n = 29, cathodal n = 28); Anodal n = 39 for Film-Related Attentiveness.
ns = nonsignificant.

Table 1.2

Descriptive Statistics of the Dependent Variables

		Sham (n = 40)	Anodal (n = 40)	Cathodal (n = 38)
	Min - Max	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
CVLT PI t1	-7.53 - 7.36	-0.18 (2.53)	-0.09 (2.56)	0.45 (2.69)
CVLT PI t2	-2.59 - 8.90	2.86 (2.41)	2.42 (2.73)	2.97 (2.83)
Post-Film Rumination	9.00 - 45.00	25.05 (8.84)	25.88 (8.94)	23.26 (9.67)
Post-Film Number of IM	0.00 - 20.00	4.78 (5.75)	3.93 (3.93)	3.45 (3.17)
Post-Film % of time IM	0.00 - 100.00	31.35 (26.12)	32.33 (30.05)	27.45 (27.60)
Post-Film Distress of IM	1.00 - 6.00	3.15 (1.33)	3.77 (1.28)	3.38 (1.35)
Post-Film Control of IM	1.00 - 6.00	4.06 (1.39)	3.29 (1.58)	3.66 (1.57)
Post-Film Vividness of IM	1.00 - 6.00	3.12 (1.41)	3.81 (1.28)	3.45 (1.24)

Notes. CVLT = California Verbal Learning Test, PI = Proactive Interference, IM = Intrusive Memories; Analyses for Distress, Control and Vividness of Intrusive Memories were performed only for individuals who reported at least one Intrusive Memory (sham n = 34, anodal n = 31, cathodal n = 29).

Link between resistance to PI, post-film intrusive memories, and post-film rumination

Since tDCS did not differentially affect resistance to PI on t2, post-film rumination or intrusive memories, we explored links between these variables across stimulation groups. Correlations are depicted in Table 1.3. The more individuals had ruminated during the resting period, the more intrusive memories they had experienced. Furthermore, the more intrusive memories occurred, the more distressing, uncontrollable and vivid they were rated. Surprisingly, there were no significant positive correlations between experience of PI on t2 and number of intrusive memories (H4) or rumination (H5). Since there was a significant change in resistance to PI from t1 to t2, we also calculated correlation coefficients between resistance to PI on t1, rumination and intrusive memories to assess possible associations before any manipulation. However, these correlation patterns were generally in line with the ones found for resistance to PI on t2 (see Table 1.3) except that a negative correlation between the experience of PI and vividness of post-film intrusive memories still reached significance after Bonferroni-Holm correction.

Post-hoc analyses

Exploratory correlation analyses. Recent research reported that decrements in cognitive performance in the face of stress are relevant for psychopathology (e.g., Quinn & Joorman, 2015). Thus, we exploratory analyzed associations between change in PI, as calculated by subtracting PI on t2 from PI on t1, and intrusive memories and rumination. However, these analyses did not show substantial correlations, all *p*s > .10. Additionally, we explored correlations between PI on t2, rumination, number of intrusive memories and control measures. After Bonferroni-Holm correction, post-film rumination was still significantly correlated with trait film-related rumination, $r = .47$, $p < .001$, mood during the film, $r = -.54$, $p < .001$, and arousal during the film, $r = .49$, $p < .001$. Similarly, post-film intrusive memories showed significant correlations with a trait tendency for film-related intrusive memories, $r = .33$, $p < .05$, mood during the film, $r = -.35$, $p < .01$, and arousal during the film, $r = .38$, $p < .01$.[2]

Evaluation of the modified CVLT. Previous research also administering the CVLT reported a between-lists performance decrease for shared trials and a between-lists performance increase for non-shared trials (Verwoerd et al., 2011). For the CVLT on t1, there was no between-lists performance decrease for shared trials ($M = 10.09$, $SD = 2.71$ for List 1; $M = 10.09$, $SD = 2.69$ for List 2), $F(1, 115) = 0.00$, $p = .98$, $\eta^2 = .00$, but a significant increase in recall performance for non-shared trials from List 1 ($M = 5.05$, $SD = 1.63$) to List 2 ($M = 5.79$, $SD = 1.60$), $F(1, 115) = 18.78$, $p < .001$, $\eta^2 = .14$. In contrast, for the CVLT on t2, all individuals showed a decreased recall performance for shared trials on List 2 ($M = 10.72$, $SD = 3.18$) compared to List 1 ($M = 13.42$, $SD = 3.07$), $F(1, 115) = 108.76$, $p < .001$, $\eta^2 = .49$. However, increase in recall performance for non-shared items on List 2 ($M = 6.72$, $SD = 1.72$) compared to List 1 ($M = 6.61$, $SD = 1.65$) did not reach significance, $F(1, 115) = 0.43$, $p = .51$, $\eta^2 = .00$. The three tDCS groups did not significantly differ in these results, all *p*s > .10.

Bayesian analyses

To quantitate the relative strength of evidence for the non-significant findings, Bayesian hypothesis testing was additionally performed. A Bayes factor (BF_{01}) is a statistical index that quantifies how well a hypothesis predicts observed data over an alternative hypothesis

[2] Control variables that showed significant correlations with dependent variables were inserted as covariates in the main analyses. However, they did not significantly change the main findings.

(Dienes, 2014). We calculated BF_{01} using JASP statistical software version 0.9.0.1 for our main hypotheses (JASP Team, 2018). Whereas a $BF_{01} < 1$ implies that a result is more likely to occur under an alternative hypothesis (H_1) than under a null hypothesis (H_0), a $BF_{01} > 1$ indicates that a result is more likely to occur under a H_0 than under a H_1 (Wagenmakers, Wetzels, Borsboom, & van der Maas, 2011). For the first hypothesis, we expected a significant tDCS x time interaction on PI. A Bayesian mixed ANOVA was performed with default prior scales. The results showed a BF_{01} of 8.387, with the interaction model (assuming the main effects of tDCS and time and their interaction) as the H_1 versus the main-effect model (assuming the main effects only) as the H_0. Thus, there was substantial evidence in favor of the H_0 (Wagenmakers et al., 2011), indicating no interaction between tDCS condition and time. For testing the second and third hypotheses on the effects of tDCS on post-film intrusive memories and post-film rumination, we ran three separate Bayesian ANOVAs with the number of post-film intrusive memories, the percent of time they have been experienced (both measures square-root transformed), and post-film rumination as dependent variables. The H_1 stated that the three tDCS groups differed in these variables whereas the H_0 stated no group differences. We found a BF_{01} of 8.551 for the number of intrusive memories, a result indicating that the observed data is 8.551 times more likely to occur under the H_0 than under the H_1 and thus providing substantial evidence for no effect of tDCS condition (Wagenmakers et al., 2011). Furthermore, there was $BF_{01} = 9.730$ for percent of time of intrusive memories and $BF_{01} = 6.321$ for post-film rumination. These analyses also provided substantial evidence in favor of the H_0 (Wagenmakers et al., 2011). Lastly, we calculated Bayesian Pearson correlations for the associations between PI and both post-film intrusive memories measures as well as post-film rumination. In line with our hypotheses, we tested whether the data were more likely to occur under the H_0 (no association between PI and intrusive memories or rumination) or under the H_1 (a positive association between PI and intrusive memories or rumination). Results are depicted in Table 1.4. Similar to previous analyses, sample correlations were weak and negative. Bayesian analyses implied strong evidence in favor of the H_0, indicating no positive associations between PI and intrusive memories or rumination (Wagenmakers et al., 2011).

Table 1.3

Spearman-Rho-Correlation Coefficients for the Dependent Variables

	2.	3.	4.	5.	6.	7.	8.
1. CVLT PI t1	.36**	-.19	-.11	-.15	-.27	.08	-.31*
2. CVLT PI t2	-	-.23	-.22	-.20	-.24	-.06	-.22
3. Post-Film Rumination		-	.59***	.71***	.65***	-.60***	.40**
4. Post-Film Number of IM			-	.81***	.51***	-.45***	.33*
5. Post-Film % of time IM				-	.73***	-.57***	.42***
6. Post-Film Distress of IM					-	-.58***	.60***
7. Post-Film Control of IM						-	-.45***
8. Post-Film Vividness of IM							-

Notes. CVLT = California Verbal Learning Test, PI = Proactive Interference, IM = Intrusive Memories; Analyses for Distress, Control and Vividness of Intrusive Memories were performed only for individuals who reported at least one Intrusive Memory, $n = 94$.
* $p < .05$, ** $p < .01$, *** $p < .001$; two-tailed; Bonferroni-Holm-corrected p-values are reported.

Table 1.4

Bayesian Pearson Correlation Coefficients

		CVLT PI t2	Post-Film Rumination	Post-Film Number of IM	Post-Film % of time IM
CVLT PI t1	*r*	.35	-.21	-.12	-.17
	BF_{0+}	0.003	27.84	18.61	23.72
CVLT PI t2	*r*	-	-.21	-.19	-.19
	BF_{0+}		28.47	26.20	25.63

Notes. CVLT = California Verbal Learning Test, PI = Proactive Interference, IM = Intrusive Memories. For all tests, the H_1 specifies that the correlation is positive.

Discussion

The present study tested causal relations between cognitive control and intrusive memories as well as rumination in a healthy sample. A brain area associated with cognitive control, the left dlPFC, was stimulated via tDCS. We hypothesized cathodal tDCS to decrease and anodal tDCS to increase resistance to PI, an indicator of cognitive control, as well as cathodal tDCS to increase and anodal tDCS to decrease intrusive memories and rumination after a trauma film. We found neither an effect of tDCS on resistance to PI nor on intrusive memories or rumination. Furthermore, we expected individuals with higher resistance to PI to show less intrusive memories and less rumination after the trauma film. However, there was no significant positive association between experience of PI in the CVLT and intrusive memories or rumination. In contrast, the trait tendency for film-related rumination and intrusive memories as well as valence and arousal during the film were linked to post-film intrusive memories and rumination.

The absence of a significant positive association between susceptibility to PI and intrusive memories is surprising as a link between these variables has been found in earlier research (Verwoerd et al., 2009; Verwoerd et al., 2011; Wessel et al., 2008). However, the present study slightly differed from previous research in the assessment of intrusive memories and resistance to PI. Whereas previous studies recorded the occurrence of post-film intrusive memories after a period of 24 hours (Wessel et al., 2008) or during a 1-week diary assessment (Verwoerd et al., 2011), we measured intrusive memories after a short post-film resting period. This procedure had been used before in studies testing the short-term tDCS effects on ru-

mination (e.g., Vanderhasselt et al., 2013), and therefore seemed appropriate to be used in our study, too. Interestingly, participants in the current study reported an even greater number of intrusive memories in this short period compared to the one-week assessment by Verwoerd and colleagues (2011). Thus, the film fragment we used appears to be suitable for inducing intrusive memories. Furthermore, to enhance comparability, we administered the modified CVLT also used by Verwoerd and colleagues (2011) for measuring resistance to PI. Using this modified version also carried the advantage of a high number of items, which was expected to be useful to preclude ceiling effects in a healthy sample. However, all participants showed a performance decrease in the modified CVLT from session 1 to session 2, although positive practice effects on the regular CVLT have been reported (Duff, Westervelt, McCaffrey, & Haase, 2001; Woods, Delis, Scott, Kramer, & Holdnack, 2006). It cannot be ruled out that this decrease was caused by somewhat higher stress levels in session 2, which may have been triggered by the tDCS electrode placement, reduced motivation by participants, or increased task difficulty caused by word interferences from session 1. Furthermore, in contrast to Verwoerd and colleagues (2011), there was no significant between-lists performance decrease for shared trials on session 1 and no between-lists performance increase for non-shared trials on session 2 in the present study. These changes were to be expected and—according to Verwoerd and colleagues (2011)—would have underlined the sensitivity of the modified CVLT for interference effects. It should be noted that we examined an exclusively female sample and Verwoerd and colleagues (2011) reported interference effects to be stronger for men compared to women. Nevertheless, the modified CVLT has only rarely been used in earlier research and information regarding convergence with other established measures or on sensitivity to tDCS are largely lacking. Our results indicate that the modified CVLT index should be used with caution in future research. Apart from restrictions of the modified CVLT, in a recent study by Swick, Cayton, Ashley, and Turken (2017), the ability to overcome PI (as assessed by a probes working memory task with non-affective verbal and visual stimuli) was also unrelated to the severity of re-experiencing symptoms in combat veterans diagnosed with PTSD. Therefore, our results support recent research that questions the link between resistance to PI and intrusive memories in general.

Concerning rumination, previous research posited that deficits in resolving interference from no-longer relevant information in working memory are related to recurring ruminative thoughts (De Lissnyder et al., 2012; Pe et al., 2012; Vanderhasselt et al., 2013; Zetsche et al., 2012; Zetsche & Joormann, 2011). However, most of these studies applied interference tasks with affective stimuli or focused on naturally occurring rumination. In contrast, we examined

the link between resistance to PI and experimentally induced rumination by use of non-affective stimuli. Thus, persistent rumination might be exclusively linked to deficits in controlling no-longer relevant emotional information. Interestingly, a recent meta-analysis by Zetsche and colleagues (2018) analyzed a large body of published and unpublished research on the link between cognitive control and self-reported trait repetitive negative thinking. Results from this meta-analysis also showed that ruminators do rather experience specific deficits in removing no-longer relevant information from working memory than general deficits in cognitive control, although effects were small in magnitude after controlling for depressive symptoms. Importantly, stimulus valence was not a significant moderator of this association. Nevertheless, the authors pointed out that, due to task heterogeneity, analyses only contrasted emotionally neutral versus emotionally mixed stimuli and thus did not differ between positive and negative affective material. Future research should further clarify whether deficits in resolving PI is selectively linked to negative information as well as investigate the role of varying induction and assessment methods of rumination.

Furthermore, we did not find the expected tDCS effect on resistance to PI. As already mentioned in the introduction, the ability to resist PI is supported by a complex network including various brain areas (e.g., Blasi et al., 2006; D'Esposito et al., 1999; Johnson et al., 2001). We focused on the left dlPFC as one part of this network as neuromodulation of this region has been associated with cognitive control shifts in former studies (Andrews et al., 2011; Fregni et al., 2005; Frings, Brinkmann, Friehs, & van Lipzig, 2018; Wolkenstein & Plewnia, 2013; Zaehle et al., 2011). However, these studies used different tasks to assess cognitive control. Thus, it is possible that there are other brain areas supporting the requirements of the modified CVLT more than the left dlPFC; these brain areas may then be more suitable stimulation sites when aiming to modify the resistance to PI. Therefore, we encourage future studies to further clarify causal relations by stimulating different brain areas or by using varying assessment methods of cognitive control. We recommend the use of tasks other than the modified CVLT due to the constraints mentioned above. In particular, tasks that rely on reaction times instead of accuracy rates might be more adequate, given that a recent meta-analysis reported that, at least for healthy individuals, effects of tDCS over the dlPFC on cognitive control become manifest predominantly in altered reaction times (Dedoncker et al., 2016a).

Despite the non-significant results concerning resistance to PI, general deficits in cognitive control have been empirically linked to intrusive memories and rumination in different samples (Aupperle et al., 2012; Brewin & Beaton, 2002; Brewin & Smart, 2005; Klein & Boals, 2001; Polak et al., 2012; Whitmer & Gotlib, 2013) and tDCS over the left dlPFC has been

reported to influence cognitive control processes (e.g., Andrews et al., 2011; Fregni et al., 2005; Wolkenstein & Plewnia, 2013). Moreover, the activation of the left dlPFC has not only been associated with cognitive control but also with intrusive memories and rumination (e.g., Anderson et al., 2004; Benoit et al., 2014; Vanderhasselt et al., 2013). Therefore, even with no tDCS effect on resistance to PI and no significant correlation between resistance to PI and intrusive memories or rumination, we would have expected tDCS-induced changes in intrusive memories and rumination following stimulation of the dlPFC. However, similar to resistance to PI, the control of unwanted memories and thoughts relies on a complex network, also including other brain structures such as the right dlPFC or the anterior cingulate cortex (Anderson et al., 2004; Anderson et al., 2015; Kühn et al., 2012; Mandell, Siegle, Shutt, Feldmiller, & Thase, 2014). At least for rumination, two studies that combined working memory training with bilateral or left stimulation of the dlPFC also found no effects of tDCS on rumination (De Putter, Vanderhasselt, Baeken, De Raedt, & Koster, 2015; Vanderhasselt et al., 2015). Compared with the present study, both studies relied on smaller sample sizes, used different stimulation parameters, or focused on naturally occurring rumination. Nevertheless, since our results also indicate no effects of tDCS over the left dlPFC on the occurrence of unwanted thoughts, it might be worthwhile to examine other brain areas in future research. Furthermore, we found that individuals with a trait tendency for post-film rumination and intrusive memories experienced more rumination and intrusive memories after film presentation. Therefore, future research could benefit from selecting participants based on these trait tendencies to strengthen the effects of neuromodulation. This assumption is also supported by a recent study indicating that base-level performance in cognitive control moderates tDCS effects—that is, participants whose cognitive control is impaired the most, profit the most from anodal tDCS (Wolkenstein et al., in prep.).

In general, there is an ongoing debate about the effectiveness of neuromodulation. This study fits into this debate and some general limitations regarding tDCS should be considered. First, the stimulation period of 20 minutes only comprised the CVLT administration and not the trauma film. Nitsche and colleagues (2008) claimed even shorter periods to produce stable effects that last for at least one hour. However, the stability of effects varies as a function of stimulation period, current intensity, and target brain area (Nitsche et al., 2008). Thus, it cannot be ruled out that the manipulation of the dlPFC rapidly declined after tDCS. Second, we used an extracephalic position of the reference electrode to avoid effects on other brain areas. Although this procedure has been successfully administered in other studies (e.g., Wolkenstein & Plewnia, 2013), it may reduce stimulation intensity (Moliadze, Antal, & Paulus,

2010). Third, we had a young, highly-educated, healthy sample. Previous research has pointed towards possible ceiling effects for anodal tDCS in healthy samples (e.g., Furuya, Klaus, Nitsche, Paulus, & Altenmüller, 2014). Although we used a modified CVLT with 30 instead of 12 words per list to prevent those effects, we cannot rule them out. Furthermore, even though there are experimental studies reporting significant deteriorating effects of cathodal tDCS on cognitive control (e.g., Wolkenstein et al., 2014), a recent meta-analysis found no reliable effects of cathodal tDCS of the dlPFC on cognitive functioning in within-subject studies (Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016b). This result questions the suitability of cathodal tDCS over the dlPFC to inhibit cognitive control. Interestingly, Nieratschker, Kiefer, Giel, Krüger, and Plewnia (2015) showed that effects of cathodal tDCS can be moderated by specific genetic factors, suggesting that future studies in the area of neuromodulation should also consider genetic variability to reduce inconsistencies of results. Lastly, it should be noted that working mechanisms of tDCS are divisive. In a recent study examining the effects of direct transcranial electric stimulation on brain activity, Vöröslakos and colleagues (2018) showed that electric stimulation does influence brain networks in healthy subjects as long as induced electric fields are sufficiently strong (> 1 mV/mm at least). According to the authors, results from human cadaver brains suggest that scalp-applied current intensity is attenuated by skin, soft tissue, or skull thickness. Thus, scalp-applied currents of 4-6 mA or higher are needed to achieve a high voltage gradient. However, due to safety reasons, conventional stimulation protocols do not recommend currents larger than 2 mA. Our stimulation protocol was in line with this convention. However, tDCS-associated changes in cognitive control by use of 1 mA have been reported (e.g., Wolkenstein & Plewnia, 2013; Wolkenstein et al., 2014). Nevertheless, future studies should further investigate how to maximize direct effects on brain activity by use of alternative stimulation protocols (e.g., Chhatbar et al., 2017) or new stimulation methods (e.g., Vöröslakos et al., 2018). Furthermore, we had to keep the post-stimulation period as short as possible in this study. Therefore, we did not include a second cognitive control task to test whether cortical excitability had been achieved. Future investigation should also include additional cognitive measures to verify manipulation. Apart from these restrictions concerning tDCS, we measured the occurrence of intrusive memories retrospectively, a procedure that notoriously includes the risk of cognitive biases. The ability to remember and report the amount of film-related intrusive memories might be related to individual differences in cognitive functioning, e.g., short-term and working memory capacity. Compared to previous investigations that covered much longer assessment intervals, our measurement directly followed a relatively short resting period. Nevertheless,

an alternative assessment method could be instructing individuals to directly indicate an intrusive memory once it occurred. However, addressing the assessment of intrusive memories prior to resting period might focus participant's attention on film-related thoughts and therefore trigger rumination or further intrusive memories, an effect that would reduce validity of the assessment. Furthermore, as already noted in previous research using diary assessments for intrusive memories (e.g., Wessel et al., 2008), monitoring contents of working memory and maintaining a task goal (i.e., tapping intrusive memories) is also a core characteristic of cognitive control and in turn subject to individual differences in cognitive functioning.

Despite these limitations, this study contributed to the challenging task of establishing causality in post-trauma symptomatology. Even though the hypotheses were not confirmed, the results extend existing research. To investigate causal relations, an indicator of cognitive control as well as a corresponding brain area had to be determined that are both associated with intrusive memories/rumination and susceptible to tDCS. Based on existing findings, we chose resistance to PI as measured by the modified CVLT as well as the left dlPFC. However, we found no associations with intrusive memories or rumination as expected and no effects of tDCS. At the same time, our results highlight the potential role of boundary conditions that should be further differentiated in future research, e.g., administering cognitive control tasks that include reaction times, using affective stimuli, or focusing on other brain areas for neuromodulation. Furthermore, selecting participants based on trait-measures of cognitive control or rumination/intrusive memories could be an important step to enhance effects of neuromodulation in the future. In sum, until now we are not able to conclude whether differences in cognitive control are a risk factor for the occurrence of intrusive memories or rumination. And clearly, more research is needed to consider chances and limits of tDCS in the domain of PTSD-related symptomatology. Nevertheless, the current study offers starting points for future investigations to finally answer the question of what determines individual vulnerability for intrusive memories and rumination after life-threatening events.

3. Study II

Examining Proactive Cognitive Control and Intrusive Memories via Transcranial Direct Current Stimulation in an Experimental Analogue Study

Abstract

Investigating impairments in cognitive control has become an important avenue for identifying risk factors for intrusive memories. The dual mechanisms framework has proposed that cognitive control operates by two distinct modes: a proactive mode that is characterized by active maintenance of goal-relevant information to bias behavior before conflicting events; and a reactive mode that is characterized by the retrieval of goal-relevant information only when interference occurs. However, whether deficits in these cognitive modes are causally related to intrusive memories is unclear. In the present study we examined the effects of transcranial direct current stimulation (tDCS) over the left dorsolateral prefrontal cortex (dlPFC), an area commonly associated with cognitive control, on proactive control and intrusive memories. Furthermore, correlations between proactive control and intrusive memories were explored. In a between-subject design, N = 121 healthy individuals performed the AX-Continuous Performance Task—an established measure of proactive control—during 20-minutes tDCS (anodal, cathodal, or sham), then watched a trauma film, and later reported intrusive memories after a 10-minutes filler task. There were no effects of tDCS on proactive control or on intrusive memories. Moreover, proactive control was not related to intrusive memories. Thus, the findings question the role of the left dlPFC for proactive control and intrusive memories. Future studies in this field should consider alternative brain areas and further evaluate the susceptibility of the dual mechanisms of control to neuromodulation as well as their association with intrusive memories.

Introduction

Human functioning relies on the direction of cognitive capacity towards a particular goal despite goal-irrelevant information, an ability that is known as cognitive control. In recent years, results from studies in clinical and analogue samples indicated that impaired cognitive control might be a risk factor for the occurrence of posttraumatic intrusive memories, defined as unwanted recurring sensory fragments of a traumatic event (e.g., Aupperle et al., 2012; Brewin & Beaton, 2002; Brewin & Smart, 2005; Klein & Boals, 2001; Polak et al., 2012). It has been suggested that cognitive control works as a gatekeeper that helps individuals to stay focused on activated goals despite internal or external cues that are potentially able to activate intrusive memories (e.g., Wessel et al., 2008). However, a number of questions still remain unanswered. First, causality is unclear in most studies with clinical samples (for a review of longitudinal and cross-sectional results see Aupperle et al., 2012). Reduced cognitive control might be a risk factor for intrusive memories or a by-product of posttraumatic symptoms. In addition, results concerning the disrupted cognitive control functions are inconsistent and partially lacking a clear conceptual framework. For example, some studies identified diminished inhibition, for example, reduced resistance to proactive interference, as a precursor to intrusive memories (e.g., Verwoerd et al., 2011; Wessel et al., 2008) but more recent research failed to replicate these findings (e.g., Voss, Ehring, & Wolkenstein, 2019; Woud et al., 2019). The present study aims to overcome these limitations by exploring the causal link between cognitive control and intrusive memories within a specific concept: The dual mechanisms of control (DMC) framework.

The DMC framework conceptualizes cognitive control as operating by two distinct modes: proactive and reactive control. According to Braver (2012), proactive control is an "early selection" mode that maintains goal-relevant information to bias thoughts and actions on internal or external goals prior to conflicting events. In contrast, reactive control is a "late correction" mode that retrieves goal-relevant information only when it is needed, for example, to deal with interference after the detection of conflicting events. Although proactive control is more effective in most situations, it depends on valid contextual cues and consumes limited cognitive resources as well as working memory capacity (Braver, 2012). Thus, efficient cognitive control is dependent on both, proactive, goal-directed and reactive, stimuli-driven processing.

There is inter-individual variability in the deployment of proactive and reactive control when performing highly demanding cognitive tasks. For instance, higher fluid intelligence

and higher working memory capacity have been linked to proactive control (Burgess & Braver, 2010; Redick, 2014; Richmond, Redick, & Braver, 2015). Furthermore, Braver (2012) posited that rather than showing global deficits in cognitive control, clinical and developmental samples might differ in their utilization of proactive and reactive control. Indeed, impairments in proactive control have been found in old adults and young children (e.g., Brahmbhatt, White, & Barch, 2010; Braver et al., 2001; Bugg, 2014; Lorsbach & Reimer, 2010) as well as in individuals with schizophrenia, depressive mood, or anxiety (e.g., Barch et al., 2001; Edwards, Barch, & Braver, 2010; West, Choi, & Travers, 2010; Yang et al., 2018). Until now, little is known about the role of proactive and reactive control for the development and maintenance of posttraumatic stress disorder (PTSD) and the occurrence of intrusive memories. However, based on the predictions of the DMC framework (see Braver, 2012), it can be assumed that deficits in proactive control might be related to difficulties in maintaining goal-relevant information and in adaptively considering context information. These difficulties might impede the ability to ignore external or internal goal-irrelevant cues that activate traumatic representations, thereby facilitating the occurrence of intrusive memories that interfere with goal-directed behavior. Hence, individuals at risk for intrusive memories might not show reduced cognitive control per se but rather subtle deficits in deploying proactive control, an assumption that has not been directly tested within the DMC framework, yet. Studies examining context processing and sustained goal activation in PTSD patients provide first hints that support this assumption. For example, van Rooij and colleagues (2014) reported that veterans with PTSD show less proactive response inhibition, i.e., lower anticipated stopping that relies on contextual cues, than healthy individuals. Moreover, compared to healthy controls, individuals suffering from PTSD demonstrated deficits in sustained attention to task goals (Jenkins, Langlais, Delis, & Cohen, 2000; Vasterling et al., 2002). The main goal of the present study is to build on these results and to explore the causal link between proactive control and intrusive memories in healthy individuals in light of the DMC framework.

Since examining causality in the context of traumatic intrusions underlies practical and ethical challenges, the trauma film paradigm has been established as a useful analogue in healthy samples. By confronting healthy individuals with stressful film scenes, it is possible to test and manipulate key processes that are involved in the development of intrusive memories (Holmes & Bourne, 2008). However, even with the trauma film paradigm it cannot be ruled out that the mechanisms of interest are affected by third variables, which causes difficulties in investigating causality. Thus, we aimed to manipulate proactive control and intrusive

memories after a trauma film by modulating activation in a brain area that is associated with cognitive control via transcranial direct current stimulation (tDCS).

TDCS is as a safe, non-invasive, and effective method for the modulation of brain activity. The technique involves the hyper- or depolarization of resting membrane potentials (Nitsche & Paulus, 2001; Priori, 2003; Wassermann & Grafman, 2005) through a weak current applied over a specific brain area for several minutes. Cathodal stimulation reduces cortical excitability and anodal stimulation increases cortical excitability in the stimulated region for at least one hour (Nitsche et al., 2008). Since cognitive control is a function of the prefrontal cortex, the left dorsolateral prefrontal cortex (dlPFC) has been identified as a promising area to induce cognitive control shifts (e.g., Blasi et al., 2006; Bunge et al., 2001; Curtis & D'Esposito, 2003; Dulas & Duarte, 2016; Nee et al., 2007; Postle et al., 2001; Postle et al., 2004; Wolf et al., 2010). Also within the DMC framework, proactive control was associated with sustained activation of the lateral PFC whereas reactive control was linked to a wider network involving transient activation of the lateral PFC but also the anterior cingulate cortex and the posterior cortical or medial temporal lobe areas (Braver, 2012). Moreover, a number of studies demonstrated that the left dlPFC is associated with changes in the cognitive control mode (e.g., Braver, Paxton, Locke, & Barch, 2009; Lesh et al., 2013; Lopez-Garcia et al., 2016). For example, Braver and colleagues (2009) reported that the left dlPFC shows enhanced sustained activity in older adults that have been trained in proactive control and a more transient activation in young adults that have been motivated for a reactive mode via monetary rewards. Furthermore, the dlPFC was also associated with intrusive memories (e.g., Anderson et al., 2004; Arnsten et al., 2015; Clark et al., 2003). For example, Benoit and colleagues (2014) found that healthy individuals showed highest dlPFC activation when controlling intrusive memories in a suppressing versus recalling task of memory contents. Taken together, based on conceptual considerations and empirical evidence, the left dlPFC appears to be a central component for the modulation of cognitive control in general, proactive control in particular, and intrusive memories.

Nevertheless, there is also evidence that contradicts the prominent role of the left dlPFC in proactive control. Within the DMC framework, Gómez-Ariza and colleagues (2017) examined whether tDCS over the left dlPFC changes control modes in healthy young adults. Similar to previous research, the authors utilized the well-validated AX-Continuous Performance Task (AX-CPT) to assess proactive and reactive control. In this modified version of the classic Continuous Performance Task, participants have to respond to an A (cue) followed by an X (probe) and not respond to all other letter combinations (AY, BX, BY). Importantly, be-

cause of a higher proportion of AX-sequences, both letters are strongly associated. The activated control mode is expected to translate into different performance patterns. Proactive control should be associated with the maintenance of contextual information and therefore lead to high target expectancies when an A cue is detected. Thus, individuals who engage in proactive control should show reduced error rates and faster reaction times in BX trials and increased error rates and slower reaction times in AY trials. However, in contrast to the predictions of the DMC, Gómez-Ariza and colleagues (2017) found no effect of tDCS over the left dlPFC on performance in AY or BX trials. Interestingly, offline cathodal tDCS over the right dlPFC, a region that had been included as a control side, led to a slight decrease in proactive control. Nevertheless, given that the involvement of the left dlPFC in proactive control has been theoretically and empirically well-proven, the researchers encouraged future studies to further evaluate the manipulation of AX-CPT performance via tDCS of the left dlPFC with alternative task and stimulation parameters. Thus, in the current study we also used the AX-CPT but administered a version modified by Richmond and colleagues (2015) that included 40 % AX trials, 10 % AY trials, 10 % BX trials and 40 % BY trials. This trial proportion was used in previous studies that induced proactive control shifts (e.g., Gonthier, Macnamara, Chow, Conway, & Braver, 2016) and rules out possible confounding first-order frequency effects. Moreover, we used a constant current of 1 mA and a stimulation protocol that was successfully applied to manipulate cognitive control before (Wolkenstein & Plewnia, 2013; Wolkenstein et al., 2014).

In sum, the aim of this randomized, sham-controlled, double-blind analogue study was to investigate causal links between the activation of the left dlPFC (as manipulated by tDCS), cognitive control, in particular proactive control as defined within the DMC framework, and intrusive memories. We applied anodal, cathodal, and sham tDCS to the left dlPFC of healthy individuals to examine effects on proactive control as well as on the occurrence of intrusive memories after a trauma film. Thereby, we tested the following hypotheses: First, we predicted cathodal tDCS to decrease and anodal tDCS to increase proactive control, compared to sham stimulation (H1). Second, we predicted cathodal tDCS to lead to more intrusive memories and anodal tDCS to lead to less intrusive memories after a trauma film, compared to sham stimulation (H2). Third, we examined associations between proactive control and intrusive memories. We proposed higher proactive control to be associated with less intrusive memories after the trauma film (H3).

Method

Design, randomization, and blinding

The study followed a between-subject design with three tDCS groups (anodal vs. cathodal vs. sham). Participants were randomized to a tDCS group by use of automated randomization software (randomizer.org). They were informed that they would be assigned to one of three tDCS conditions that differ in electrode placement and stimulation intensity but not in stimulation length. Furthermore, the stimulator was started via predefined codes, a technique that allowed a double-blind assignment to the sham or verum stimulation.

Sample

N = 123 healthy adults between 18 and 41 years were recruited via advertisements and a lab database at LMU Munich. After excluding two participants due to error rates above 45 % in the AX-CPT (Goméz-Ariza et al., 2017), the final sample comprised 121 participants (67.8 % female) with a mean age of 24.46 (*SD* = 5.14). Participants were eligible if they had sufficient knowledge of the German language and an educational qualification of university entrance diploma or higher. None of the participants reported diseases of the central nervous system; cardiovascular, respiratory or neuroendocrine diseases; seizures; first-degree relatives suffering from epilepsy; a history of traumatic brain injury; metallic particles around the head; a cardiac and cerebral pacemaker, cochlea implants and hearing aid devices; strong allergic reactions to sensing electrodes; current pregnancy; left- or mixed handedness as indicated by a short version of the Edinburgh Handedness Inventory (Veale, 2014); psychotropic medication; a substance use disorder with less than 2 years of abstinence; a history of psychiatric disorders as assessed by the M.I.N.I. International Neuropsychiatric Interview for DSM-5 (Sheehan, 2016) and the PTSD Checklist for DSM-5 (PCL-5; Krüger-Gottschalk et al., 2017); or a history of psychological treatment. All participants gave informed consent and received monetary compensation or course credit. The study protocol was in compliance with the Declaration of Helsinki and approved by the local ethics committee.

Stressful film fragment

Participants watched a 9-minutes film depicting scenes of injury and death on an 18-inch screen in a darkened room. The scenes were derived from Holmes, James, Coode-Bate, and Deeprose (2009) and contained self-injury, a traffic accident, the killing of a man by an ele-

phant as well as two fragments from the movie "American History X" by Tony Kaye. All participants were informed about the exposition to violent content in the study advertisement and in the informed consent.

TDCS

A direct current of 1 mA was delivered by a CE-certified stimulator (NeuroConn GmbH, Ilmenau, Germany). Using a pair of 0.9 % NaCL-soaked sponge electrodes (35cm^2 surface), the anode/cathode was fixated on the scalp over F3 according to the international 10-20 system of electrode placement. To avoid polarization of another brain area, the reference electrode was placed on the right deltoid muscle. Verum stimulation was administered for 20 minutes plus a 5-seconds fade-in and fade-out phase. Sham stimulation was ramped down after 30 seconds, thereby eliciting a slight tingling on the head but no effects in the brain.

Cognitive control measure

AX-continuous performance task (AX-CPT). We used a version of the AX-CPT based on Gonthier and colleagues (2016). The task was presented on an 18-inch screen via EPrime. In each trial, participants saw a cue (any letter except X, K, or Y) in the center of the screen for 1000ms. Following an unfilled inter-stimulus interval of 4000ms, a probe (any letter except A, K, or Y) appeared on the same position for 500ms. After the probe, a 1000ms inter-trial interval followed in which a row of asterisks was presented. Participants had to respond as quickly as possible after they observed the second letter, i.e. the probe. They were instructed to press the target button with the middle finger of their right hand when they saw an A followed by an X, and to press the non-target button with the index finger of the right hand when they saw any other pair. Responses were recorded during the 500ms probe presentation and the 1000ms inter-trial interval. Participants completed 200 trials presented in four blocks. As reported in Gonthier and colleagues (2016) and Richmond and colleagues (2015), 40 % of the trials in each block contained an A followed by an X (AX trials), 10 % of the trials in each block contained an A followed by a letter other than X (AY trials), 10 % of the trials in each block contained a letter other than A followed by an X (BX trials), and 40 % of the trials in each block contained a letter other than A followed by a letter other than X (BY trials). Trials within each block were randomized. For each of these four trials, error rates and average response times (RTs) for correct responses were computed. Higher proactive control is indicated by reduced error rates and faster reaction times in BX trials and increased error rates and

slower reaction times in AY trials. Similar to Gonthier and colleagues (2016), we additionally calculated the Proactive Behavioral Index (PBI), an index for the ratio of interference in AY and BX trials. A positive PBI reflects more interference on AY trials, indicating more proactive control. It was calculated separately for error rates and RTs with (AY - BX)/(AY + BX). Importantly, prior to calculating the PBI, all error data was corrected for trials where error rates were equal to zero via (number of errors + 0.5)/(number of trials + 1) (Gonthier et al., 2016).

Post-film intrusive memories

Intrusive memories. Having watched the film, participants read a neutral filler text with technical information about a German airport (the Cologne Bonn airport) for 10 minutes. The aim of this filler text was to avoid that participants deliberately think about the film during an unguarded resting period and to measure the occurrence of intrusive memories during a situation that resembles everyday life. After this period, intrusive memories were assessed by a 6-item questionnaire adapted from Weidmann and Papsdorf (2010). First, participants were provided a short definition of intrusive memories and indicated how often they had experienced intrusive memories of the film during text reading, the time taken up by experiencing intrusive memories of the film while reading (from 0 to 100 % of the time) and—in case they had reported at least one intrusive memory—the predominant quality ("thought", "image", "short film scene", "feeling", "sound", "something else", "I do not know"). Furthermore, level of distress caused by the intrusive memories, level of vividness, and level of control were each measured on a 10-point scale (1 = "not at all" to 10 = "very").

Impact of movie scale (IMS). In accordance with previous studies (e.g., Verwoerd et al., 2011), a film-adapted version of the *Impact of Event Scale* (Horowitz, Wilner, & Alvarez, 1979) was additionally used. The IMS contained six items relating to intrusive memories during the 10-minutes reading period (e.g., *"*Images of the film came up spontaneously") that were rated on a 4-point scale (1 = "not at all*",* 4 = *"*often*")* with item weights of 0, 1, 3, 5 (cf. Horowitz et al., 1979). Internal consistency of the scale was high (Cronbach's $\alpha = .91$).

Control measures

Trait film-related intrusive memories. The trait tendency for intrusive memories after stressful films was measured by modified versions of the questionnaires for post-film intrusive memories. Participants indicated their habitual responses to films that trigger negative

emotions in general. For the frequency of intrusive memories, answers were now given on a 5-point scale (1 = “never” to 5 = “always”).

Trait response to intrusive memories. We applied a modified version of the 19-item Response to Intrusions Questionnaire (RIQ; e.g., Clohessy & Ehlers, 1999; Ehring et al., 2008) to capture how participants habitually respond to intrusive memories of stressful events. The RIQ consists of five subscales measuring suppression (6 items), rumination (8 items), dissociation (3 items), the consumption of alcohol or drugs (1 item) and the distraction with music or TV (1 item). The latter two subscales were not of interest for this study. Answers were given on a 4-point scale (1 = “never”, 4 = “always”). Reliability and predictive validity were acceptable to good in previous research (e.g., Ehring et al., 2008; Murray et al., 2002).

Neuropsychological measures. The Trail Making Test (TMT A/B; Reitan, 1992) and a digit span test forward/backward (a version similar to the Wechsler Adult Intelligence Scale; Petermann, 2012) were administered to control for individual differences in visual-motor conceptual screening, cognitive flexibility as well as short-term and working memory capacity.

Mood and arousal. We assessed whether tDCS and the film scene affected participants’ mood and arousal by two Self-Assessment-Manikins (SAM; Bradley & Lang, 1994). Participants had to indicate how they felt (1 = “very negative” to 9 = “very positive”) and how aroused they were (1 = “very calm” to 9 = “very high arousal”) on a scale that included five non-verbal pictorial stimuli.

Film control measures. To assess how attentively participants had followed the film, participants completed six self-generated multiple choice questions about the fragment from American History X (e.g., “What was the name of the perpetrator?”). A sum score for correct answers was calculated. Furthermore, we asked whether participants had seen the film scenes before, whether they watched similar films frequently, and how often they had looked away during the film on a 5-point scale (1 = “never”, 5 = “always”). Subjective distress during the film was measured by two additional SAMs for mood (1= “very negative” to 9 = “very positive”) and arousal (1 = “very calm” to 9 = “very high arousal”).

Motivation. Participants were asked to indicate their motivation to complete the study, to perform the AX-CPT, and to fill out the questionnaires on three visual analogue scales (0 = “not at all”, 10 = “very”).

Procedure

Participants were tested at the outpatient center of LMU Munich in a 2-2.5 hours session. First, sociodemographic and health questionnaires, the EHI short form and the M.I.N.I. and PCL-5 were administered to check eligibility. Next, participants completed TMT A/B and digit span test. After a 10-minutes break, tDCS was applied for 20 minutes. The computerized AX-CPT started 5 minutes after the onset of stimulation and took 25 minutes. Afterwards, the experimenter darkened the room and left the lab while the film was presented. SAMs were completed at baseline, after 5 minutes of tDCS before the start of the AX-CPT and after film presentation. Having watched the film, participants read the filler text for 10 minutes and then completed the measures of intrusive memories as well as the remaining questionnaires via Unipark (EFS Survey, Questback GmbH).

Data analyses

Data were analyzed by use of SPSS® Version 24.0. To check comparability of stimulation groups, we examined group differences in any of the baseline or post-film control measures via Analyses of Variance (ANOVAs) and Kruskal–Wallis-Tests. Furthermore, we analyzed mood and arousal ratings by use of two mixed ANOVAs with the between-subject factor tDCS group (sham vs. anodal vs. cathodal) and the within-subject factor time point (baseline vs. pre AX-CPT vs. post film). To test the effects of tDCS on proactive control in the AX-CPT (H1), we performed mixed Analyses of Variance (ANOVA) with the between-subject factor tDCS group (sham vs. anodal vs. cathodal) and the within-subject factor trial type (AY vs. BX) and with error rates or RTs (for correct responses), respectively, as dependent variables. In addition, we performed a Multivariate Analysis of Variance (MANOVA) with the between-subject factor tDCS group and the PBIs as dependent variables. Participants in the anodal condition were expected to show greater proactive control, as indicated by worse AY performance, better BX performance, and higher PBI values whereas participants in the cathodal condition were expected to demonstrate lower proactive control as indicated by better AY performance, worse BX performance, and lower PBI values. To test effects of tDCS on intrusive memories (H2), we used a MANOVA with the number of post-film intrusive memories, the percent of time they had been experienced and the IMS score as dependent variables. An exploratory MANOVA was performed for all individuals reporting intrusive memories with level of distress, vividness and control of intrusive memories as dependent variables. Finally, Bonferroni-Holm--corrected Spearman-Rho-correlation coefficients were calculated

to test associations between the AX-CPT indices and the intrusive memories measures (H3). If not otherwise stated, all effects were tested at the .05 α-level (two-tailed) and Greenhouse-Geisser corrected tests were used when the sphericity assumption was violated in mixed ANOVAs. Moreover, we computed Bayes Factors for each hypothesis to quantify the relative strength of evidence for our main findings. In addition to the main analyses, we calculated split-half reliabilities of the AX-CPT by creating two data sets (even, odd trials) and correlating mean RTs for correct responses and error rates for each trial type between the two data sets using Spearman-Brown correction. Reliability coefficients can be found in Table A.1 in the supplementary material. Sample size was determined via G*power (version 3.1, University of Duesseldorf, Germany), assuming a statistical power of .80 and an alpha level of .05. Results showed that in order to examine the effect of tDCS on cognitive control a total sample of 42 participants was required to test the interaction between tDCS condition and trial type (f = 0.25). For the global effect of tDCS on the three characteristics of intrusive memories post-film (number of memories, percent of time experiencing intrusions, IMS score), the power analysis suggested that a sample of 114 participants ($f^2(V)$ = 0.0625) was needed. For the correlational analyses, a total sample of 84 (r = 0.3) participants was required, according to the power analysis.

Results

The data of this study is openly accessible in the associated OSF repository (https://osf.io/vak9y/).

Descriptive statistics and group differences in control measures

In general, 30.6 % of participants were familiar with at least one of the film scenes and 26.4 % of participants reported watching films with violent content regularly. There was a significant main effect of time on mood, $F(1.28, 150.62) = 305.79$, $p < .001$, $\eta_p^2 = .72$, with mood decreasing from baseline (M = 7.09, SD = 1.27) to pre AX-CPT (M = 6.75, SD = 1.46) to post film (M = 3.73, SD = 1.62). Similarly, a significant main effect of time on arousal emerged, $F(1.40, 165.34) = 217.28$, $p < .001$, $\eta_p^2 = .65$, with arousal increasing from baseline (M = 3.16, SD = 1.89) and tDCS start (M = 3.03, SD = 1.74) to post film period (M = 6.06, SD = 1.80). There was no main effect of group and no group x time interaction, neither for mood nor for arousal (all Fs ≤ 1.04, all ps ≥ .369). Descriptive statistics and group comparisons for

all other control measures are depicted in Table 2.1. The tDCS groups did not differ in any of these measures.

Table 2.1

Descriptive Statistics and Group Comparisons of Control Measures

		Sham (n = 41)	Anodal (n = 38)	Cathodal (n = 42)	
	Min - Max	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*p*
Age	18.00 - 41.00	24.49 (5.48)	25.37 (5.17)	23.62 (4.73)	*ns*
TMT-A	11.00 - 60.00	21.78 (6.42)	20.76 (7.61)	22.50 (7.61)	*ns*
TMT-B	24.00 - 167.00	51.51 (24.21)	44.53 (12.87)	52.60 (21.25)	*ns*
Digit Span forward	4.00 - 12.00	8.63 (1.83)	8.89 (1.71)	9.02 (1.68)	*ns*
Digit Span backward	3.00 - 12.00	7.37 (1.64)	7.55 (2.10)	7.76 (1.94)	*ns*
Trait Film-Related IM	1.00 - 5.00	2.39 (0.77)	2.32 (0.74)	2.50 (0.86)	*ns*
Trait Distress of IM	1.00 - 9.00	4.03 (1.60)	4.47 (1.99)	4.27 (1.61)	*ns*
Trait Vividness of IM	1.00 - 10.00	5.50 (2.29)	5.53 (2.33)	5.05 (1.68)	*ns*
Trait Control of IM	1.00 - 10.00	6.28 (2.43)	6.88 (2.21)	6.62 (1.69)	*ns*
Trait IMS	0.00 - 24.00	6.54 (5.18)	5.63 (4.91)	6.64 (4.81)	*ns*
RIQ Suppression	6.00 - 24.00	15.95 (3.67)	14.89 (3.45)	15.10 (3.34)	*ns*
RIQ Rumination	8.00 - 27.00	15.44 (4.76)	13.89 (4.01)	15.31 (4.05)	*ns*
RIQ Dissociation	3.00 - 10.00	4.73 (1.70)	4.71 (1.65)	4.86 (1.65)	*ns*
Time Looked away	1.00 - 4.00	1.88 (0.93)	1.79 (0.91)	1.95 (0.96)	*ns*
SAM Valence during Film	1.00 - 8.00	2.78 (1.46)	2.87 (1.26)	3.36 (1.43)	*ns*
SAM Arousal during Film	2.00 - 9.00	6.59 (1.86)	6.95 (1.72)	6.24 (1.71)	*ns*
Film-Related Attentiveness	1.00 - 6.00	4.15 (1.37)	4.42 (0.98)	4.31 (1.30)	*ns*
Motivation Start of study	3.00 - 10.00	8.83 (1.32)	8.55 (1.83)	8.60 (1.35)	*ns*
Motivation AX-CPT	2.00 - 10.00	7.12 (2.35)	7.29 (2.35)	6.67 (2.31)	*ns*
Motivation Questionnaire	1.00 - 10.00	8.49 (2.06)	9.13 (1.26)	8.93 (1.02)	*ns*

Notes. TMT = Trail Making Test, IM = Intrusive Memories, IMS = Impact of Movie Scale, RIQ = Response to Intrusions Questionnaire, SAM = Self-Assessment Manikin, AX-CPT= AX-Continuous Performance Task; Analyses for Distress, Control and Vividness of Intrusive Memories were performed only for individuals who reported to experience Intrusive Memories at least seldom.
ns = nonsignificant; two-tailed.

Cognitive control

Descriptive statistics for mean RTs and error rates (not transformed) for all trial types as well as the proactive control indices are presented in Table 2.2. For analyses, mean RTs and error rates were square-root transformed to reduce the impact of extreme values. The analyses

of error rates (AY and BX) revealed a significant effect of trial type, with all participants making less errors in BX (M = 0.06, SD = 0.08) than in AY (M = 0.18, SD = 0.12) trials, F(1, 118) = 141.37, p < .001, η_p^2 = .56. The same pattern of results was found for RTs, participants responded faster in BX (M = 440.05, SD = 136.49) than in AY (M = 567.71, SD = 103.93) trials, F(1, 118) = 383.80, p < .001, η_p^2 = .77. However, contrary to H1, none of the interaction effects reached significance, all Fs ≤ 0.36, all ps ≥ .698. Additionally, there were no group differences for the PBIs, V = 0.009, F(4, 236) = 0.28, p = .891, η_p^2 = .005 (Pillai's trace).

Post-film intrusive memories

Descriptive statistics of the intrusive memories measures are shown in Table 2.3. In general, 24.8 % of participants reported no intrusive memories at all. In contrast, 14.9 % of participants experienced intrusive memories as thoughts, 13.2 % as images, 34.7 % as a short film scene, 8.3 % as feelings, and 1.7 % as sounds. 2.5 % of participants did not specify the quality of the intrusive memory. For analyses, the dependent measures were square-root transformed to reduce the impact of extreme values. In contrast to H2, the tDCS groups did not differ in the three intrusive memories measures, V = 0.03, F(6, 234) = 0.62, p = .711, η_p^2 = .02 (Pillai's trace). Furthermore, there were no effects of tDCS on level of distress, level of vividness, or level of control of intrusive memories for those individuals who had experienced intrusive memories, V = 0.04, F(6, 174) = 0.63, p = .707, η_p^2 = .021 (Pillai's trace).

Table 2.2

Descriptive Statistics of the AX-CPT

		Sham (n = 41)	Anodal (n = 38)	Cathodal (n = 42)	Overall (n = 121)
	Trial type	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
Average error rate	AX	0.08 (0.08)	0.06 (0.06)	0.07 (0.06)	0.07 (0.07)
	AY	0.21 (0.12)	0.17 (0.13)	0.17 (0.09)	0.18 (0.12)
	BX	0.08 (0.10)	0.04 (0.06)	0.06 (0.07)	0.06 (0.08)
	BY	0.06 (0.09)	0.05 (0.06)	0.05 (0.06)	0.05 (0.07)
Average RTs	AX	441.58 (103.50)	445.30 (97.37)	445.85 (66.25)	444.23 (89.43)
	AY	564.97 (115.25)	578.06 (99.37)	561.03 (97.95)	567.71 (103.93)
	BX	436.75 (156.95)	448.92 (124.30)	435.24 (128.10)	440.05 (136.45)
	BY	428.06 (141.08)	418.62 (102.50)	417.46 (104.25)	421.42 (116.66)
PBI error		0.40 (0.38)	0.45 (0.37)	0.39 (0.33)	0.41 (0.36)
PBI RT		0.14 (0.08)	0.14 (0.08)	0.14 (0.07)	0.14 (0.08)

Notes. RTs = Reaction times in ms for trials with correct responses, PBI = Proactive behavioral shift index.

Table 2.3

Descriptive Statistics of the Intrusive Memories Measures

		Sham (n = 41)	Anodal (n = 38)	Cathodal (n = 42)	Overall (n = 121)
	Min - Max	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
Post-Film number of IM	0.00 - 20.00	3.12 (3.12)	3.18 (4.23)	2.67 (2.82)	2.98 (3.39)
Post-Film % of time IM	0.00 - 85.00	16.90 (18.21)	16.13 (23.94)	15.48 (19.98)	16.17 (20.59)
Post-Film distress of IM	1.00 - 10.00	4.31 (2.45)	3.96 (2.53)	3.82 (2.28)	4.05 (2.41)
Post-Film control of IM	1.00 - 10.00	6.51 (2.44)	6.61 (2.75)	6.04 (2.30)	6.40 (2.49)
Post-Film vividness of IM	1.00 - 10.00	4.83 (2.36)	5.18 (2.50)	4.93 (2.00)	4.97 (2.28)
IMS	0.00 - 26.00	7.34 (6.31)	6.34 (7.66)	5.60 (6.31)	6.42 (6.75)

Notes. IM = Intrusive Memories, IMS = Impact of Movie Scale; Analyses for Distress, Control and Vividness of Intrusive Memories were performed only for individuals who reported at least one Intrusive Memory: sham n = 35, anodal n = 28, cathodal n = 28.

Link between cognitive control and post-film intrusive memories

Given that there were no group differences for proactive control or intrusive memories, we examined correlations across tDCS groups. Correlations between performance in AY and BX trials as well as indices of proactive control and intrusive memories are depicted in Table 2.4. The intrusive memories measures were highly inter-correlated but there were no significant correlations between intrusive memories and proactive control. When repeating these analyses only in the sham subgroup to exclude any effect of stimulation, the results did not change.

Bayesian analyses

We quantitated the relative strength of evidence for the non-significant findings by use of Bayesian hypothesis testing. A Bayes factor (BF_{01}) quantifies how well a hypothesis predicts observed data over an alternative hypothesis (Dienes, 2014). We computed BF_{01} using JASP statistical software version 0.11.1.0 for our main hypotheses (JASP Team, 2019). A $BF_{01} < 1$ implies that a result is more likely to occur under an alternative hypothesis (H_1) than under a null hypothesis (H_0). In contrast, a $BF_{01} > 1$ indicates that a result is more likely to occur under a H_0 than under a H_1 (Wagenmakers et al., 2011). For the first hypothesis, we expected a significant tDCS x trial type interaction for error rates and RTs for correct responses as dependent variables (both measures square-root transformed). Thus, a Bayesian mixed ANOVA was performed with default prior scales. Testing the interaction model (assuming the main effects of tDCS and time and their interaction) as the H_1 versus the main-effect model (assuming the main effects only) as the H_0, the results showed a BF_{01} of 9.606 for error rates and a BF_{01} of 14.585 for RTs. Thus, we found substantial to strong evidence in favor of the H_0 (Wagenmakers et al., 2011), indicating no interactions. Furthermore, we computed two separate ANOVAs with default prior scales with the PBIs as dependent variables to examine significant effects of tDCS group, with the H_0 stating no differences between the three tDCS groups and the H_1 stating group differences. Bayes factors for PBI on error rates (BF_{01} = 10.205) and PBI on reaction times (BF_{01} = 11.272) suggested strong evidence in favor of the H_0 (Wagenmakers et al., 2011). For the second hypothesis, we expected a significant effect of tDCS group on intrusive memories measures. Hence, we ran three separate Bayesian ANOVAs with default prior scales with the number of post-film intrusive memories, the percent of time they had been experienced and the IMS score (all measures square-root transformed) as dependent variables. The H_0 stated no differences between the three tDCS groups in these variables whereas the H_1 stated group differences. Results showed a BF_{01} of

7.334 for number of post-film intrusive memories, a BF_{01} of 8.375 for percent of time they had been experienced, and a BF_{01} of 3.695 for the IMS scores, implying substantial evidence for no effect of tDCS condition (Wagenmakers et al., 2011). For the third hypothesis, Bayesian Pearson correlations were calculated to analyze associations between the AX-CPT indices and the intrusive memories measures. The H_0 stated no significant correlations. Results are summarized in Table 2.5. Bayesian analyses indicated no associations between AX-CPT indices and intrusive memories.

Table 2.4

Spearman-Rho-Correlation Coefficients for the Dependent Variables

	2.	3.	Error Rate AY	Error Rate BX	RTs AY	RTs BX	PBI Errors	PBI RTs
1. Post-Film number of IM	.87***	.75***	-.01	-.01	.00	-.08	.03	.09
2. Post-Film % of time IM	-	.72***	-.06	-.06	.02	-.03	.03	.02
3. IMS		-	.05	.09	.04	-.04	-.03	.06

Notes. IM = Intrusive Memories, IMS = Impact of Movie Scale, RTs = Reaction times in ms for trials with correct responses, PBI = Proactive behavioral shift index.
*** $p < .001$; two-tailed, Bonferroni-Holm-corrected.

Table 2.5

Bayesian Pearson Correlation Coefficients

		Error Rate AY	Error Rate BX	RTs AY	RTs BX	PBI Errors	PBI RTs
Post-Film number of IM	*r*	.049	.003	.030	-.044	.034	.120
	BF_{01}	7.657	8.789	8.347	7.836	8.209	3.786
Post-Film % of time IM	*r*	-.036	-.080	.032	.002	.046	.053
	BF_{01}	8.147	6.057	8.282	8.792	7.768	7.452
IMS	*r*	.056	.089	.057	-.008	-.039	.075
	BF_{01}	7.333	5.500	7.268	8.760	8.029	6.307

Notes. IM = Intrusive Memories, IMS = Impact of Movie Scale, RTs = Reaction times in ms for trials with correct responses, PBI = Proactive behavioral shift index. For all tests, the H_0 specifies no significant correlations.

Discussion

In this randomized, sham-controlled, double-blind analogue study we examined causal relations between the activation of the left dlPFC, cognitive control, and intrusive memories after a trauma film in healthy individuals. In particular, we applied anodal, cathodal, and sham tDCS to the left dlPFC, a brain region that is highly relevant for cognitive control mechanisms as well as intrusive memories. Importantly, we relied upon the DMC framework to define cognitive control and investigated tDCS effects on indices of proactive control as well as correlations with intrusive memories. In contrast to our hypotheses, the results indicated no effects of tDCS over the left dlPFC on proactive control or intrusive memories after a trauma film. Moreover, the occurrence of intrusive memories was not related to proactive control.

Overall, individuals showed a positive PBI as well as slower reaction times and more errors in AY trials, which points towards a proactive control mode in our sample. This finding is in line with previous research suggesting proactive control as a default mode in healthy young adults (e.g., Braver, 2012; Gómez-Ariza et al., 2017; Paxton, Barch, Racine, & Braver, 2008). The predictions of the present study were that anodal tDCS over the left dlPFC increases and cathodal tDCS decreases proactive control, as compared to sham stimulation. However, there was no difference in performance in the AX-CPT across the three stimulation groups. This result is unexpected as theoretical accounts stress the central role of the left dlPFC in the DMC framework (Braver, 2012), and as previous neuroimaging studies have demonstrated correlations between left dlPFC activation and performance in the AX-CPT (e.g., Braver et al., 2009; Lesh et al., 2013; Lopez-Garcia et al., 2016). Moreover, previous research emphasized the central role of the left dlPFC for the cognitive control network in general (e.g., Blasi et al., 2006; Bunge et al., 2001; Curtis & D'Esposito, 2003) and for tasks that involve information maintenance in particular (e.g., Tremblay et al., 2014). However, our findings are not unprecedented. For example, Gómez-Ariza and colleagues (2017) also examined whether a manipulation of the left dlPFC via tDCS changes performance in the AX-CPT and found no stimulation effect. The present study confirms this finding by use of a larger sample size and altered task as well as stimulation parameters. Thus, our results further question the lateralization of proactive control within the prefrontal cortex as well as its susceptibility to tDCS. In general, cognitive control involves a complex neuronal network (e.g., Alvarez & Emory, 2006) and especially the DMC framework postulates time-dependent changes of activation patterns that have yet to be further empirically evaluated (Braver, 2012). More

attention should be paid to the role of the right dlPFC given that Gómez-Ariza and colleagues (2017) reported offline cathodal tDCS over the right dlPFC to decrease the PBI for error rates. This finding was surprising since previous conceptual and fMRI studies argued the right dlPFC to be less relevant for AX-CPT performance so that stimulation of this area was expected to be less effective (e.g., Braver et al., 2009). Thus, future stimulation studies must further clarify the lateralization of the dlPFC for the local and temporal dynamics of proactive control, preferably by combining neuromodulation with functional imaging.

Alternatively, the nonsignificant findings of the current study might also be a result of low sensitivity of the utilized proactive control task. We used the AX-CPT because it is a widely applied measure within the DMC framework, therefore enhancing comparability to previous research. In addition, it combines RTs and error rates, an important advantage given that a recent meta-analysis reported that for healthy individuals, effects of tDCS over the dlPFC on cognitive control are predominantly shown in altered RTs instead of error rates (Dedoncker et al., 2016a). However, reliability of the AX-CPT in healthy young adults has been subject to methodological discussion (Cooper, Gonthier, Barch, & Braver, 2017). As already mentioned, healthy young adults usually employ proactive control, leading to high performance in all trials except AY. Thus, as argued by Cooper and colleagues (2017), there might be ceiling effects that reduce discriminating power. This is especially relevant given that ceiling effects for anodal tDCS in healthy samples have also been discussed (e.g., Furuya et al., 2014). Indeed, in our sample we also found low split-half reliabilities for the AY and BX trials for error rates (see Table A.1 in the supplementary material). Hence, although the AX-CPT is an established task, future neurostimulation studies might profit from using alternative tasks or including no-go trials in the AX-CPT to decrease the baseline utilization of proactive control as suggested by Gonthier and colleagues (2016).

In addition to the absent effects of tDCS over the left dlPFC on performance in the AX-CPT as an indicator of proactive control, there was also no effect of tDCS on the occurrence of intrusive memories after the trauma film. These non-significant results underline a recent study by Voss and colleagues (2019) that also found no effects of 20 minutes tDCS over the left dlPFC on intrusive memories although activation of the left dlPFC has been frequently associated with intrusions (e.g., Anderson et al., 2004; Aupperle et al., 2012; Benoit et al., 2014). In accordance with the involvement of other brain areas in proactive control as described above, other brain areas have also been found to play a role in the regulation of unwanted images and thoughts (Anderson et al., 2004; Anderson et al., 2015; Kühn et al., 2012). Thus, future research should also focus on the modulation of intrusive memories via stimula-

tion of these areas. Interestingly, in an fMRI study, Benoit and colleagues (2014) reported increased engagement of the dlPFC when unwanted memories had to be suppressed and individuals with negative coupling between dlPFC and hippocampus during early suppression reported fewer intrusive memories later on. At the behavioral level, intrusive memories were assessed by use of the think/no-think paradigm (Anderson & Green, 2001). In this paradigm, participants are instructed to either suppress or recall memories of previous learned pictures and have to report their success in doing so. Although our assessment of intrusive memories is common within the trauma film research, it was retrospective, based on self-report and without any instruction to control intrusive memories. To avoid these limitations, future research might benefit from including the think/no think paradigm as reported by Benoit and colleagues (2014). This task might also be helpful to further explore the relationship between proactive control and intrusive memories. Given that there was no stimulation effect in the current study, we examined whether indices of proactive control prior to a stressful experience are linked to the development of post-stressor intrusive memories across stimulation groups. Surprisingly, there were no significant correlations. Future studies should further investigate the role of the dual mechanisms of control for posttraumatic symptomatology, especially in clinical samples. We proposed that a pre-stressor diminished proactive control would make it difficult to maintain current goals, use context information and ignore goal-irrelevant cues that activate stressful or traumatic representations, leading to higher levels of intrusive memories. However, it might also be that distressed individuals show reduced proactive control only after a traumatic event due to the constant preoccupation with other posttraumatic symptoms or possibly threatening stimuli. This preoccupation might lead to reduced cognitive resources for maintaining the cognitive more demanding proactive control mode. Thus, investigating causality within the DMC framework should further be focused in future research. In this context it should also be investigated whether an inflexible deployment of proactive and reactive control during different situational demands instead of per se diminished proactive control might be related to symptomatology.

Some methodological limitations of this study have to be addressed. First, effectivity of tDCS highly depends on stimulation period, current intensity, position of the reference electrode and online versus offline stimulation. Moreover, although some experimental studies have shown significant declining effects of cathodal tDCS on cognitive control, a recent meta-analysis questioned whether cathodal tDCS of the dlPFC has reliable effects on cognitive functioning (Dedoncker et al., 2016b). However, we used a stimulation protocol that demonstrated stable effects on cognitive control parameters in previous investigations (e.g., Wolken-

stein & Plewnia, 2013; Wolkenstein et al., 2014). Nevertheless, we cannot rule out that the extracephalic position of the reference electrode or the low current intensity in this study led to reduced stimulation strength or a rapid decline of stimulation effects (e.g., Moliadze et al., 2010; see also Voss et al., 2019). Furthermore, working mechanisms of tDCS are still controversial. Vöröslakos and colleagues (2018) emphasized that scalp-applied current intensity is influenced by skin, soft tissue, or skull thickness and therefore currents of 4-6 mA or higher are needed to achieve a high voltage gradient. It has yet to be shown how effects on neuronal activity can be maximized by use of alternative stimulation protocols (e.g., Chhatbar et al., 2017) or methods (e.g., Vöröslakos et al., 2018). Second, in this study, participants started to complete the AX-CPT 5 minutes after the onset of tDCS. Whereas tDCS lasted for additional 15 minutes, completion of the AX-CPT took approximately 25 minutes. Thus, 10 minutes of the AX-CPT were completed offline without active stimulation. We chose this procedure because tDCS-induced changes in brain activity were reported to persist for at least one hour (Nitsche et al., 2008) and offline designs successfully induced cognitive control shifts in previous studies (e.g., Dedoncker et al., 2016a; Hill et al., 2016; Vanderhasselt et al., 2013; Wolkenstein et al., 2014). However, in the study by Gómez-Ariza and colleagues (2017), tDCS effects on performance in the AX-CPT depended on target brain area and on online versus offline application. Thus, future tDCS studies that strive to achieve a better understanding of the temporal dynamics of the DMC have to take into account state-dependency and the differentiation between online and offline stimulation. Third, our participants were highly-educated healthy young adults who demonstrated low trait stress induced by intrusive memories. Future studies should also examine more heterogeneous samples to prevent floor effects for the occurrence of intrusive memories. In this context, it might also be worthwhile to preselect individuals based on criteria such as a disposition for intrusive memories or base-level performance in cognitive control to strengthen tDCS effects.

In conclusion, by re-examining the susceptibility of proactive control to neuromodulation of the left dlPFC; by investigating the causal role of the left dlPFC for intrusive memories after a trauma film; and by exploring associations between proactive control and intrusive memories, this study extends existing research on the DMC framework and on risk factors for posttraumatic symptoms. We chose the left dlPFC as a target brain area for tDCS because of its well-established relation to proactive control and intrusive memories as well as its suitability for tDCS manipulation. However, taking the nonsignificant findings of previous research (Gómez-Ariza et al., 2017; Voss et al., 2019) into account, our results further highlight the importance to consider alternative brain areas and boundary conditions that

might increase effects of neurostimulation in the future. Furthermore, our study is one of the first that explored whether the DMC framework also applies to post-stressor intrusive symptomatology. Clearly, more research in this field is needed, most of all research that also includes clinical samples and real-life assessments. Thus, our results are only a starting point for future explorations of whether cognitive control—the central component of human cognitive functioning—does conceptually and causally influence why some individuals cannot get rid of unwanted, intruding memories.

4. Study III

Cognitive Control Training to Reduce Intrusive Re-experiencing and Rumination in PTSD Patients: A Randomized Controlled Trial

Abstract

Deficits in cognitive control are assumed to play an important role in the development and maintenance of intrusive re-experiencing in Posttraumatic Stress Disorder (PTSD). Moreover, deficient cognitive control has been linked to rumination, a maladaptive processing style that maintains symptomatology. There is an emerging field of neurobehavioral interventions targeting cognitive control impairments but empirical evidence in PTSD is still limited. In this pilot study, we tested whether a 6-session cognitive control training influences intrusive re-experiencing, rumination (repetitive negative thinking and brooding) as well as comorbid depressive symptoms in a sample of $N = 33$ PTSD patients. The pilot study followed a double-blind, randomized, controlled design with a cognitive control versus placebo training group and three measurement points (baseline, post, 1-month follow-up). The cognitive control training consisted of Wells's Attention Training and the adaptive Paced Auditory Serial Addition Task. Both groups showed a significant reduction in re-experiencing, repetitive negative thinking, and depressive symptoms after training. Surprisingly, only the placebo group reported a significant reduction in brooding. Cognitive transfer tasks indicated no effects on working memory updating or inhibition. The results are in contrast to previous studies testing components of the training in healthy individuals with intrusive memories as well as in depressive individuals. Recommendations for future studies include differentiating between trauma types, administering additional online training sessions, and increasing sample size.

Introduction

In recent years, cognitive processes have been discussed as risk factors for the development and maintenance of psychopathology in general (e.g., Goschke, 2014) and Posttraumatic Stress Disorder (PTSD) in particular (Aupperle et al., 2012; Bomyea et al., 2012). Whereas traditional cognitive models focus mainly on the *content* of trauma-related cognitions, recent approaches highlight the neuropsychological basis of these cognitions with the aim to expand etiological models and enhance therapy outcome (Bomyea et al., 2015). In this context, cognitive control has been identified as a promising target for research and intervention.

Cognitive control refers to higher-order executive processes that assign limited cognitive capacity towards goal-relevant information. At the cognitive level, these processes include inhibiting distracting and goal-irrelevant stimuli, shifting between stimuli, or updating representations in working memory. At the neuronal level, they are associated with activation in the prefrontal brain network, for example in the dorsolateral prefrontal cortex (dlPFC; e.g., Miller & Cohen, 2001; Robinson et al., 2014). Impairments in cognitive control have been discussed to be responsible for variability in the development of posttraumatic stress symptoms such as re-experiencing (e.g., Aupperle et al., 2012). Re-experiencing can take the form of intrusive memories defined as vivid, unwanted, and recurring sensory fragments of the traumatic event (APA, 2013). It has been suggested that traumatized individuals with low cognitive control might exhibit difficulties in disengaging attention from trauma-related stimuli and in controlling activated representations of the trauma in working memory (Aupperle et al., 2012; Wessel et al., 2008). These difficulties are thought to result in a constant confrontation with internal or external trauma reminders and therefore facilitate persistent intrusive memories. Indeed, reduced cognitive control has been found in a wide range of PTSD patient groups (for overviews see Aupperle et al., 2012; Bomyea et al., 2012; Polak et al., 2012) and was associated with the development of intrusive memories in analogue samples (e.g., Verwoerd et al., 2011; Wessel et al., 2008). Moreover, disruptions in cognitive control are consistent with observed frontal lobe abnormalities linked to PTSD key symptoms (Aupperle et al., 2012; Etkin & Wager, 2007; Kühn & Gallinat, 2013).

In addition to the link between impaired cognitive control and PTSD symptoms, cognitive control might also influence maladaptive processing styles that maintain symptomatology, for example rumination. Similar to intrusive memories, rumination is a recur-

ring, cognitive phenomenon. However, it does not involve the short sensory reliving of the event but refers to uncontrollable, repetitive thinking about the trauma, its causes, and its consequences for a longer period of time (Ehlers & Clark, 2000). Moreover, rumination is not a key symptom of PTSD but has been identified as a maintaining factor that might provide internal cues for intrusive memories and inhibit the acceptance of the traumatic event (e.g., Ehlers & Clark, 2000; Ehring et al., 2008; Elwood, Hahn, Olatunji, & Williams, 2009; Szabo et al., 2017). For instance, Wild and colleagues (2016) reported that rumination predicted posttraumatic stress symptoms in paramedics over a period of two years. Importantly, persistent rumination has also been associated with reduced cognitive control as reflected by deficits in updating, inhibiting, or shifting away from irrelevant negative representations in working memory (e.g., Brinker et al., 2013; Joormann et al., 2010; Yang et al., 2016; Zetsche et al., 2018). Furthermore, the prefrontal cortex was also found to play an important role in ruminative thinking (e.g., De Raedt et al., 2017; Vanderhasselt et al., 2013).

Even though associations between reduced cognitive control and PTSD symptoms—such as intrusive re-experiencing—or maintaining factors—such as rumination—are empirically well-supported, the causal directions remain unclear. For example, low cognitive control might be a risk factor for the development of posttraumatic stress symptoms or merely a consequence of posttraumatic stress symptoms diminishing cognitive resources. One approach to clarify causality is to randomize PTSD patients to interventions that directly target cognitive control and examine the effects on symptomatology. Only few studies have followed this approach thus far. Schweizer and colleagues (2017), for example, tested whether a working memory training including trauma-related material affects cognitive control and emotion regulation and reduces symptom severity in an adolescent sample of Iranian PTSD patients. When compared to a placebo training, participants in the cognitive control group showed less error rates in a cognitive transfer task, less PTSD symptoms, and used more adaptive emotion regulation strategies after the training. However, the training did not influence maladaptive emotion regulation. Moreover, in a recent randomized, controlled trial, women diagnosed with PTSD after a sexual trauma completed a high- versus low-intensive, neutral training of resistance to proactive interference, a component of cognitive control that guides inhibition of no-longer relevant information in working memory (Bomyea et al., 2015). After the training, the high-intensive group showed higher working memory capacity and reduced intrusive re-experiencing as compared to the low-intensive group. Besides these studies on clinical populations, data

gained from healthy samples have demonstrated that a low-dose cognitive control training reduces intrusive memories of a distressing event as compared to a control training (Callinan et al., 2015; Nassif & Wells, 2014). Although these studies are highly informative, all of them were limited to only one specific trauma-type and none of them reported follow-up data. Moreover, research also investigating the effects of a cognitive control training on rumination in the context of PTSD is missing.

Given the link between cognitive control and rumination and the important role of rumination for maintaining PTSD, interventions that modulate cognitive control might also affect rumination and therefore influence symptomatology. Indeed, data from depressive samples show that practicing cognitive control alters rumination. For example, Siegle and colleagues (2007) designed a 2-week computerized training that aimed to increase prefrontal inhibitory control and thereby reduce symptom severity and rumination in unipolar depression. Specifically, the training included two well-established tasks: 1) Wells's Attention Training that enhances prefrontal activation and controlled selective attention despite automatic cognitions. This task has been administered in a number of studies focusing on anxiety disorders and was also used in the above mentioned trainings for intrusive memories in healthy individuals (Callinan et al., 2015; Nassif & Wells, 2014). 2) The adaptive Paced Auditory Serial Addition Task (PASAT), a task that increases activity in the prefrontal cortex and trains working memory in the face of frustration (e.g., Lazeron, Rombouts, de Sonneville, Barkhof, & Scheltens, 2003). Previous research indicated poor performance in the PASAT in traumatized individuals (e.g., Stein, Kennedy, & Twamley, 2002) and PTSD patients (e.g., Jenkins et al., 2000). Siegle and colleagues (2007) compared this training as an add-on to an outpatient day-treatment program with only the day-treatment program in depressed individuals. They found more reduced rumination and depressive symptoms as well as altered brain functioning in the cognitive control group as compared to the day-treatment only group. In the following years, several studies used parts of this training to decrease rumination in healthy and clinical samples. For example, a training only including the adaptive PASAT decreased rumination in response to a naturalistic stressor in a sample of high-ruminating healthy individuals (Hoorelbeke, Koster, Vanderhasselt, Callewaert, & Demeyer, 2015) as well as rumination, depressive symptoms, and maladaptive emotion regulation strategies in remitted depressed patients (Hoorelbeke & Koster, 2017), as compared to a placebo training. Yet, until now the effects of this cognitive control training on rumination have not been explored in PTSD patients.

Taken together, examining the effects of a cognitive control training in PTSD will extend earlier research in numerous ways. First, it provides further insights into the causal relation between basic cognitive mechanisms and intrusive re-experiencing, thereby helping to identify risk factors that contribute to the development of persistent PTSD symptoms. Second, although the importance of rumination for reinforcing PTSD symptoms is empirically well-supported, no study has explored whether modulating cognitive control in trauma patients also influences rumination. Thus, in this double-blind, randomized, controlled pilot study we investigate the effects of the computerized cognitive control training introduced by Siegle and colleagues (2007) on intrusive re-experiencing in a sample of mixed-trauma PTSD patients. Moreover, we examine effects on posttraumatic rumination. We chose the training by Siegle and colleagues (2007) since components of this training have been shown to reduce intrusive memories in healthy individuals and rumination in healthy and depressed individuals as described above. Participants were randomized to either 6-session cognitive control training or placebo training and completed baseline, post and 1-month follow-up assessments of cognitive measures and symptomatology. We hypothesized that the cognitive control training but not the placebo training would enhance cognitive control, reflected by training progress and performance increases in transfer tasks for working memory updating and inhibition. Furthermore, we expected the cognitive control group to report reduced PTSD symptoms—in particular reduced intrusive re-experiencing (primary outcome)—after training relative to the placebo group. Based on the evidences described above, we also hypothesized the cognitive control group to show reduced rumination operationalized as brooding and repetitive negative thinking after training as compared to the placebo group (secondary outcomes). Moreover, given the well-established effect of the training on depressive symptoms and the high comorbidity of depression and PTSD (Campbell et al., 2007), we expected the cognitive control training but not the placebo training to reduce comorbid depressive symptoms (secondary outcome). Lastly, we exploratory examined changes in general PTSD symptoms as well as in regulation strategies for intrusive memories and investigated the tolerability of the training.

Method

Design, randomization, and blinding

This randomized, double-blind pilot study followed a 2 x 3 design with the between-factor training group (cognitive control vs. placebo training) and the within-factor measurement point (baseline, post, 1-month follow-up). Allocation to training group was randomized via automated randomization software (randomizer.org). The randomization plan was generated by the first author prior to the start of the study and was then kept by the last author who informed the staff conducting the trainings about group allocation. Participants were informed that they would be randomly assigned to one of two groups that vary in training intensity but were blind for the exact training condition. Interviewers for symptom assessments were also blind for training condition and participants were instructed not to talk to the interviewer about the content of their training.[3]

Sample

Participants between 22 and 66 years of age (M = 41.97, SD = 11.29) were recruited from the waitlist of the outpatient center at LMU Munich. Participant flow is depicted in Figure 3.1. Participants with both a single traumatic experience and with complex traumatic experiences were included. Further inclusion criteria were a) age of consent, b) sufficient proficiency of the German language, and c) a diagnosis of PTSD as assessed by the German version of the Clinician-administered PTSD Scale for DSM-5 (CAPS; Müller-Engelmann et al., 2018; Weathers et al., 2013). Exclusion criteria were a) a primary diagnosis of major depressive disorder or bipolar disorder, a substance use disorder with less than 1 month of abstinence, a borderline personality disorder, or a history of psychosis, all assessed by the German version of the Structured Clinical Interview for DSM-IV (SCID I and II; Wittchen, Zaudig, & Fydrich, 1997), b) current psychological treatment, and c) impaired and not-corrected hearing disability. All participants were tested at the outpatient center, signed informed consent and were paid 8 Euro per hour for baseline, post and follow-up assessment. There was no reimbursement for training sessions. The study was ap-

[3] Please note that the blinding of the interviewers did not work for the first six participants. Here, interviews and trainings had to be conducted by the same person due to personnel changes in the research staff.

proved by the local ethics committee and conducted in accordance with the World Medical Association Declaration of Helsinki.

Interventions

Both trainings consisted of two computerized tasks. All auditory stimuli were presented via headphones. Mood (angry, frustrated, stressed) was assessed before and after each training session on a 5-point scale (1 = "not at all"; 5 = "very") via EPrime 2.0.

Cognitive control training. In line with Siegle and colleagues (2007), the cognitive control training aimed to activate the prefrontal cortex and increase control over contents of working memory. It contained German versions of Wells's Attention Training and the adaptive PASAT. (1) Wells's Attention Training was designed as part of the metacognitive therapy (Wells, 2000) to increase selective attention, attention switching as well as divided attention and to exercise prefrontal control in the face of automatic cognitions. We used a version retrieved from www.metakognitivetherapie.de. Participants were briefly informed that the goal of this task is neither to suppress disturbing thoughts or feelings nor to get distracted from them but to learn how to control attention. They were presented naturalistic sounds while looking on a fixation cross and instructed to focus on one sound at a time, switch between sounds, or count the number of sounds, despite co-occurring automatic thoughts. The task ran via EPrime 2.0 for approximately 12 minutes. (2) The adaptive PASAT was designed to activate prefrontal control in the face of amygdala activity by exercising working memory during low level negative affect (Gronwall, 1977; Siegle et al., 2007). We used a version of the adaptive PASAT by Hoorelbeke, Koster, Demeyer, Loeys, and Vanderhasselt (2016). Participants were presented a series of auditory digits (1-9) and instructed to indicate the sum of the last two digits presented by clicking on the corresponding digit on the screen (1-18). Task difficulty, as defined by speed of number presentation, was continuously adapted based on participants' performance. Each session began with an inter stimulus interval (ISI) of 3000 ms that speeded up or slowed down with 100 ms after four consecutive correct/incorrect responses. For each session, participants performed ten practice trials with individual feedback as well as 400 verum trials. To capture individual progress in task performance over time, we assessed Median ISI levels per session, with decreases indicating training progress. The task ran via INQUISIT 4.0 Millisecond software for approximately 15 minutes.

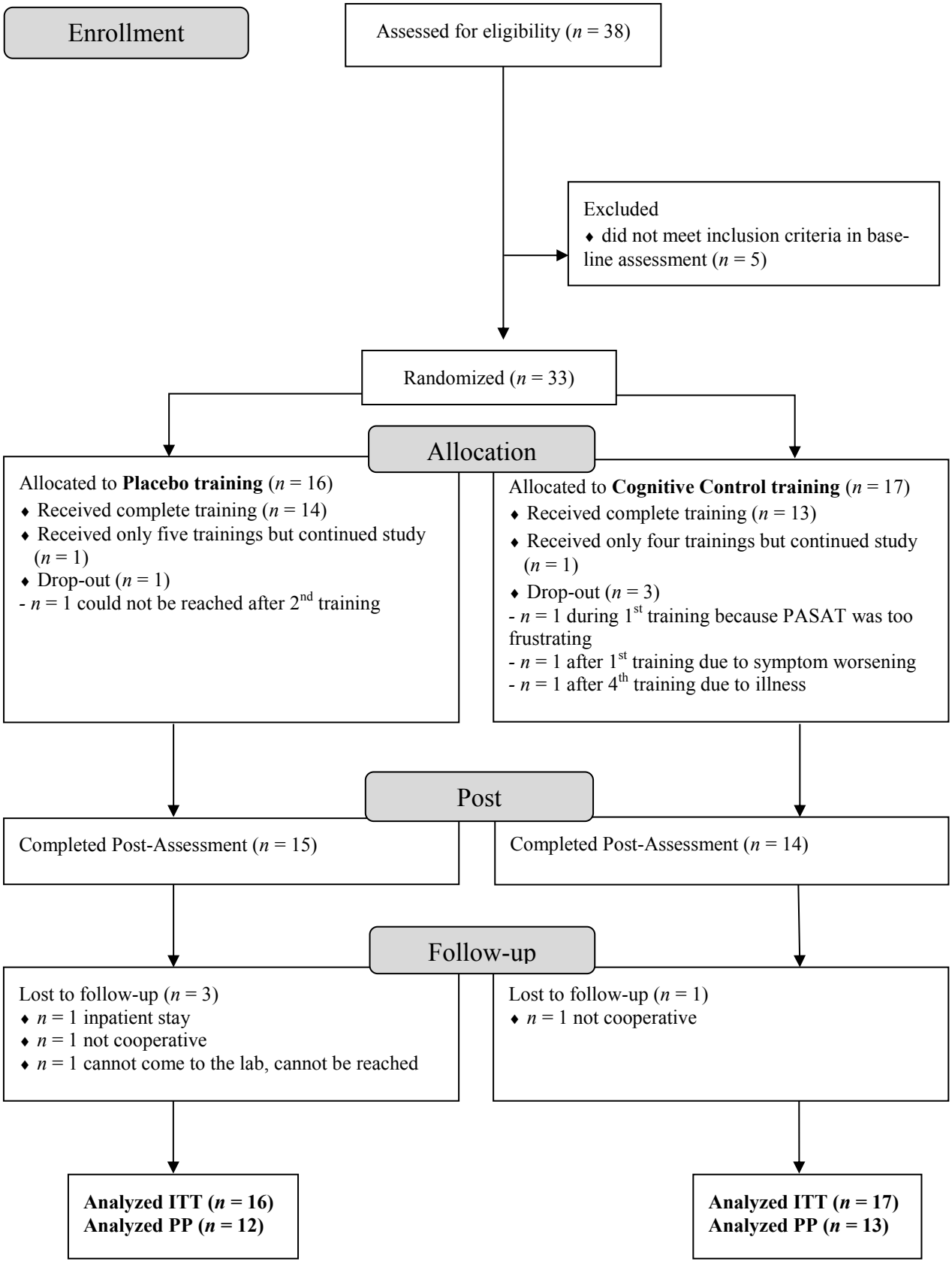

Figure 3.1. Flow of Participants.

Placebo training. For a placebo version of Wells's Attention Training, participants were also presented naturalistic sounds but only instructed to listen to them while looking on a fixation cross. Thus, no further instructions concerning attentional control were given. For the adaptive PASAT, we used a placebo version invented by Hoorelbeke and colleagues (2016). Instead of summing the digits, participants were instructed to immediately click on the last heard digit. All other task features were similar to the cognitive control training. Thus, although low-level attention might have been exercised in both trainings, no effects on cognitive control were expected for the placebo training.

Cognitive transfer tasks

To test transfer effects, we administered the *Operation-span Task* (O-span; Turner & Engle, 1989; Unsworth, Heitz, Schrock, & Engle, 2005) and the *Stroop Task* (Stroop, 1935), taken from the Millisecond Test Library (https://www.millisecond.com/download/library/) and ran via INQUISIT 4.0 Millisecond software.

Operation-span. The O-span is a complex span task to measure updating of working memory. In each trial, participants were presented a math problem, e.g., (2*3) + 1 = ?, as well as a possible solution and had to indicate whether this solution was correct or incorrect as fast as possible. After each math problem, a letter appeared on the screen for 800 ms. Having completed a set of variably frequent math problems and letters, participants had to indicate the correct order of the afore presented letter sequence by choosing the letters from a 4x3 matrix. The task consisted of a practice phase for letters (four trials), a practice phase for math problems (15 trials) and a practice phase in which both tasks were combined (three trials with two math problems and two letters). A time limit that restricted presentation for math problems in the final test phase was automatically calculated based on reaction times in the practice phase for math problems. In the final test phase, participants completed 15 trials containing three repetitions of five set sizes with three to seven letters. Furthermore, participants were instructed to answer at least 85 % of trials correctly and were informed about their current accuracy rate. The total task took about 20 minutes. Outcome was the O-span score as calculated from the sum of the number of letters in correctly recalled sets. Higher scores indicated better performance.

Stroop. The Stroop task assesses inhibitory control. Participants were shown a color word ("red", "black", "blue", "green") and asked to indicate the color in which the word was presented by pressing the corresponding response button as fast as possible. The tasks consisted

of congruent trials, in which color word and color were identical; incongruent trials, in which color word and color differed; and control trials, in which colored rectangles instead of words were presented. Participants had to complete a total of 84 trials presented in random order, with an inter-trial-interval of 200 ms and a 400 ms error feedback. A Stroop score was calculated as the difference between mean response times in incongruent and control trials, with higher scores indicating lower inhibitory control (Stroop, 1935).

Self-report measures

Primary outcome measures. PTSD symptoms were assessed by the German *PTSD checklist for DSM-5* (PCL-5) and the CAPS. The PCL-5 (Krüger-Gottschalk et al., 2017) is a 20-item scale that asks participants to rate distress caused by DSM-5 PTSD symptoms on a 5-point scale (0 = "not at all" to 4 = "very strong"). This measure was adapted to assess symptoms during the last week instead of the last month. The CAPS (Müller-Engelmann et al., 2018; Weathers et al., 2013) is a structured interview that assesses DSM-5 PTSD symptoms during the last month. Answers were rated on a 5-point scale (0 = "symptom is absent" to 4 = "extreme/incapacitating"). For both measures, a total score as well as scores for each symptom cluster (re-experiencing; avoidance; altered mood or cognition; hyperarousal and reactivity) were calculated, with higher scores indicating higher severity. Given that our main hypothesis is related to re-experiencing, the scores of these subscales were the primary outcomes and total scores as well as the other symptom scores were additional outcomes. Psychometric qualities of the PCL-5 and the CAPS have proven to be good (Krüger-Gottschalk et al., 2017; Müller-Engelmann et al., 2018).

Secondary outcome measures. Rumination in terms of brooding was measured by the 10-item *Response Styles Questionnaire* (RSQ-10D; German version by Huffziger & Kühner, 2012). Participants rated habitual thoughts and actions in response to sad or depressed mood on a 4-point scale, ranging from 1 = "almost never" to 4 = "almost always". The questionnaire consists of the subscales brooding (moody pondering, e.g., "I think 'Why do I have problems other people don't have?' ") and reflection (resolution-oriented analysis, e.g., "I write down what I am thinking about and analyze it."), with brooding representing a more maladaptive response style and therefore being in the focus of this study (Treynor, Gonzalez, & Nolen-Hoeksema, 2003). Furthermore, we administered the *Perseverative Thinking Questionnaire* (PTQ; German version by Ehring et al., 2011), a 15-item questionnaire that assesses rumination as repetitive thinking in response to negative experiences independent of content (e.g., "I

keep thinking about the same issue all the time"). Items were rated on a 5-point scale (1 = "never" to 5 = "almost always"). Internal consistencies of the RSQ-10D brooding subscale (Cronbach's α = .76-.93) and of the PTQ total score (Cronbach's α = .96-.97) were acceptable to excellent. Depressive symptoms were captured by the *Inventory of Depressive Symptoms-self rating* (IDS-SR; German version by Drieling, Schärer, & Langosch, 2007). The 30-item questionnaire asks participants to indicate how he or she felt during the past seven days on up to four possible responses that range in intensity (e.g., 0 = "I do not feel sad"; 3 = "I feel sad nearly all of the time."). Internal consistency of the IDS-SR was good to excellent (Cronbach's α = .85-.91). For all measures, higher scores indicated more symptoms.

Additional measures. For exploratory analyses, we applied a modified version of the 19-item *Response to Intrusions Questionnaire* (RIQ; e.g., Clohessy & Ehlers, 1999; Ehring et al., 2008) to capture how participants deal with intrusive memories. The RIQ consists of five sub-scales measuring suppression, rumination, dissociation, the consumption of alcohol or drugs (1 item), and the distraction with music or TV (1 item). For this study, only the first three sub-scales were analyzed. Answers were given on a 4-point scale (0 = "never" to 3 = "always"). Higher scores indicated a more frequent use of the response style. Internal consistency of the subscales was acceptable to good except for dissociation (suppression: Cronbach's α = .72-.80, rumination: Cronbach's α = .76-.85, dissociation: Cronbach's α = .52-.58). Participants' evaluation of the training was assessed by a short questionnaire consisting of four visual analogue scales. Participants rated the trainings' difficulty, logic, and helpfulness for improving symptomatology as well as how competent they had felt in doing the training (0 = "not at all" to 100 = "very"). Furthermore, participants were asked to make a guess whether they were in the high or low intensive training condition.

Control measures

Neuropsychological measures. To compare baseline neuropsychological characteristics between the two groups, we administered paper-pencil versions of the *Trail Making Test* (TMT A/B; Reitan, 1992) to measure visual-motor conceptual screening and cognitive flexibility, the *Digit Span Test* forward and backward (a version similar to the Wechsler Adult Intelligence Scale; Petermann, 2012) to assess short-term and working memory capacity, and the vocabulary test (WST; Schmidt & Metzler, 1992) to estimate verbal intelligence.

Childhood maltreatment. The *Childhood Trauma Questionnaire - Short Form* (CTQ; German version by Wingenfeld et al., 2010) was used to check group differences in childhood

maltreatment. The CTQ is a 28-item self-report measure that retrospectively assesses emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect during childhood. Participants are asked to rate a number of statements (e.g., 'When I was growing up I didn't have enough to eat') on a 5-point scale (1 = "never true" to 5 = "very often true"). An overall score was used, with higher score indicating a higher amount of abuse and neglect.

Procedure

After a telephone screening for a first check of eligibility, potential participants were invited for the baseline assessment. Having signed written informed consent, sociodemographic data were assessed and PCL-5, CAPS, SCID I & II were administered. If no exclusion criterion was met, participants completed the neuropsychological tasks as well as a baseline assessment of the transfer tasks. Furthermore, participants were given the self-report measures (CTQ, RSQ-10D, PTQ, IDS-SR, RIQ) and instructed to complete them at home and bring them to the first training session. Next, participants were randomized to a training group, received training instructions, and performed six training sessions within a period of approximately 14 days, with a maximum of one session per day. Having completed the training, participants were invited for the post assessment in which they completed the CAPS, the PCL-5, the transfer tasks, the self-report measures (except CTQ) as well as the training evaluation. Participants returned to the lab approximately four weeks later for a follow-up assessment that followed the identical procedure (except training evaluation). Upon completion of the follow-up, participants were debriefed and reimbursed. Please note that additional clinical questionnaires that were only relevant for the following psychological treatment in the outpatient center were completed during the assessments.

Data analyses

Data were analyzed using SPSS® Version 24.0. All effects were tested at the .05 α-level (two-tailed). Baseline group differences on demographic, clinical, and neuropsychological measures as well as drop-out rates for the training were examined using independent sample *t* tests or Mann-Whitney-U-tests for continuous measures and Fisher's Exact tests for categorical measures. Group differences in training evaluation were tested using a Multivariate Analysis of Variance (MANOVA) with perceived difficulty, logic, and helpfulness of the training as well as perceived individual competence as dependent variables. For all further analyses, linear mixed models (LMMs) were used. LMMs are an intention-to-treat (ITT) approach that

includes all available data and handles missing data under the missing at random assumption (Gueorguieva & Krystal, 2004). Thus, the ITT-sample comprised all randomized participants and missing data were not imputed. A compound symmetric covariance structure was specified for all models first. If these models failed to converge, an identical covariance structure was used. To test the effects of training session on mood (angry, frustrated, stressed), difference scores (Δ; post-training assessment minus baseline assessment) were computed for each session, with positive scores indicating an increase of anger, frustration, or stress. Group differences, changes over time, and group x time interactions were analyzed. The basic model was a two-level (participants and measurement points) repeated-measures design with the difference scores as dependent variables and time effects varying across participants (random effects) and across training group (cross-level interaction). Group was dummy coded (0 = placebo training, 1 = cognitive control training). When analyzing training task progress, the basic model was a two-level (participants and measurement points) repeated-measures design with Median ISI of the training task as dependent variable. Time effects varied across participants (random effects). Importantly, in accordance with Hoorelbeke and colleagues (2016), separate analyses for each training group were conducted since outcome measures of the training tasks differed. Training progress was indicated by a decrease in Median ISI over time. For main analyses on cognitive transfer and clinical variables, the basic model was also a two-level (participants and measurement points) repeated-measures design. An outcome variable was predicted by dummy codes of time, group, and their interaction. The time dummies reflected the differences between baseline and post-training (t1, coded as 0, 1, 0) and between baseline and follow-up (t2, coded as 0, 0, 1). The group dummies reflected the differences between placebo (0) and cognitive control training (1). Time effects varied across the group (cross-level interaction) and participants (random effects). The O-span score and Stroop score were used as outcome variables when testing cognitive transfer effects. Primary clinical outcomes were PCL-5 and CAPS re-experiencing scores and secondary clinical outcomes were RSQ-10D brooding, PTQ, and IDS-SR scores. Additionally, we conducted exploratory analyzes for training effects on RIQ subscales, PCL-5 and CAPS total scores as well as other PCL-5 and CAPS symptom clusters. For the CAPS, only baseline to follow-up assessments were compared because the interview referred to a 4-week interval that did not adequately capture symptom changes after two weeks of training. In addition to ITT analyses, per-protocol (PP) analyses were performed that only included participants who completed all assessments and attended at least four training sessions. For the primary and secondary clinical outcomes, Cohen's *d* was calculated from the observed means and standard deviations ac-

cording to Carlson and Schmidt (1999; see also Morris, 2008). Differences within group were computed via $d_{within} = (M_i - M_{pre})/SD_{pooled}$ with $SD_{pooled} = \sqrt{[((n_i - 1)SD_i^2 + (n_{pre} - 1)SD_{pre}^2)/(n_i + n_{pre} - 2)]}$. Differences between within-group effects were computed via $\Delta d = ((M_{iCC} - M_{preCC}) - (M_{iPl} - M_{prePl}))/SD_{pooled\text{-}pre}$ with $SD_{pooled\text{-}pre} = \sqrt{[((n_{CC} - 1)SD_{preCC}^2 + (n_{Pl} - 1)SD_{prePl}^2)/(n_{CC} + n_{Pl} - 2)]}$.

Results

Baseline group characteristics

Descriptive statistics for ITT and PP demographic, clinical, and neuropsychological control measures are presented in Table 3.1. The two groups did not differ in any of these measures. In general, baseline PTSD symptom severity as measured via CAPS can be considered as moderate in the present sample (ITT: M = 36.03, SD = 9.03; PP: M = 35.52, SD = 9.28), ranging from 14 to 58. 78.80 % of the sample (ITT) reported comorbid DSM-IV disorders as assessed by SCID I. Comorbid disorders included current or past mood disorders (45.45 %), anxiety disorders (21.82 %), substance use disorders (18.18 %), eating disorders (12.73 %), and somatoform disorders (1.82 %). Baseline IDS-SR scores indicated a severe level of depressive symptoms across all participants (ITT: M = 41.32, SD = 13.19; PP: M = 38.18, SD = 11.66).

Table 3.1

Demographic and Control Variables by Group for the Intention-to-treat (ITT) and the Per-protocol (PP) Sample

	ITT			PP		
Variable	Cognitive Control (n = 17)	Placebo (n = 16)	p	Cognitive Control (n = 13)	Placebo (n = 12)	p
Age in years ($M \pm SD$)	41.59 ± 10.24	42.38 ± 12.63	*ns*	40.92 ± 11.32	43.08 ± 13.60	*ns*
Gender (male: female)	2:15	5:11	*ns*	2:11	3:9	*ns*
Education in years ($M \pm SD$)	15.24 ± 4.58	14.50 ± 3.52	*ns*	14.69 ± 5.11	14.17 ± 2.69	*ns*
Days from pre to post ($M \pm SD$)	19.86 ± 3.94	18.67 ± 3.15	*ns*	19.92 ± 4.09	18.42 ± 3.03	*ns*
Days from post to follow-up ($M \pm SD$)	30.77 ± 4.25	30.42 ± 4.10	*ns*	30.77 ± 4.25	30.42 ± 4.10	*ns*
Duration of PTSD in months[a] ($M \pm SD$)	99.71 ± 132.69	144.00 ± 154.52	*ns*	124.60 ± 153.13	151.50 ± 163.43	*ns*
Current use of psychopharmaca (yes: no)	11:6	8:8	*ns*	10:3	6:6	*ns*
Previous psychological treatment (yes: no)	15:2	12:4	*ns*	11:2	8:4	*ns*
CTQ total score ($M \pm SD$)	60.81 ± 24.74	68.66 ± 24.41	*ns*	59.13 ± 25.57	63.17 ± 23.51	*ns*
TMT-A in sec ($M \pm SD$)[b]	45.59 ± 74.35	32.06 ± 8.90	*ns*	51.46 ± 84.88	31.33 ± 3.85	*ns*
TMT-B in sec ($M \pm SD$)[b]	99.35 ± 119.78	73.00 ± 24.05	*ns*	107.62 ± 136.88	69.67 ± 15.23	*ns*
Digit span forwards ($M \pm SD$)	7.76 ± 2.20	8.25 ± 2.18	*ns*	7.38 ± 2.14	8.50 ± 2.07	*ns*
Digit span backwards ($M \pm SD$)	6.41 ± 2.09	7.56 ± 2.45	*ns*	6.00 ± 1.68	7.92 ± 2.39	*ns*
Vocabulary test ($M \pm SD$)	30.94 ± 6.24	30.88 ± 4.87	*ns*	29.46 ± 6.41	30.75 ± 4.88	*ns*

Notes. PTSD = Posttraumatic Stress Disorder, CTQ = Childhood Trauma Questionnaire, TMT = Trail Making Test. [a] scores only include participants who could indicate the number of months; [b] inverse transformation was applied to TMT scores for significance testing to reduce the impact of outliers,
ns = nonsignificant.

Training evaluation

The number of participants who started the training but did not complete all six sessions did not differ between the two groups (p = .656). Analyses of training evaluation were performed on all individuals who completed the post assessment. Across groups, participants rated the training as moderately difficult (M = 49.70, SD = 24.90), moderately logical (M = 59.87, SD = 29.05), and moderately helpful for improving symptomatology (M = 51.83, SD = 29.69). Furthermore, they felt moderately competent in doing the training (M = 56.60, SD = 24.56). There was a significant effect of training group on this evaluation, $F(4, 24) = 5.73$, p = .002, Wilk's Λ = .511, η_p^2 = .49. Separate ANOVAs were conducted for each dependent variable, with each ANOVA evaluated at an alpha level of .0125. A significant group difference emerged on difficulty of the training, $F(1, 27) = 11.04$, p = .003, η_p^2 = .29, with participants in the cognitive control group perceiving the training as more difficult (M = 63.34, SD = 16.31) than participants in the placebo group (M = 36.96, SD = 25.17). Group effects on all other dependent variables did not reach significance. At post assessment, participants' estimates whether they were in the high versus low intensity training condition were at about chance level, with 51.70 % of participants making a correct estimate. Descriptive statistics of changes in mood during training sessions are depicted in Table B.1 in the supplementary material. Data indicates more frustration, stress, and anger in the cognitive control compared to the placebo group. ITT-analyses revealed significant effects of training group for frustration (B = 0.89, SE = 0.26, 95% CI [0.37, 1.41], p = .001), stress (B = 0.58, SE = 0.29, 95% CI [0.02, 1.15], p = .042), and anger (B = 0.77, SE = 0.25, 95% CI [0.27, 1.26], p = .002), with participants in the cognitive control group showing higher difference scores. No other effects reached significance. Results in the PP-sample confirmed these findings except that there was only a trend towards higher stress levels in the cognitive control group (B = 0.55, SE = 0.33, 95% CI [-0.10, 1.19], p = .098). However, LMM analyses should be interpreted with caution since visual inspection of residual plots showed violations of the assumption of normality as well as extremely low variance in difference scores, with only a few individuals reporting mood changes at all.

Training task progress

Training task progress for each group for the ITT- and the PP-sample is displayed in Figure 3.2. Importantly, as suggested by Hoorelbeke and colleagues (2016), separate analyses for each training group were performed since outcome measures of both training tasks were of a

different nature. Analyses indicated a trend towards a performance improvement of participants in the placebo group across sessions (ITT: B = -29.23, SE = 15.17, 95% CI [-59.90, 1.45], p = .061; PP: B = -30.36, SE = 17.97, 95% CI [-66.76, 6.03], p = .099)[4]. However, there was a significant extreme value that could not be handled by data transformation. After removing this participant from the analyses, the trend disappeared (ITT: B = -19.98, SE = 36.82, 95% CI [-95.51, 55.55], p = .592; PP: B = -20.87, SE = 41.36, 95% CI [-107.15, 65.41], p = .619). For the cognitive control group, both ITT- and PP-analyses showed a trend towards a significant improvement across training sessions (ITT: B = -158.50, SE = 88.18, 95% CI [-345.64, 28.63], p = .091; PP: B = -167.93, SE = 84.96, 95% CI [-350.75, 14.89], p = .069).

Cognitive transfer outcomes

Mean scores for baseline, post, and follow-up assessments of cognitive transfer tasks are provided in Table 3.2. Table 3.3 depicts the results of the LMMs for the cognitive transfer outcomes in the ITT- and in the PP-sample. ITT-analyses indicated no significant effects on updating of working memory as measured with the O-span task or on inhibitory control as measured with the Stroop task. For the Stroop task, there was a significant extreme value at the baseline assessment for one participant in the ITT-sample. Excluding this participant did not change results. Analyses in the PP-sample confirmed the results for the O-span task. For the Stroop task, the main effect of group reached significance, indicating less inhibitory control in the cognitive control group.

[4] For one participant, the PASAT score for the third training session was missing due to computer malfunction. Thus, although the participant had received the training, this data point could not be included in the analyses.

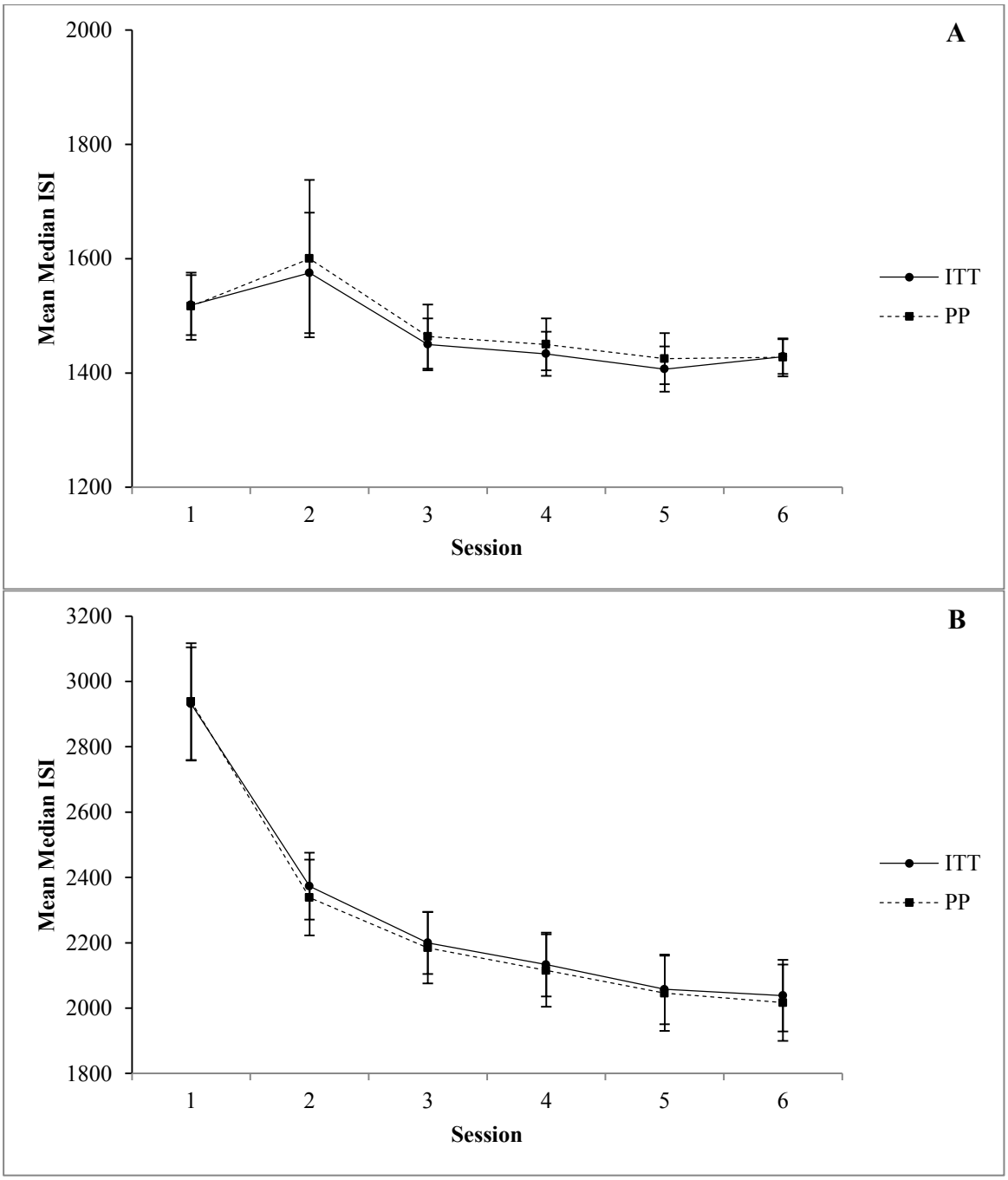

Figure 3.2. Means and Standard Deviations for Training Progress in the Intention-to-treat (ITT) and the Per-protocol (PP) Sample for (A) Placebo Group and (B) Cognitive Control Group.

Table 3.2

Group Characteristics for Dependent Variables for the Intention-to-treat (ITT) and the Per-protocol (PP) Sample

	Training Group											
	Cognitive Control						Placebo					
	Baseline		Post		Follow-up		Baseline		Post		Follow-up	
Variable	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
ITT (*n* = 33)	***n* = 17**		***n* = 14**		***n* = 13**		***n* = 16**		***n* = 15**		***n* = 12**	
Operation-span	30.06[a]	19.38	31.46	17.94	30.31	17.54	36.25	17.03	37.93	17.70	42.50	20.34
Stroop	330.86	444.99	433.80	318.93	277.86	249.10	371.77	623.49	383.64[b]	295.26	229.67	173.86
PCL-5 Re-experiencing	12.41	5.08	10.86	5.02	10.62	4.27	10.63	4.32	9.00	5.30	6.92	5.11
CAPS Re-experiencing	9.82	3.05	-	-	8.70	3.04	9.06	3.40	-	-	5.75	4.52
Brooding	12.76	3.15	12.07	3.69	11.31	4.50	13.13	3.58	9.73	3.31	10.17	4.30
Repetitive Negative Th.	36.04	12.04	35.50	11.78	34.31	12.80	35.75	14.77	32.33	16.94	28.58	16.41
Depressive Symptoms	44.00	12.68	39.54	14.05	37.45	13.01	38.47	13.52	33.84	17.47	26.60	15.44
PP (*n* = 25)	***n* = 13**		***n* = 13**		***n* = 13**		***n* = 12**		***n* = 12**		***n* = 12**	
Operation-span	29.69	19.00	31.46	17.94	30.31	17.54	36.08	17.77	37.92	18.95	42.50	20.34
Stroop	493.24	357.60	444.23	329.46	277.86	249.10	256.31	385.59	394.75 [b]	310.27	229.69	173.86
PCL-5 Re-experiencing	12.62	5.14	10.62	5.14	10.62	4.27	9.58	4.46	7.92	5.28	6.92	5.11
CAPS Re-experiencing	9.77	3.30	-	-	8.69	3.04	8.33	3.39	-	-	5.75	4.52
Brooding	13.08	3.48	12.38	3.64	11.31	4.50	12.58	3.85	9.42	2.78	10.17	4.30
Repetitive Negative Th.	35.93	10.45	35.38	12.26	34.31	12.80	34.92	14.76	32.00	15.89	28.58	16.41
Depressive Symptoms	42.50	11.37	38.85	14.36	37.45	13.01	33.50	10.48	28.72	14.23	26.60	15.44

Notes. PCL-5 = PTSD checklist for DSM-5, CAPS = Clinician administered PTSD Scale for DSM-5. [a]one missing value due to abort by participant [b]one missing due to computer malfunction.

Table 3.3

Results of the Linear Mixed Models for Cognitive Transfer Variables in the Intention-to-treat (ITT) and in the Per-protocol (PP) Sample

	Operation-span			Stroop		
Fixed parts	*B*	*SE*	*p*	*B*	*SE*	*p*
ITT (*n* = 33)						
Intercept	36.25	3.38	**<.001**	371.77	98.68	**<.001**
Group	-6.19	4.71	.193	-40.90	137.49	.767
Time (t1)	0.83	3.80	.828	21.92	118.75	.854
Time (t2)	6.23	4.23	.146	-102.84	124.25	.411
Group x t1	0.88	5.58	.875	44.43	167.62	.792
Group x t2	-5.67	5.88	.338	-10.79	173.35	.951
PP (*n* = 25)						
Intercept	36.08	3.74	**<.001**	256.31	77.75	**.002**
Group	-6.39	5.18	.222	236.92	107.82	**.032**
Time (t1)	1.83	4.24	.668	115.45	102.13	.264
Time (t2)	6.42	4.24	.139	-26.63	98.96	.789
Group x t1	-0.06	5.88	.991	-164.46	139.54	.245
Group x t2	-5.80	5.88	.331	-188.75	137.24	.176

Notes. t1= dummy for baseline-post comparison; t2= dummy for baseline-follow-up comparison; ITT Operation-span: baseline score for one participant is missing due to abort by participant; ITT & PP Stroop: post score for one participant is missing due to computer malfunction.

Clinical outcomes

Primary outcomes. Mean scores for baseline, post, and follow-up assessment are depicted in Table 3.2. Table 3.4 shows the results of the LMMs. For PCL-5 re-experiencing and CAPS re-experiencing, all ITT-participants reported a significant symptom improvement from baseline to follow-up (PCL-5: d_{withinCC} = -0.38, d_{withinPl} = -0.79; CAPS: d_{withinCC} = -0.37, d_{withinPl} = -0.85) but there was no significant group x time interaction. Repeating the analyses in the PP-sample did not change the significant main effect of time for the CAPS (d_{withinCC} = -0.34, d_{withinPl} = -0.65) but for the PCL-5 the main effect of time missed the significance level.

Table 3.4

Results of the Linear Mixed Models for Primary and Secondary Outcome Measures in the Intention-to-treat (ITT) and in the Per-protocol (PP) Sample

	Re-experiencing (PCL-5)			Re-experiencing (CAPS)			Depressive Symptoms (IDS-SR)			Brooding (RSQ-10D)			Repetitive Negative Thinking (PTQ)		
Fixed parts	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*
ITT (*n* = 33)															
Intercept	10.63	0.97	**<.001**	9.06	0.78	**<.001**	38.47	2.55	**<.001**	13.13	0.66	**<.001**	35.75	2.32	**<.001**
Group	1.79	1.36	.192	0.76	1.09	.489	5.53	3.56	.125	-0.36	0.92	.695	0.29	3.23	.928
Time (t1)	-1.57	1.24	.212	-	-	-	-4.17	3.00	.172	-3.34	0.84	**<.001**	-3.33	2.39	.167
Time (t2)	-2.92	1.36	**.036**	-2.91	.99	**.007**	-6.08	3.22	.064	-2.54	0.90	**.007**	-6.33	2.68	**.020**
Group x t1	-0.16	1.78	.930	-	-	-	1.03	4.32	.813	2.56	1.21	**.041**	3.78	3.45	.275
Group x t2	1.07	1.89	,573	1.81	1.38	.199	1.49	4.52	.744	0.73	1.27	.566	4.71	3.71	.208
PP (*n* = 25)															
Intercept	9.58	1.12	**<.001**	8.33	0.93	**<.001**	33.50	2.56	**<.001**	12.58	0.79	**<.001**	34.92	2.92	**<.001**
Group	3.03	1.55	.055	1.44	1.28	.274	9.01	3.55	**.014**	0.49	1.10	.654	1.02	4.05	.803
Time (t1)	-1.67	1.42	.247	-	-	-	-4.78	3.01	.120	-3.17	0.88	**.001**	-2.92	1.32	**.035**
Time (t2)	-2.67	1.42	.067	-2.58	1.02	**.018**	-6.90	3.01	**.027**	-2.42	0.88	**.008**	-6.33	3.07	**.043**
Group x t1	-0.33	1.97	.867	-	-	-	1.12	4.18	.790	2.47	1.22	**.046**	2.37	1.83	.207
Group x t2	0.67	1.97	.737	1.51	1.41	.295	1.85	4.18	.661	0.65	1.22	.596	4.71	4.26	.273

Notes. t1= dummy for baseline-post comparison; t2= dummy for baseline-follow-up comparison; PCL-5 = PTSD checklist for DSM-5, CAPS = Clinician Administered PTSD Scale for DSM-5, IDS-SR = Inventory of Depressive Symptoms – Self-Rating, RSQ-10D = Response Styles Questionnaire, PTQ = Perseverative Thinking Questionnaire.

Secondary outcomes. Mean scores for baseline, post, and follow-up assessments are also shown in Table 3.2. Looking at depression, there was a non-significant trend towards a reduction of depressive symptoms from baseline to follow-up in all ITT-participants but no differences between groups or group x time interactions. In the PP-sample, this reduction was significant ($d_{withinCC}$ = -0.41, $d_{withinPl}$ = -0.52). Additionally, there was a significant group effect in the PP-sample, with participants in the cognitive control group reporting in general more depressive symptoms. Regarding rumination, ITT-analyses showed that brooding scores significantly declined in the short term ($d_{withinCC}$ = -0.20, $d_{withinPl}$ = -0.98) as well as in the long term ($d_{withinCC}$ = -0.38, $d_{withinPl}$ = -0.76) in all participants. However, there was a significant group x t1 interaction (Δd = 0.75). This interaction was broken down by conducting separate LMMs for the placebo and for the cognitive control group: The models specified were identical to the main models but excluded main effect and interaction term for the training conditions. In contrast to our hypothesis, these analyses showed a significant reduction of brooding from baseline to post assessment only in the placebo group (B = -3.34, SE = 0.85, 95% CI [-5.18, -1.51], p = .002) but not in the cognitive control group (B = -0.79, SE = 0.83, 95% CI [-2.51, 0.94], p = .355). This result pattern was also found in the PP-sample. For repetitive negative thinking assessed by the PTQ, ITT-analyses indicated a significant reduction from baseline to follow-up across training groups ($d_{withinCC}$ = -0.14, $d_{withinPl}$ = -0.46) but no significant interactions. In the PP-sample, a model with an identical covariance structure did not converge. Therefore, we repeated the analyses with a fixed slope for the t1 dummy variable. Now, the model converged and confirmed the results of the ITT-sample.

Additional outcomes. Group characteristics for the additional outcome measures for each time point are summarized in Table B.2 in the supplementary material. Results of ITT-analyses revealed that, compared to baseline, all participants showed significantly less suppression of intrusive memories and less rumination in response to intrusive memories at post assessment (suppression: B = -1.62, SE = 0.79, 95% CI [-3.23, -0.02], p = .048; rumination: B = -2.89, SE = 1.04, 95% CI [-4.97, -0.80], p = .007) and at follow-up assessment (suppression: B = -2.20, SE = 0.86, 95% CI [-3.94, -0.47], p = .014; rumination: B = -3.10, SE = 1.16, 95% CI [-5.41, -0.78], p = .010). Unexpectedly, the group x time interaction reached significance for the suppression subscale, both for the post assessment (B = 2.36, SE = 1.13, 95% CI [0.06, 4.66], p = .045) and the follow-up assessment (B = 3.24, SE = 1.20, 95% CI [0.81, 5.66], p = .010). These interactions were quantified by separate LMMs for the placebo and for the cognitive control training group that excluded main effect and interaction term for the training

conditions. For the placebo group, analyses showed decreased suppression of intrusive memories in the short-term (B = -1.62, SE = 0.79, 95% CI [-3.24, 0.00], p = .050) and in the long-term (B = -2.12, SE = 0.85, 95% CI [-3.85, -0.38], p = .019). This reduction was not found in the cognitive control training group (post: B = 0.76, SE = 0.78, 95% CI [-0.82, 2.35], p = .335; follow-up: B = 0.90, SE = 0.81, 95% CI [-0.73, 2.53], p = .271). Repeating the analyses in the PP-sample confirmed these findings. Total PCL-5 and CAPS scores decreased from baseline to follow-up across all ITT-participants (PCL-5: B = -8.46, SE = 3.98, 95% CI [-16.39, -0.53], p = .037; CAPS: B = -9.38, SE = 2.79, 95% CI [-15.00, -3.76], p = .002). In PP-participants, the symptom improvement from baseline to follow-up for PCL-5 total scores just missed the significance level (B = -7.67, SE = 3.93, 95% CI [-15.52, 0.18], p = .055) and the main effect of group reached significance (B = 10.22, SE = 4.92, 95% CI [0.41, 20.03], p=.041), with the cognitive control group showing more severe symptomatology. The PP-results for the CAPS total scores confirmed the ITT-analyses but a main effect of group was also additionally found (B = 7.41, SE = 3.43, 95% CI [0.52, 14.30], p = .036). Regarding symptom clusters, there was a significant reduction from baseline to follow-up in symptoms of avoidance across ITT-groups (PCL-5: B = -2.35, SE = 0.73, 95% CI [-3.80, -0.89], p = .002; CAPS: B = -1.51, SE = 0.49, 95% CI [-2.51, -0.52], p = .004). For the CAPS, we also found a significant reduction in hyperarousal and reactivity symptoms from baseline to follow-up in both ITT-groups (B = -2.72, SE = 0.76, 95% CI [-4.24, -1.19], p = .001) and a significant main effect of group indicating more hyperarousal and reactivity symptoms in the cognitive control as compared to the placebo group (B = 2.25, SE = 0.83, 95% CI [-0.58, 3.91], p = .009). PP-analyses were mostly in line with these results. However, for the PCL-5 hyperarousal and reactivity subscale, a main effect of group also reached significance in the PP-sample (B = 4.15, SE = 1.47, 95% CI [1.22, 7.07], p = .006), indicating that individuals in the cognitive control group showed more symptoms than individuals in the placebo group.

Discussion

This pilot study evaluated the effects of a computerized 6-session cognitive control training in PTSD patients with different traumatic experiences. In particular, we tested whether a training developed by Siegle and colleagues (2007) modified intrusive re-experiencing as well as rumination and depression, as compared to a placebo training. Although performance patterns in the cognitive control group indicated a non-significant improvement in the training task, we did not find significant transfer effects on other cognitive control measures. Moreo-

ver, in contrast to our hypotheses, participants in the cognitive control and in the placebo group showed a reduction in intrusive re-experiencing, in rumination as defined by repetitive negative thinking, and in depressive symptoms over time. Surprisingly, a decline in ruminative brooding did only reach significance in the placebo but not in the cognitive control group. Additional analyses demonstrated that all participants reported a decrease in PTSD avoidance and hyperarousal and reactivity symptoms and ruminated less in response to intrusive memories after the trainings. Unexpectedly, participants in the placebo but not in the cognitive control group also showed a decrease in suppressing intrusive memories.

Most symptom measures in this pilot study indicated that participants benefited from the trainings but no differential improvements occurred between the two training groups. A number of explanations may account for these absent differences. Firstly, both trainings might have influenced cognitive control. However, in the first part of the placebo training, participants only listened to different sounds without completing a cognitive task at all. The second part consisted of a placebo version of the adaptive PASAT, a task that had been implemented in studies that demonstrated differential effects on rumination and depressive symptoms before (Hoorelbeke et al., 2016; Hoorelbeke & Koster, 2017). Hence, we would argue that the placebo training did not influence cognitive control although we cannot fully rule this out.

Secondly, the cognitive control training might not have influenced cognitive control at all. Our results indicate non-significant performance improvements in the cognitive control training task but these changes did not translate into generalized improvements in transfer tasks. We decided to use far transfer tasks to rule out that strategy training drives the effects as possible in near transfer tasks. In particular, we applied two well-established tasks of working memory updating and inhibition, components of cognitive control that had been associated with posttraumatic stress symptoms such as re-experiencing (for reviews see Aupperle et al., 2012; Polak et al., 2012). However, choosing adequate far transfer tasks is challenging (Koster et al., 2017) and our results are in line with recent other studies that also reported no training effects on far transfer tasks (e.g., Fonzo et al., 2019). Nevertheless, Hoorelbeke and colleagues (2015) also administered the adaptive PASAT as a cognitive control intervention and compared it to a visual search control training. The researchers found an improvement in O-span task performance but no differential effects between the two groups emerged. In contrast to our study, they focused on healthy individuals with high rumination but not on a clinical sample. Moreover, Siegle and colleagues (2007) used an identical training as we did in depressive individuals and reported that only the cognitive control group showed performance improvements in a near transfer task, the non-adaptive PASAT, as compared to a waitlist

group. Furthermore, participants displayed increases in dlPFC responses in a working memory digit-sorting task even though performance changes could not be interpreted due to ceiling effects. Hence, it has been demonstrated that the training used in this study is able to influence cognitive control. Future studies that focus on PTSD samples should additionally include neuroimaging and near transfer tasks such as the non-adaptive PASAT (Gronwall, 1977) to verify effects on multiple dimensions.

Thirdly—assuming that the cognitive control training induced cognitive shifts that we were just not able to capture—the trained cognitive control functions might not be as relevant as expected in PTSD patients. There is strong empirical evidence for associations between cognitive control deficits and intrusive re-experiencing as reported in cross-sectional, longitudinal, and experimental studies (Aupperle et al., 2012; Polak et al., 2012). Moreover, previous research demonstrated that components of our training have beneficial effects on intrusive memories. For example, testing healthy participants, Nassif and Wells (2014) and Callinan and colleagues (2015) reported that intrusive memories reduced while listening to a narrative of a stressful event only in a group that completed Wells's Attention Training but not in a control group that completed a filler task. The filler task consisted of circling specific letters or digits in random matrices. Our pilot study shows that translating this experimental approach into a clinical PTSD sample with comorbid disorders and using a placebo training that is more similar to the original training does not replicate the findings. However, other studies also examined cognitive control trainings in PTSD. Bomyea and colleagues (2015) explored the effects of a cognitive control training that solely relied on the modification of resistance to proactive interference. Importantly, they focused on a homogeneous female sample with PTSD after sexual traumatization to maximize study power. The researchers reported a reduction of re-experiencing after a high-intensive training as compared to a low-intensive training but no differential improvements in anxiety, depression, or other PTSD symptom clusters. Most recently, Woud and colleagues (2019) also used this training in an analogue design and examined effects on intrusive memories in healthy participants after watching a trauma film. Similar to our results, they found no group differences in various assessments of intrusive memories (intrusion provocation task, intrusion diary, intrusion questionnaire) and in O-span score. Thus, also for a training that focuses on a specific cognitive control function, results are heterogeneous. In contrast, Fonzo and colleagues (2019) recently published a randomized controlled trial in trauma survivors with acute PTSD and with chronic PTSD. Their training focused on a number of cognitive control functions and was compared to a control condition of playing computer games. The researchers also reported no differential PTSD symptom im-

provement for the acute PTSD sample, even though their training was comprehensive and used a relative unspecified control condition. Interestingly, Fonzo and colleagues (2019) demonstrated a more pronounced reduction of re-experiencing symptoms in the training group within the chronic PTSD sample. Hence, the nature of the traumatic event and symptom chronicity should be taken into account in future research on cognitive control and PTSD. Furthermore, we used a training that included neutral stimuli, i.e. stimuli without trauma-related affective valence. Given that traumatized individuals with low cognitive control should have difficulties in disengaging attention from trauma-related stimuli (Wessel et al., 2008) and Schweizer and colleagues (2017) demonstrated that a working memory training including trauma-related material reduces PTSD symptom severity, addressing "hot" cognitive control functions might be a more promising approach for future training studies.

In addition to PTSD symptoms, this study also investigated effects on rumination—a maladaptive processing style that maintains symptomatology—and on depressive symptoms. Previous research clearly demonstrated that the cognitive control training used in this study differentially improves rumination and depression when compared to treatment-as-usual (Siegle et al., 2007) or placebo interventions (Hoorelbeke & Koster, 2017; Hoorelbeke et al., 2015; Hoorelbeke et al., 2016). However, in our study no differential improvements emerged although participants showed rather high levels of depression. Moreover, only participants in the placebo group reported a significant reduction in brooding and—although interaction effects did not reach significance—effect sizes on improvements in other clinical measures were larger in the placebo group as compared to the cognitive control group. These rather contradictory findings are surprising. A major limitation that must be taken into account when interpreting the results are observed differences between groups despite randomization. Even though only significant in the PP-sample, data generally indicated that depressive and PTSD symptomatology was more severe in the cognitive control group as compared to the placebo group. This higher symptom severity might have made it more difficult for participants to profit from the cognitive more demanding cognitive control training, thereby limiting the potential of the training to alter symptomatology and increasing the threshold for achieving training effects. Moreover, although we used a version of the PASAT that adapted task difficulty to participants' performances, the general aim of the PASAT is to activate prefrontal control despite low level negative affect. Therefore, it can be perceived as frustrating and stressful by anxious participants (Tombaugh, 2006). Indeed, PTSD patients felt more stressed, frustrated, and angry during the cognitive control training as compared to the placebo training. Experiencing these negative emotions might have triggered maladaptive processing styles

that interfered with symptom reduction. Lastly, we used a placebo version of Wells's Attention Training in which participants were instructed to listen to different naturalistic sounds while looking at the computer screen. Completing this task over a period of two weeks without any other task demands might have induced some states of mindfulness that affected brooding (e.g., Perestelo-Perez, Barraca, Peñate, Rivero-Santana, & Alvarez-Perez, 2017, for a meta-analysis on mindfulness and depressive brooding). This explanation would also be in line with the placebo group showing less suppression of intrusive memories after the training, as beneficial effects of mindfulness on intrusive memories have been reported (Follette, Palm, & Person, 2006). However, future studies should evaluate these assumptions.

We are aware that a number of limitations might have biased our results. First, we chose an active control group to examine the isolated effects of one mechanism modified. Nevertheless, due to the lack of a waitlist control group we cannot draw conclusions whether the symptom changes would have also been observed with no intervention at all or rely on non-specific factors such as behavioral activation or placebo expectancies. Second, the study protocol included only six training sessions in two weeks. Studies using the identical number reported significant training-induced improvements, at least in depressive symptomatology and rumination (e.g., Siegle et al., 2007). Nevertheless, other studies using components of our training and reporting significant effects on rumination instructed participants to perform at least ten training sessions over a period two weeks (Hoorelbeke et al., 2015; Hoorelbeke & Koster, 2017). Thus, it should be examined whether more training sessions would also lead to more pronounced effects in PTSD patients, for example by including online trainings at minimal costs in future studies (Hoorelbeke & Koster, 2017). Third, this study was run as a pilot study with a small sample size. At the moment, power analyses for LMMs are not well-implemented. Hence, we calculated power by use of a post-hoc power analysis for an ANOVA with a within-between interaction via G*power (version 3.1, University of Duesseldorf, Germany). Assuming an alpha level of .05, an effect size of 0.25, and inserting our PP-sample size of 25 participants, a power of .76 was estimated. Thus, it falls shortly below the recommended threshold of .80. We recommend future studies to validate our findings by use of a larger sample size.

Taken together, although research on the cognitive underpinnings of PTSD symptoms is flourishing, there is a need for more studies on causal relations to expand etiological models and enhance interventions. The present pilot study contributed to this need and transferred an established cognitive control training to a clinical sample of PTSD patients by including a double-blind testing, an active control condition, and a follow-up assessment. Moreover, this

study is the first one that examined effects of a cognitive control training on rumination in PTSD patients. However, the obtained results did not confirm distinct effects of the administered cognitive control training on PTSD symptoms such as intrusive re-experiencing or maintaining factors such as rumination. Thus, we recommend future studies to differentiate between acute and chronic PTSD samples, administer a higher number of training sessions, and re-test our effects within a larger sample to further evaluate its potential for clinical research and practice.

5. General Discussion

The major goal of this thesis was to contribute to the understanding of impaired cognitive control as a causal risk factor for posttraumatic stress symptoms, in particular for intrusive re-experiencing. Additionally, relations between poor cognitive control and rumination, a maladaptive processing style that is closely linked to intrusive re-experiencing and maintains symptomatology, were explored. Although a lot of cross-sectional and—to a lower extent—longitudinal research exist that report associations between deficits in cognitive control and PTSD-related symptoms, research demonstrating that manipulating cognitive control alters symptomatology is lacking. However, this is a necessary condition for applying the term causal risk factor (Kraemer et al., 1997; Vogt et al., 2014). In this thesis, three studies with different methodological approaches were conducted to fill the existing gap. These studies examined whether poor cognitive control precedes symptom development (*study I* & *II*), but also aimed to experimentally manipulate cognitive control (*study I-III*). In this chapter, the main results will be summarized and interpreted in the context of earlier research, thereby discussing implications for future approaches. Additionally, general strengths and limitations will be outlined.

Summary of findings

Study I aimed to test the effects of manipulated cognitive control on intrusive memories as well as rumination in a healthy sample using tDCS and the trauma film paradigm. A brain area that plays a major role in cognitive control—the left dlPFC—was stimulated via anodal, cathodal, or sham tDCS. Conceptually, this study relied on the unity/diversity framework and assessed changes in cognitive control via a modified version of the CVLT, a common measure of resistance to proactive interference. It was hypothesized that cathodal tDCS would diminish and anodal tDCS would enhance resistance to proactive interference as compared to sham stimulation. Furthermore, cathodal tDCS was expected to increase and anodal tDCS to decrease intrusive memories and rumination after a trauma film, compared to sham tDCS. However, stimulation did neither affect resistance to proactive interference nor intrusive memories or rumination. Moreover, based on previous analogue studies (Verwoerd et al., 2009; Verwoerd et al., 2011; Wessel et al., 2008), it was expected that individuals with higher pre-stressor resistance to proactive interference would report less intrusive memories and less rumination after the trauma film. Surprisingly, there were no significant correlations in the expected direction. To address methodological shortcomings of *study I*, slight methodological changes were made in *study II*, for example in the trauma film and in the assessment of

intrusive memories. Most importantly, this study conceptually relied on the DMC framework and examined the relation between proactive control—assessed by the AX-CPT—and intrusive memories. Given the significance of the left dlPFC within the DMC framework, this region was again chosen as the stimulation target. Cathodal tDCS was predicted to diminish and anodal tDCS to enhance proactive control, compared to sham tDCS. Moreover, cathodal tDCS was hypothesized to increase and anodal tDCS to decrease intrusive memories after the trauma film, compared to sham tDCS. Again, these hypotheses were not supported by the data. There was no stimulation effect on proactive control or on intrusive memories. Moreover, *study II* explored whether low pre-stressor proactive control would be associated with more film-related intrusive memories but no significant correlations emerged.

Taken together, the results of *study I* and *study II* speak against causal associations between activation in a brain region associated with cognitive control, performance in cognitive control tasks, and intrusive memories or rumination; at least when cognitive control is conceptualized as resistance to proactive interference in terms of the unity/diversity framework or as a proactive control mode in terms of the DMC framework. However, the manipulation of cognitive control via tDCS is controversial and the conclusions that can be drawn from analogue samples are limited (Holmes & Bourne, 2008). Hence, *study III* went beyond the analogue approach and explored whether a cognitive control training induces symptom changes in mixed-trauma PTSD patients. In this randomized, controlled, double-blind pilot study it was hypothesized that patients who had completed six sessions of a cognitive control training designed by Siegle and colleagues (2007) would show increased cognitive control as compared to patients who had completed a placebo training. Moreover, it was predicted that only the cognitive control group would demonstrate reduced intrusive re-experiencing, rumination, and depressive symptoms. However, although non-significant training progress occurred in the cognitive control group, there were no significant improvements in far transfer tasks measuring working memory updating and inhibition. Also in contrast to hypotheses, the cognitive control training did not outperform the placebo training in its effects on clinical outcomes. Both groups showed a decline in intrusive re-experiencing, rumination defined as repetitive negative thinking, and depressive symptoms. Exploratory analyses indicated that both groups also demonstrated reduced avoidance symptoms, arousal and reactivity symptoms as well as rumination in response to intrusive memories after completing the training. Surprisingly, reductions in rumination defined as brooding and in suppression of intrusive memories were only found in the placebo group but

not in the cognitive control group. Thus, *study III* does not support the assumption that a cognitive control training shows better effects on symptomatology than a placebo intervention.

Integration of results and implications for future research

The results question whether impaired cognitive control is indeed a causal risk factor for symptoms of PTSD—in particular intrusive re-experiencing—or maladaptive processing styles that maintain PTSD—in particular rumination. Thus, the current view on cognitive control in PTSD has to be re-evaluated by considering alternative models and methods. This is especially important in a research field that is mainly based on heterogeneous, cross-sectional, empirical findings and notoriously lacks clear conceptual assumptions. In previous chapters, the results were already discussed within their theoretical context and with regard to methodological limitations. Hence, some general implications for future research will be presented in the following.

The model: changing the perspective on cognitive control in PTSD

Using Ehlers and Clark's cognitive model (2000) and Brewin's dual representation theory (Brewin, 2008; Brewin et al., 1996), possible pathways via which impaired cognitive control might influence PTSD symptom development were introduced in chapter one. However, the results presented in this thesis indicated no link between cognitive control and the development of intrusive memories in analogue samples; no effects of tDCS over the cognitive control brain network on intrusive memories in analogue samples; and no differential effects of a cognitive control training on intrusive re-experiencing in a clinical sample. Thus, the assumption that impaired cognitive control could be a causal risk factor for PTSD was not supported. However, this thesis examined a limited number of cognitive control functions. As a result, global interpretations should be made with caution. Furthermore, methodological shortcomings concerning the manipulation of cognitive control limit the generalizability of findings. Nevertheless, the obtained results are in line with latest research that also questions cognitive control deficits to be associated with, to precede, or to influence PTSD symptomatology. Most recently, results were published indicating that PTSD patients do not differ from healthy controls in cognitive control functions such as resistance to proactive interference (Swick et al., 2017), that resistance to proactive interference does not precede symptom development (Woud et al., 2019), and that cognitive control trainings do

not differently influence posttraumatic stress symptoms in analogue (Woud et al., 2019) or acute PTSD samples as compared to placebo interventions (Fonzo et al., 2019). However, as presented in chapter one, prospective and experimental research is still scarce and results are inconsistent. For example, the most recent findings by Woud and colleagues (2019) speak against previous analogue and training research also focusing on resistance to proactive interference (see chapter one). In contrast to prospective and experimental approaches, a large body of retrospective, cross-sectional research confirmed poor performance of PTSD patients in different cognitive control tasks (e.g., Aupperle et al., 2012; Polak et al., 2012) as well as reduced activation in the cognitive control brain network (Jacob, Dodge, & Vasterling, 2019, for a most recent review). These observed impairments might only be a consequence of extreme stress exposure during the traumatic event or of depleted cognitive resources due to distressing posttraumatic or comorbid symptoms. For instance, intense stress exposure might itself have a toxic effect on brain functioning, thereby leading to hypoactivation of prefrontal brain regions (e.g., Rasmusson & Shalev, 2014, for an overview) that morph into diminished cognitive control functions. Furthermore, deficits in working memory updating or inhibition in terms of the unity/diversity framework might be a result of intrusive re-experiencing or hyperarousal. These symptoms might exhaust cognitive resources and create distraction during cognitive control tasks. Additionally, deficits in proactive control in terms of the DMC framework might result from diminished resources to implement the more demanding proactive control mode. Alternatively, they might also be a consequence of absent reliable contextual cues from the environment due to the poorly contextualized trauma memory or of threat perception that induces a preference for reactive control. For example, Steudte-Schmiedgen and colleagues (2014) reported that traumatized individuals show higher conflict-driven adjustments of cognitive control when dealing with interference as compared to healthy individuals. The researchers explained this result by traumatized individuals actively engaging in a reactive control mode to adapt to changes in the environment. However, some important restrictions of the theoretical assumptions presented in this thesis must be emphasized before drawing final conclusions.

First, this thesis focused on “cold” cognitive functions: the applied cognitive control tasks included neutral but not emotional or trauma-related stimuli. Aupperle and colleagues (2012) suggested that trauma exposure draws attention towards trauma-related stimuli in all individuals but that basic pre-traumatic cognitive control deficits should amplify their impact and lead to PTSD symptoms. Moreover, they assumed that brain regions supporting cognitive

control in neutral and affective situations should overlap. Furthermore, although the model suggestions in chapter one emphasized the control of specific threat-related/trauma-related stimuli, it was assumed that basic cognitive control functions and activation in prefrontal brain areas might underlie or even dictate these processes. However, these assumptions could be wrong and it might be important to take the content of the to-be-controlled information into account. Especially disturbances in exerting cognitive control over emotional material such as difficulties in updating trauma-related information in working memory or in inhibiting trauma-related stimuli might influence intrusive re-experiencing. For example, decreased performance of PTSD patients in tasks involving negative emotional material such as the emotional Stroop task has been reported (Bomyea, Johnson, & Lang, 2017; Cisler & Koster, 2010, for overviews). Moreover, as already mentioned, Schweizer and colleagues (2017) demonstrated that adolescents with PTSD who completed a working memory training with trauma-related stimuli showed better performance in a cognitive transfer task and less PTSD symptoms than a placebo group. Additionally, even for rumination, a large body of research reported significant links between rumination and impaired cognitive control in tasks with emotional material (De Lissnyder et al., 2012; Pe et al., 2012; Zetsche et al., 2012; Zetsche & Joormann, 2011). Hence, we cannot rule out that impaired "hot" but not "cold" cognitive control functions are a causal risk factor for PTSD. Future research should examine whether diminished cognitive control over emotional material precedes or influences symptom development—for example, by testing the ability to inhibit highly-valued but irrelevant stimuli in a trauma film design (see also Aupperle et al., 2012). In this context, it will be essential to combine research on cognitive control with research on attention, interpretation, and memory biases. These biases might affect the processing of emotional material in PTSD (see also Bomyea et al., 2017) and should be clearly differentiated from "hot" cognitive control functions.

Second, impaired cognitive control might not be a causal risk factor but a proxy risk factor for PTSD, i.e. it is associated with another risk factor but does not directly affect the outcome (Kraemer et al., 1997). Pre-traumatic cognitive control deficits might operate by influencing other peri-traumatic or posttraumatic variables such as dissociation (Breh & Seidler, 2007; Özdemir, Özdemir, Boysan, & Yilmaz, 2015), visuospatial processing and integration of contextual information (Hayes et al., 2012; Holmes & Bourne, 2008, for summaries), emotion-regulation attempts and success (Bomyea & Lang, 2016; Hendricks & Buchanan, 2016, for reviews), or effectiveness of extinction learning (Lommen, Engelhard, Sijbrandij,

van den Hout, & Hermans, 2013; Marin, Camprodon, Dougherty, & Milad, 2014, for reviews). For example, it has been assumed that immediately after a traumatic event, periods of not thinking about the trauma help processing of and adapting to the event (e.g., McNally, 2003). In this context, Bomyea & Lang (2015) differentiated automatic thought regulation from deliberate thought suppression. Automatic thought regulation includes implicit processes that maintain activated goals and inhibit distracting stimuli. Thus, these processes might be similar to the cognitive control functions described in chapter one. In contrast, deliberate thought suppression is to actively avoid thinking about certain trauma-related targets. Ineffective thought suppression typically evokes rebound effects of the to-be-suppressed content and therefore increases unwanted thoughts and negative affect (Bomyea & Lang, 2015; Hayes et al., 2012). Analogue research showed that better inhibitory control was correlated with more effective deliberate suppression of neutral thoughts (Brewin & Beaton, 2002) and negative, personally relevant thoughts (Brewin & Smart, 2005) directly after stress exposure. Thus, even if impaired automatic thought regulation does not causally influence PTDS symptoms, traumatized individuals with poor cognitive control might more often fail in effective deliberate thought suppression. These assumptions could be tested by instructing participants to suppress upcoming intrusive memories in future analogue designs.

Third, Wessel and colleagues (2010) aimed to manipulate pre-stressor cognitive control in an analogue design via testing healthy "evening-type" participants during a non-optimal or optimal time of the day. Although the manipulation did not affect cognitive control in terms of working memory updating and inhibition, the researchers found weak negative correlations between pre-stressor cognitive control and intrusive memories after a trauma film only in non-optimal but not in optimal environments. Thus, they suggested that pre-trauma deficits in cognitive control might become more relevant for PTSD when individuals need to compensate for non-optimal life conditions. In contrast, Thompson and Gottesman (2008) tested whether performance in a broad test of cognitive abilities before entering the military predicts later combat-related PTSD in war veterans. Interestingly, higher cognitive abilities reduced the risk for PTSD only in veterans with low-combat exposure but not with high-combat exposure. The researchers interpreted these results in such a way that the detrimental effect of trauma exposure on cognitive functioning outperforms the protective effect of high cognitive abilities. Hence, boundary conditions of the environment might affect the way in which cognitive control vulnerabilities operate on PTSD symptom development and need to be further explored in the future.

Last, the proposed models and the presented studies did not focus on the flexible adjustment of cognitive control functions in interaction with individual appraisals of situational demands. For the unity/diversity framework, it was assumed that impairments in inhibiting no-longer relevant information in working memory would predict intrusive memories since activated representations of traumatic experiences belong to the past and need to be controlled. However, it remains unclear whether this process requires an evaluation of information as being no-longer relevant in the particular situation. With regard to the assumptions of Ehlers and Clark's cognitive model and of the dual representation theory, this requirement should not always be met given the poor integration of the trauma memory into its context and the here-and-now quality of activated representations. Thus, whether inhibition of no-longer relevant information or other inhibitory functions are relevant for dealing with intrusive memories might depend on the here-and-now quality of the specific situation. Also regarding the DMC framework, it was assumed that low proactive control should be associated with PTSD symptom development. However, we do not know in which way individuals define the goal that needs to be maintained in a specific situation. When trauma victims are confronted with a specific situation that most likely triggers intrusive re-experiencing, the maintained goal might be to avoid trauma cues. Thus, increased proactive control might support maintaining this goal and prevent inhibitory-learning in the long-term, therefore being a risk factor for symptom persistence. Therefore, future theoretical and methodological approaches should further specify the circumstances under which cognitive control might influence PTSD.

The method: implications for analogue research using tDCS

In clinical psychology, psychiatry, and neurosciences, tDCS has received much attention as a promising method for manipulating brain activation related to cognitive control (Plewnia, Schroeder, & Wolkenstein, 2015). However, the confidence in this method is decreasing due to the high fragility and low specificity of tDCS effects as well as the diversity in stimulation protocols. TDCS effectivity can be influenced by current intensity, stimulation duration, sponge sizes, electrode positions, or state-dependency (Tremblay et al., 2014). For example, an extracephalic position of the reference electrode can have a decreasing effect (e.g., Plewnia et al., 2015; Wörsching et al., 2016), an increasing effect (Tremblay et al., 2014), or no effect at all (Dedoncker et al., 2016) on stimulation outcome. Such complexities challenge a systematic analysis of what works best to make the stimulation most effective and achieve the antic-

ipated outcomes. Moreover, Bestman and colleagues (2015) stated that the enthusiasm in tDCS does not match the current understanding of its working mechanisms and its use has "outspaced the mechanistic rationales for its application" (p. 13). This statement is supported by recent research that questions whether tDCS over prefrontal regions has a reliable effect on cognitive control indices (e.g., Gordon et al., 2018; Vöröslakos et al., 2018); that highlight the uncertainty about dose-effect relationships (e.g., Hoy et al., 2013) and sham stimulation effects (Fonteneau et al., 2019); or that criticize the oversimplification of anodal/cathodal tDCS leading to excitatory/inhibitory effects (Bestman et al., 2015). For instance, Imburgio and Orr (2018) meta-analytically quantified the effects of single-session tDCS over the dlPFC on cognitive control tasks defined by the unity/diversity framework. The researchers found significant effects only on tasks measuring working memory updating but not on tasks measuring shifting or inhibition. Also in *study I* and *study II,* we did not find stimulation-induced changes in indices of cognitive control. However, as presented in chapter one, a large body of research exists that demonstrated significant effects of tDCS on cognitive control measures. Nevertheless, some general recommendations should guide future analogue tDCS research in the context of cognitive control and posttraumatic stress symptoms:

TDCS is a non-focal stimulation method that does not selectively affect a single brain region but leads to a widespread distribution of currents across brain areas and thereby might influence neuronal activity even in opposite directions. In this thesis, the left dlPFC was chosen as the center of stimulation. However, several other candidate brain regions for targeting cognitive control exist (see chapter one). Even with an extracephalic reference electrode, we do not know whether tDCS over the left dlPFC has influenced other brain regions and if so, in which way, to what extent, and to which consequences. Equally, electrode placement over another candidate brain region—or at least over the right dlPFC—might increase stimulation effects on cognitive and behavioral measures (e.g., Gómez-Ariza et al., 2017; Hayes et al., 2012; Tremblay et al., 2014). Thus, studies are needed that test alternative brain regions and combine our design with neurophysiological measures or neuroimaging to have additional indicators of changed brain activity (e.g., see Wörsching et al., 2016). These studies might also use stimulation methods with greater spatial precision such as transcranial magnetic stimulation or high definition tDCS (e.g., Dayan, Censor, Buch, Sandrini, & Cohen, 2013). Since tDCS over the dlPFC was also argued to act via neurotransmitter alterations by modifying synaptic microenvironment (e.g., Brunoni et al., 2012), it would also be interesting to integrate measures of brain metabolites in the future. Importantly—considering the low statisti-

cal power resulting from small sample sizes in most tDCS studies and the large number of degrees of freedom in stimulation protocols—future research would benefit from multi-centered approaches. Moreover, having identified successful stimulation protocols, case series testing repeated tDCS in PTSD patients would further inform about causality in clinical symptomatology. However, it must be emphasized that there are still large gaps in our knowledge on tDCS working mechanisms. Thus, the presented suggestions for future tDCS research should not culminate in a neuro-reductionism, breaking down complex mental processes into brain areas, neuronal processes, or transmitter systems without profound theoretical foundations. Rather, clinical psychology, psychiatry, and neurosciences should stimulate each other and lead to a more integrated perspective on clinical and neurobiological phenomena associated with PTSD.

Additionally, the analogue studies presented in this thesis combined tDCS with the trauma film paradigm. The trauma film paradigm is a highly useful prospective method for examining exposure and reactions to a traumatic experience (James et al., 2016). More specifically, film-exposure has been shown to provoke responses that are similar to real-life posttraumatic stress symptoms, for example intrusive memories, but that typically decline within a few hours or days (Holmes & Bourne, 2008, for a review). Thus, the analogue trauma does not induce persistent distress but allows studying risk factors under laboratory conditions. For example, even though *study I* did not show that pre-stressor cognitive control predicted post-stressor intrusive memories, we replicated earlier findings that more negative peri-traumatic emotional responses to the stressor increase the likelihood of intrusive re-experiencing (e.g., Clark & Mackay, 2015). Although the trauma film paradigm opens up multiple chances to investigate symptom development, its limitations should also be taken into account. First, the majority of tDCS studies reporting stimulation effects on cognitive control used within-subject designs (e.g., Brunoni & Vanderhasselt, 2014). Within-subject designs take physiologically different stimulation effects between individuals into consideration, for example, due to differences in head anatomy (see also Tremblay et al., 2014). However, implementing a within-subject design in the trauma film approach is challenging as presenting a film fragment twice might limit the occurrence of intrusive memories due to habituation, and presenting an alternative film fragment might affect comparability. Nevertheless, when examining thought suppression as described above, paradigms that integrate behavioral tasks with trauma film reminders, for example, the modified think/no-think paradigm (e.g., Anderson & Green, 2001) might facilitate the implementation of within-subject designs in future analogue re-

search. In addition, the trauma film paradigm has been repeatedly criticized for lacking ecological validity since viewing a distressing film is passive and fails to mimic the complexity of real-life traumatization. Thus, some of the assumptions of the theoretical models described in chapter one—for example the need to deal with trauma reminders or the impact of threat perception on imbalance in control modes—might not be met when investigating intrusive memories in analogue trauma. As a result, the proposed pathways by which impaired cognitive control influences posttraumatic stress symptoms might not be adequately reflected. To increase ecological validity, virtual reality has been proposed as a method that enhances the active involvement of the individual and the complexity of the experience (Dibbets & Schulte-Ostermann, 2015). However, due to ethical reasons, analogue trauma in non-clinical populations will never be as complex and as disturbing as real life traumatization. Hence, the implications for real-life experiences that can be drawn from analogue samples and the generalizability of results will always be limited.

The meaning: implications for clinical research and practice

Investigating the causal association between impaired cognitive control and PTSD symptom development cannot only extend etiological models but also prevention programs and interventions. Thus, the presented non-significant results also raise important questions for clinical research and practice:

1) Does cognitive control not play a role for the prevention of PTSD? Certainly, it is too early to draw final conclusions as more research examining cognitive control manipulations and temporal precedence is needed. As described above, alternative models and methods for exploring the link between impaired cognitive control and PTSD symptoms exist and have yet to be tested. Moreover, this thesis relied on analogue samples and patients who suffer from PTSD. Previous research approaches also suggested interesting pre-trauma paradigms to identify risk factors for PTSD in real-life settings, for example testing fire-fighters prior to their first exposure to real fire (Bryant & Guthrie, 2005). Although these approaches are challenging in terms of ethics and participants' commitment, investigating—or even training—different cognitive control functions in high-risk populations such as emergency personnel would further inform about the role of cognitive control for symptom development under natural conditions.

2) Are cognitive control trainings ineffective in PTSD patients? Even though previous research reported that the cognitive control training by Siegle and colleagues (2007) has the

potential to reduce intrusive memories and rumination in healthy and depressed individuals, the training did not outperform a placebo intervention in PTSD patients as reported in *study III*. Surprisingly, effects sizes were even higher for the placebo intervention. Additionally, recent research on alternative cognitive control trainings also reported null-effects or no differential improvements on PTSD-related symptoms in clinical or analogue samples. These trainings either focused on a single cognitive control function such as resistance to proactive interference (Woud et al., 2019) or included a number of cognitive control tasks (Fonzo et al., 2019). However, future training research might pay more attention to the interplay between cognitive control, trauma type, and temporal dynamics in symptom development. *Study III* was performed in a natural setting, including PTSD patients with single or repeated traumatic experiences during adulthood, single or repeated traumatic experiences during childhood, or even a mixture of all. Due to the small sample size, subgroup analyses were not feasible. However, the nature and time course of the traumatization as well as its occurrence during childhood, adolescence, or adulthood might influence the effects of cognitive control manipulations on PTSD. In contrast to individuals who have experienced traumatization during adulthood, individuals who were traumatized during critical periods of brain development—for instance as a result of childhood maltreatment or domestic violence—might show diverse patterns of impaired cognitive and brain functions that are more difficult to influence. For example, childhood trauma has been associated with underdevelopment of the prefrontal cortex (e.g., De Bellis et al., 1999). This underdevelopment might further interact with other higher-order functions such as memory, emotion, or stress adaption (Brown, Becker-Weidman, & Saxe, 2014, for an overview), that in turn affect posttraumatic symptoms. Therefore, theoretical models are needed that focus on the particular role of cognitive control in individuals with childhood trauma and future clinical research should take this factor into account when aiming to manipulate symptomatology via cognitive control trainings.

3) Is it important to take individual differences in cognitive control into account in the psychological treatment of PTSD? Even if future studies further supported the null-findings presented in this thesis, cognitive deficits might be a barrier to effectiveness of established psychological treatments. In general, 20-50 % of PTSD patients do not profit from current PTSD treatments (Schottenbauer, Glass, Arnkoff, Tendick, & Gray, 2008). Most of these treatments consist of interventions that are cognitive demanding, for example cognitive restructuring or mental imagery, and therefore rely on cognitive control. Deficits—even if

emerging as a consequence of symptomatology—might make it more difficult for individuals to modify thoughts and actions during interventions and these difficulties might reduce treatment response. For example, previous research has shown that individuals with better performance in cognitive control tasks respond more favorable to cognitive-behavioral interventions (Falconer, Allen, Felmingham, Williams, & Bryant, 2013). In this context, future research could study whether adding an easy-to-administer cognitive control intervention to an established PTSD treatment augments treatment progress and outcome. For example, focusing on depression, Siegle and colleagues (2007) included the training described in this thesis as an add-on to an intensive outpatient day-treatment program. They reported more improvements in depressive symptoms in the training group as compared to a control group only receiving the day-treatment program. Thus, investigating whether cognitive control trainings interact with specific components of PTSD treatments and increase treatment response would further inform about working mechanisms and could improve the effectiveness of interventions. In addition, future research should examine whether providing cognitive control trainings to patients who are at risk for cognitive control impairments facilitates other interventions. Risk groups could be individuals with a history of alcohol or substance abuse—as chronic substance abuse is associated with decreased cognitive control (e.g., Bartzokis et al., 2002; Jovanovski, Erb, & Zakzanis, 2005; Rourke, 2009) and is highly prevalent in PTSD patients (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; Scherrer et al., 2008)—as well as individuals who suffer from attention-deficit/hyperactivity disorder, a syndrome that is highly comorbid with PTSD (e.g., Adler, Kunz, Chua, Rotrosen, & Resnick, 2004; Harrington et al., 2012). In sum, this thesis encourages future research to pay more attention to subgroups that might benefit from cognitive control interventions.

General strengths and limitations

The studies reported in this thesis made a distinct contribution to the existing research on cognitive control in PTSD. At the conceptual level, they explored cognitive control within two different frameworks. Especially *study II* is one of the first investigations that examined intrusive re-experiencing in the context of the dual mechanisms of control and additionally evaluated the susceptibility of control modes to tDCS. At the methodological level, *study I* and *study II* introduced a novel analogue approach by combining the trauma film paradigm with neurostimulation. *Study III* implemented a famous cognitive control training by Siegle and colleagues (2007) in PTSD patients and also focused on posttraumatic rumination.

Although hypotheses have not been confirmed, all three studies expand our knowledge on the role of cognitive control for intrusive re-experiencing and posttraumatic rumination by questioning causal associations. Moreover, all three studies distinguish themselves through their high methodological quality. *Study I* and *II* feature a large number of participants, a sham-controlled design, and a double-blind testing procedure. *Study III*, although a pilot study, includes double-blind testing, a highly comparable active control condition, and provides follow-up data. Despite these strengths, it is plausible that a number of limitations might have biased the results. Some major ones that apply to all three studies will be summarized in the following.

In all three studies, the assessment of clinical measures was mainly based on retrospective self-report questionnaires. What people say about themselves is a valuable access to their subjective reality and clearly important to take into account. However, retrospective self-report questionnaires lack validity. Memory biases, social desirability biases, introspective ability, intentional maximization/minimization of symptoms, item understanding, or affective states may influence the way individuals evaluate and report their experiences (Candel & Merckelbach, 2004; Stone et al., 2000). We applied a number of strategies to deal with this limitation. For example, in *study I* and *study II* we gave participants a clear definition of intrusive memories, assessed affective states throughout the study procedure, and used different methods to capture intrusive memories. Moreover, intrusive memories in both studies and rumination in *study I* had to be indicated after a short post-film period, a procedure that was used before (e.g., Vanderhasselt et al., 2013) and decreases the risk of memory biases. Furthermore, in *study III* we implemented different measures of rumination to capture different conceptualizations (repetitive negative thinking, brooding, rumination in response to intrusive memories). Additionally, PTSD symptoms were not only assessed via questionnaires but also via structured interviews conducted by a trained clinician, therefore providing a more objective evaluation of symptom severity. However, future research could improve validity in numerous ways. First, ecological validity can be enhanced by integrating *Ecological Momentary Assessment* (EMA; Shiffman, Stone, & Hufford, 2008), a measurement tool that prompts participants via smartphone signals throughout the day to answer symptom-related questions. Especially in clinical samples, this approach might provide a more comprehensive view into patients' daily symptom fluctuations and also offer information on acute stressors that might influence daily experiences. For analogue research using tDCS, this method might be less suitable as stimulation effects fade away after 1-2

hours (e.g., Nitsche et al., 2008). Thus, only after-stimulation effects could be tapped. Second, in-lab symptom provocation could be applied at baseline and post-/follow-up assessments. During symptom provocation, individuals with PTSD are presented trauma reminders such as photographs, sounds, or imagery and are asked to report acute distress, intrusive re-experiencing, or regulation strategies. Importantly, when following this approach in clinical samples, it might be necessary to prescreen patients on their typical response to trauma stimuli with intense dissociation due to ethical reasons. Third, self-report measures could be enriched by physiological indices such as heart rate variability, blood pressure, skin conductance, electromyography, or salivary cortisol as well as neuroimaging of relevant brain regions (see Lanius, Bluhm, Lanius, & Pain, 2006, for an overview). This is especially interesting as an interaction of intrusive re-experiencing, cognitive control, and physiology has been proposed (De Putter et al., 2015; Gillie, Vasey, & Thayer, 2014). Thus, evaluating symptom changes, for example after a cognitive control training, using this multimodal approach would provide a more comprehensive picture of individuals' reaction to trauma reminders and increase the potential to capture manipulation effects.

Another limitation is the assessment of cognitive control. We did not replicate the well-established correlation between pre-stressor cognitive control and post-stressor intrusive memories (*study I* & *II*) and we did not find effects of the cognitive control manipulations on performance in most cognitive control tasks. In this context, low reliability of cognitive control measures must be discussed. Low reliability affects effect sizes and therefore decreases statistical power (Nicewander & Price, 1983; Vasey, Dalgleish, & Silverman, 2003). In our studies, the modified CVLT did not seem to be sensitive enough to interference effects and the AX-CPT showed low reliability for error rates in AY and BX trials. However, all tasks applied in this thesis are considered as standard measures of cognitive control and were chosen to increase comparability to previous investigations. Thus, low reliability is a common problem in cognitive control research and should be treated more critically in the future. Moreover, even if tasks are reliable, they might not be valid to capture the construct of interest (Vasey et al., 2003). In this context, the impurity problem of cognitive control tasks becomes relevant. It assumes that most cognitive control tasks are not a pure measure of a single construct but also include other cognitive processes, with the consequence that a large proportion of variance in the specific task might result from variation in other requirements of the task and not from variation in the construct of interest (e.g., Miyake et al., 2000). This limitation biases the interpretation of low scores on a task as well as low or absent

correlations with other tasks or constructs (Miyake et al., 2000). For example, the Stroop task and the O-span task as applied in *study III* are two of the most famous cognitive control measures within the unity/diversity framework and were identified as measures of inhibition (Stroop) and updating of working memory (O-span) using latent-variable analysis (Friedman & Miyake, 2004; Miyake et al., 2000). Nevertheless, the Stroop task has also been conceptualized as a measure of selective attention, processing speed, or cognitive flexibility (Jensen & Rohwer, 1966; Lamers, Roelfos, & Rabeling-Keus, 2010) and the O-span task has also been related to shifting between different task demands (e.g., Miyake et al., 2000). Thus, it might be important to integrate a number of tasks assessing the same construct of interest when investigating effects of cognitive manipulations to acknowledge the multifaceted nature of this construct in future research. Additionally, it should be mentioned that circadian rhythms were found to affect performance in cognitive control tasks (Hasher, Lustig, & Zacks, 2007, for an overview). We tried to avoid testing participants very early in the morning or very late in the evening to reduce effects of fatigue but we did not assess individuals' optimal testing times. This is especially important given the influence of optimal testing environments on the link between cognitive control and intrusive memories as mentioned above (Wessel et al., 2010).

Lastly, it must be emphasized that *study III* was a pilot study consisting of a small sample and lacking a waitlist control group. Given the challenge of recruiting PTSD patients in a naturalistic, outpatient setting, we were only able to compare two groups to ensure a reasonable number of participants in each group. A highly competitive active control condition was chosen. In doing so, we could examine whether potential training effects were indeed a result of manipulating cognitive control and not driven by placebo expectancies. Thus, the active control condition is a strength of *study III*. However, with the significant improvements seen in both training groups we do not know whether symptom improvement would have also occurred with no training at all. Hence, future studies with larger samples would benefit from including a waitlist control group to facilitate the interpretation of findings.

Conclusion

To conclude, the present thesis strived for the challenging task of examining causality in posttraumatic stress symptoms and therefore contributed to the limited knowledge on causal risk factors for PTSD. In particular, this thesis focused on impaired cognitive control, thereby

shifting attention from investigating cross-sectional links to exploring temporal precedence and cognitive manipulations in the context of posttraumatic intrusive re-experiencing. This thesis proposed theoretical models that combined established theories on cognitive control and PTSD for illustrating the possible pathways by which this risk factor might operate. In addition, this thesis also focused on the link between impaired cognitive control and rumination, an important maintaining factor of PTSD. In three empirical studies with analogue as well as clinical samples, novel methodological approaches to experimentally manipulate cognitive control were tested. In summary, the absent effects of tDCS over a brain region associated with cognitive control on post-stressor intrusive memories and rumination; the absent correlations between pre-stressor cognitive control and post-stressor intrusive memories and rumination; the absent differential symptom improvements in PTSD patients completing a cognitive control or a placebo training; all of these results speak against causal associations between impaired cognitive control and posttraumatic stress symptoms or processing styles. Nevertheless, final conclusions cannot be drawn since the body of research on causality is clearly too small and methodological shortcomings of the presented studies must be taken into account. A number of model modifications and methodological changes have been proposed. Future investigations are needed that build on the theoretical and methodological suggestions of this thesis and that unravel the complex brain-cognition-emotion interactions in PTSD. This is of particular importance to further understand and to finally prevent the emotional, behavioral, and cognitive disturbances some individuals have to suffer from after experiencing a life-threatening event ever since the beginning of mankind.

Zusammenfassung

Reduzierte kognitive Kontrolle als kausaler Risikofaktor für intrusives Wiedererleben und Rumination bei der Posttraumatischen Belastungsstörung: Ergebnisse aus analogen und klinischen Studien

Verkehrsunfälle, gewalttätige Übergriffe oder der plötzliche Tod einer nahestehenden Person – in Deutschland wird ein Viertel aller Menschen mindestens einmal im Leben mit einem traumatischen Ereignis konfrontiert (Mearcker et al., 2008). Obwohl solch ein Ereignis meist mit einschneidenden Veränderungen einhergeht, erholt sich der Großteil der betroffenen Personen im Laufe der Zeit von der akuten Belastung und findet ins Leben zurück. Manche Personen leiden jedoch auch noch Monate oder Jahre nach dem Ereignis unter akuten, belastenden Symptomen, die die Lebensqualität erheblich einschränken: Alpträume, aufdrängende Erinnerungen, das Gefühl, wieder in die traumatische Situation zurückversetzt zu sein, hohe Anspannung und Wachsamkeit oder das Vermeiden von Situationen oder Orten, die mit dem Trauma in Verbindung stehen. All diese Symptome können Ausdruck einer Posttraumatischen Belastungsstörung (PTBS) sein (APA, 2013). Trotz der hohen Prävalenz traumatischer Ereignisse ist die Lebenszeitprävalenz einer PTBS mit 2 % in Deutschland vergleichsweise gering (Mearcker et al., 2008). Aus diesem Grund muss es bestimmte Faktoren geben, die das Risiko beeinflussen, eine PTBS zu entwickeln. Die Identifikation dieser Faktoren ist nicht nur entscheidend für die Entwicklung ätiologischer Modelle, sondern auch für die Konzipierung individueller Präventionsmaßnahmen sowie effektiver Therapiemethoden. Ein möglicher prä-traumatischer Risikofaktor, der in den vergangenen Jahren immer mehr Aufmerksamkeit erhalten hat, ist reduzierte kognitive Kontrolle.

Kognitive Kontrolle bezeichnet die Fähigkeit, zielgerichtetes Verhalten zu initiieren, aufrechtzuerhalten und zu regulieren, vor allem im Angesicht sich stetig verändernder Anforderungen durch die Umwelt (Cohen, 2017, für einen Überblick). Auf neuronaler Ebene wird kognitive Kontrolle mit Strukturen des Frontalhirns, insbesondere mit Aktivität im anterioren cingulären Cortex und im dorsolateralen präfrontalen Cortex (dlPFC), assoziiert (z.B. Mansouri et al., 2009; Niendam et al., 2012). Auf konzeptueller Ebene besteht jedoch Uneinigkeit darüber, wie sich kognitive Kontrolle am besten operationalisieren lässt. Zwei der populärsten Modelle sind dabei der *Unity/Diversity Ansatz* nach Miyake und Kolleg*innen (2000) und der *Dual Mechanisms of Control (DMC) Ansatz* nach Braver (2012). Gemäß dem Unity/Diversity Ansatz (Miyake et al., 2000) besteht kognitive Kontrolle aus drei getrennten Funktionen, die hoch miteinander korrelieren: Aktualisierung und Überwachung von Inhalten des Arbeitsgedächtnisses, Inhibition von automatischen Reaktionstendenzen und Wechsel zwischen verschiedenen Zielen, Aufgaben oder Handlungen. Friedman und Miyake (2004) ergänzten das Modell zudem um die Inhibition von zielirrelevanten, ablenkenden Informationen sowie die Inhibition von Informationen, die nicht länger relevant sind, auch

bekannt als proaktive Interferenzkontrolle. Demgegenüber besteht kognitive Kontrolle gemäß dem DMC Ansatz (Braver, 2012) aus zwei qualitativ unterschiedlichen Kontrollmodi, die flexibel angewandt werden: Proaktive Kontrolle stellt einen frühen Selektionsprozess dar, bei dem zielrelevante Informationen aktiv im Arbeitsgedächtnis aufrechterhalten werden, um das Verhalten darauf auszurichten und Interferenzen früh zu inhibieren. Reaktive Kontrolle stellt einen späten Korrekturprozess für Zielkonflikte dar. Zielrelevante Informationen werden erst aktiviert, wenn Interferenzen von zielirrelevanten Informationen bereits aufgetreten sind und diese unterdrückt werden müssen.

In Hinblick auf PTBS gehen verschiedene Modelle davon aus, dass eine reduzierte kognitive Kontrolle vor allem mit intrusivem Wiedererleben, einem Kernsymptom der PTBS, zusammenhängen könnte. Intrusives Wiedererleben äußert sich insbesondere in intrusiven Erinnerungen, d.h. kurzes, unkontrollierbar wiederkehrendes Wiedererinnern des traumatischen Ereignisses in Form von lebhaften Sinneseindrücken (Marks et al., 2018). Beispielsweise postulieren Aupperle und Kolleg*innen (2012), dass fast alle Menschen direkt nach einem Trauma besonders aufmerksam für traumabezogene Reize seien, aber nur Personen mit verminderter kognitiver Kontrolle Schwierigkeiten darin hätten, Reaktionen auf diese Reize zu regulieren. Dies könne intrusives Wiedererleben begünstigen. In der Dissertation wurden diese Prozesse noch detaillierter am Beispiel zweier bekannter Modelle für PTBS, dem *Kognitiven Modell nach Ehlers und Clark* (2000) und der *Dual Representation Theory* nach Brewin (2008) dargestellt. Dabei wurde vor allem davon ausgegangen, dass reduzierte Inhibition und reduzierte Aktualisierung von Arbeitsgedächtnisinhalten gemäß dem Unity/Diversity Ansatz und reduzierte proaktive Kontrolle gemäß dem DMC Ansatz die zentralen kognitiven Kontrollfunktionen sind, die intrusives Wiedererleben beeinflussen.

Wenn eine reduzierte kognitive Kontrolle tatsächlich einen kausalen Risikofaktor für Symptome der PTBS, insbesondere für intrusives Wiedererleben, darstellen soll, müssen gemäß Vogt und Kolleg*innen (2014) die folgenden Voraussetzungen erfüllt sein: Defizite in der kognitiven Kontrolle müssen (a) mit PTBS-Symptomen assoziiert sein, (b) PTBS-Symptomen zeitlich vorausgehen und (c) manipulierbar sein und diese Manipulation muss zu Veränderungen in der PTBS-Symptomatik führen. In der Tat liefern zahlreiche querschnittliche Studien mit klinischen Stichproben Hinweise darauf, dass eine niedrige kognitive Kontrolle mit PTBS-Symptomatik, insbesondere intrusivem Wiedererleben,

zusammenhängt (u.a. Aupperle et al., 2012; Polak et al., 2012). Hier ist jedoch unklar, ob Unterschiede in der kognitiven Kontrolle bereits vor dem Trauma vorhanden waren oder durch die PTBS-Symptomatik selbst bedingt sind. Bei der Untersuchung von zeitlichen Zusammenhängen steht die Traumaforschung vor erheblichen ethischen und methodischen Herausforderungen. Aus diesem Grund haben sich in den vergangenen Jahren insbesondere Analogstudien etabliert, die gesunde Personen mit Hilfe des Traumafilm-Paradigmas untersuchen (Holmes & Bourne, 2008). Dabei wird den Versuchsteilnehmer*innen ein Filmausschnitt gezeigt, der sehr belastende oder traumatische Inhalte darstellt, und anschließend werden filmbezogene, intrusive Erinnerungen gemessen. In Bezug auf kognitive Kontrolle haben verschiedene Studien beschrieben, dass insbesondere Defizite in proaktiver Interferenzkontrolle im Sinne des Unity/Diversity Ansatzes eine erhöhte Anzahl intrusiver Erinnerungen vorhersagen (u.a. Verwoerd et al., 2011; Wessel et al., 2008). Die Studienlage ist jedoch insgesamt eingeschränkt und Befunde zum DMC Ansatz fehlen ganz. Zudem mangelt es erheblich an Studien, die untersuchen, inwiefern eine Manipulation von kognitiver Kontrolle intrusives Wiedererleben beeinflussen kann. Erste vielversprechende Hinweise liefern diesbezüglich Ansätze, bei denen kognitive Kontrolle mit Hilfe kognitiver Trainings gezielt verändert und dadurch intrusives Wiedererleben verringert wurde (z.B. Bomyea & Amir, 2011; Bomyea et al., 2015).

Ziel der vorliegenden Arbeit war es, einen Beitrag zur Aufklärung kausaler Zusammenhänge zu leisten und aufbauend auf den bisherigen Ergebnissen zu untersuchen, inwiefern eine reduzierte kognitive Kontrolle der Entwicklung intrusivem Wiedererlebens vorausgeht und inwiefern eine gezielte Manipulation kognitiver Kontrolle die Symptome beeinflussen kann. Neben kausalen Zusammenhängen zwischen kognitiver Kontrolle und intrusivem Wiedererleben sollte in dieser Arbeit zudem die kausale Beziehung zwischen reduzierter kognitiver Kontrolle und Rumination im Fokus stehen. Rumination ist definiert als repetitives, unkontrollierbares, verbales Denken bzw. Grübeln über die Ursachen und Konsequenzen der traumatischen Erfahrung (Michael et al., 2007). Zahlreiche quer- und längsschnittliche Untersuchungen ergaben, dass Rumination mit PTBS Symptomen assoziiert ist und diese aufrechterhalten kann (u.a. Ehring & Ehlers, 2014; Michael et al., 2007; Murray et al., 2002; Szabo et al., 2017; Wild et al., 2016). Besonders Studien mit gesunden und depressiven Proband*innen haben zudem gezeigt, dass Rumination ebenfalls mit reduzierter kognitiver Kontrolle zusammenhängt (u.a. Vălenaş & Szentágotai-Tătar, 2017; Yang et al., 2016) und durch kognitive Trainings gezielt beeinflusst werden kann (u.a. Koster et al.,

2017). Im Kontext von PTBS wurde dies bislang jedoch nicht untersucht. Insofern war ein zweites Ziel dieser Arbeit, kausale Zusammenhänge zwischen defizitärer kognitiver Kontrolle und posttraumatischer Rumination zu erforschen. Um diese Ziele zu erreichen, wurden drei empirische Studien durchgeführt, die sich unterschiedlicher Ansätze bedienten, um kognitive Kontrolle zu modulieren und Zusammenhänge mit intrusivem Wiedererleben sowie Rumination zu erfassen: Zwei Analogstudien mit gesunden Stichproben, die die Effekte von transkranieller Gleichstromstimulation (tDCS) untersuchten und eine Pilotstudie mit einer PTBS Stichprobe, die die Effekte eines kognitiven Kontrolltrainings erforschte.

Studie I und Studie II kombinierten das Traumafilm-Paradigma mit tDCS, einem gut etablierten, verträglichen Verfahren zur Manipulation kortikaler Aktivität und damit verbundenen kognitiven Kontrollfunktionen. Bei tDCS wird für einen kurzen, begrenzten Zeitraum Gleichstrom mittels Schwammelektroden über einer zuvor definierten Hirnregion appliziert. Als grundlegender Wirkmechanismus wird dabei eine durch den Gleichstrom bedingte Verschiebung des neuronalen Ruhemembranpotentials angenommen. Dadurch kommt es zu einer kortikalen Erregbarkeitssteigerung bei anodaler und zu einer Erregbarkeitsverminderung bei kathodaler Stimulation, die bis zu eine Stunde anhalten kann (Nitsche et al., 2008). Da der linke dlPFC ein wesentlicher Bestandteil des der kognitiven Kontrolle zugrunde liegenden Netzwerkes ist (u.a. Fassbender et al., 2004) und in bisherigen Studien bereits gezeigt wurde, dass eine anodale tDCS des dlPFC kognitive Kontrollprozesse erhöhen und eine kathodale tDCS des dlPFC kognitive Kontrollprozesse reduzieren kann (Wolkenstein & Plewnia, 2013; Wolkenstein et al., 2014), wurde der linke dlPFC in beiden Studien als Zielstruktur gewählt. Beide Studien zielten darauf ab, kognitive Kontrolle mittels tDCS über dem linken dlPFC zu manipulieren und Effekte dieser Manipulation auf intrusive Erinnerungen (Studie I & II) sowie Rumination (Studie I) in Reaktion auf einen Traumafilm zu erforschen. Zudem untersuchten beide Studien, ob eine gering ausgeprägte kognitive Kontrolle vor dem Traumafilm spätere filmbezogene intrusive Erinnerungen oder Rumination vorhersagt. Konzeptuell orientierte sich Studie I am Unity/Diversity Ansatz und fokussierte auf proaktive Interferenzkontrolle als relevanten kognitiven Kontrollprozess. $N = 118$ gesunde Frauen absolvierten den modifizierten California Verbal Learning Test zur Erfassung von proaktiver Interferenzkontrolle zweimal – einmal vor und einmal während 20-minütiger Stimulation des linken dlPFC. Dabei wurden sie randomisiert einer von drei Stimulationsgruppen zugeordnet: anodaler, kathodaler oder Scheinstimulation. Anschließend wurde den Teilnehmerinnen eine traumatische Filmszene gezeigt und nach einer

zehnminütigen Ruhephase intrusive Erinnerungen und Rumination erfasst. In dieser Studie zeigten sich weder Effekte von tDCS über dem linken dlPFC auf proaktive Interferenzkontrolle und filmbezogene intrusive Erinnerungen oder Rumination noch signifikante Zusammenhänge zwischen diesen Maßen. Studie II folgte einem ähnlichen Design wie Studie I, definierte kognitive Kontrolle aber im Rahmen des DMC Ansatzes und richtete den Fokus auf reduzierte proaktive Kontrolle. N = 121 gesunde Männer und Frauen absolvierten die AX-Continuous Performance Task – ein etabliertes Maß für proaktive Kontrolle – während 20-minütiger Stimulation. Anschließend sahen sie eine traumatische Filmszene, lasen für zehn Minuten einen neutralen Text und gaben im Anschluss intrusive Erinnerungen während des Textlesens an. Auch in dieser Studie gab es weder einen tDCS Effekt auf das Maß für kognitive Kontrolle noch auf filmbezogene intrusive Erinnerungen. Zudem zeigte sich kein signifikanter Zusammenhang zwischen proaktiver Kontrolle vor dem Film und filmbezogenen intrusiven Erinnerungen. Insgesamt sprechen die Ergebnisse der beiden Studien also gegen kausale Zusammenhänge zwischen reduzierter kognitiver Kontrolle und intrusiven Erinnerungen oder Rumination, zumindest wenn kognitive Kontrolle als proaktive Interferenzkontrolle im Rahmen des Unity/Diversity Ansatzes oder als proaktiver Kontrollmodus im Rahmen des DMC Ansatzes erfasst wird.

Im Gegensatz zu den Analogdesigns der ersten beiden Studien fokussierte Studie III auf eine klinische Stichprobe von N = 33 PTBS Patient*innen sowie auf die Effekte eines kognitiven Kontrolltrainings. Im Speziellen untersuchte diese doppelblinde, randomisierte, kontrollierte Pilotstudie, ob sechs Sitzungen eines kognitiven Kontrolltrainings intrusives Wiedererleben, Rumination sowie komorbide depressive Symptome signifikant positiv beeinflussen können. Die Teilnehmer*innen wurden randomisiert entweder dem kognitiven Kontrolltraining oder einem Placebotraining zugeordnet und an drei Messzeitpunkten (prä Training, post Training, 1 Monat Follow-up) untersucht. Das kognitive Kontrolltraining orientierte sich an Siegle und Kolleg*innen (2007) und bestand aus der adaptiven Paced Auditory Serial Addition Task sowie aus Wells's Attention Training. Obwohl sich die Proband*innen deskriptiv in den Aufgaben des kognitiven Kontrolltrainings verbesserten, zeigten sich keine Transfereffekte auf kognitive Kontrollaufgaben die Arbeitsgedächtnis oder Inhibition erfasst haben. Entgegen der Erwartungen gab es in dieser Studie außerdem eine signifikante Abnahme in intrusivem Wiedererleben, Rumination (operationalisiert als repetitives negatives Denken) und Depression bei allen Versuchspersonen nach dem Training, unabhängig von der Trainingsgruppe. Zudem fand sich in der Placebogruppe, aber nicht der

kognitiven Kontrollgruppe, eine signifikante Reduktion in Rumination, wenn diese als Grübeln in Reaktion auf negative Emotionen operationalisiert wurde. Insofern stellen die Ergebnisse die Relevanz kognitiver Kontrollprozesse infrage.

Zusammenfassend war es das Ziel dieser Dissertation, kausale Zusammenhänge zwischen verringerter kognitiver Kontrolle und Symptomen der PTBS, wie intrusives Wiedererleben, sowie aufrechterhaltenden Faktoren, wie Rumination, näher zu beleuchten. Damit sollte das Wissen über Risikofaktoren für die Entstehung und Aufrechterhaltung der PTBS erweitert und somit aktuelle ätiologische Modelle sowie Präventions- und Interventionsansätze ergänzt werden. Im Allgemeinen unterstützen die Ergebnisse der dargestellten Studien nicht die Annahme, dass reduzierte kognitive Kontrolle einen kausalen Risikofaktor für intrusives Wiedererleben oder Rumination darstellt. Vielmehr warfen sie die Frage auf, ob Einschränkungen der kognitiven Kontrolle in PTBS Patient*innen, welche bisher in zahlreichen Veröffentlichungen berichtet wurden (u.a., Aupperle et al., 2012, für eine Übersicht), eher eine Folge der Traumatisierung oder der posttraumatischen Symptomatik darstellen könnten. Bevor jedoch endgültige Schlüsse gezogen werden, müssen Limitationen der durchgeführten Studien, insbesondere in Hinblick auf die Manipulation von kognitiver Kontrolle, in Betracht gezogen werden. Aus diesem Grund wurde in der Arbeit die methodische Herangehensweise der Studien kritisch hinterfragt und es wurden mögliche Einschränkungen bei der Interpretation der Ergebnisse diskutiert. Dabei wurde vor allem auf das Potenzial aber auch die Herausforderungen von Analogdesigns mit Gleichstromstimulation eingegangen. Außerdem wurden Implikationen für theoretische Modelle sowie zukünftige analoge und klinische Forschung abgeleitet. Insgesamt ist die vorliegende Dissertation eine der wenigen Arbeiten, die sich mit kausalen Zusammenhängen im Kontext posttraumatischer Symptomatik beschäftigt hat und bereichert damit den aktuellen Forschungsstand zu Risikofaktoren für die Posttraumatische Belastungsstörung.

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Appendix A:

Supplementary Material Study II

Appendix A

Table A.1

Split-half reliability (Spearman-Brown coefficients) of the AX-CPT trials

		Sham (n = 41)	Anodal (n = 38)	Cathodal (n = 42)	Overall (n = 121)
	Trial type	*r*	*r*	*r*	*r*
Error rates	AX	.902	.720	.796	.826
	AY	.386	.639	.608	.543
	BX	.711	.568	.529	.633
	BY	.947	.886	.898	.918
RTs	AX	.990	.982	.946	.979
	AY	.952	.874	.899	.912
	BX	.942	.909	.942	.925
	BY	.988	.976	.980	.982

Notes. RTs = Reaction times in ms based on trials with correct responses.

Appendix B:

Supplementary Material Study III

Table B.1

Descriptive Statistics by Group for Changes in Mood in Training Sessions for the Intention-to-treat (ITT) and the Per-protocol (PP) Sample

	Training Group											
	Cognitive Control						Placebo					
	Δ anger		Δ frustration		Δ stress		Δ anger		Δ frustration		Δ stress	
Time point	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
ITT (*n* = 33)												
Training session 1	0.88	1.58	1.18	1.33	0.76	1.52	-0.31	0.60	-0.06	0.85	0.25	1.06
Training session 2	0.20	0.77	0.73	1.22	0.60	1.40	0.06	0.93	0.44	1.21	0.19	1.33
Training session 3	0.27	1.28	0.27	1.33	0.47	1.55	-0.07	0.70	-0.40	0.74	-0.07	1.33
Training session 4	0.67	1.59	0.80	1.21	0.67	1.11	-0.13	0.74	-0.33	0.62	0.00	0.85
Training session 5	0.54	1.27	0.69	1.18	0.62	1.12	-0.13	0.52	-0.20	0.68	-0.27	1.10
Training session 6	0.15	0.90	0.31	1.11	0.38	1.04	-0.07	0.47	-0.21	0.70	0.50	0.94
PP (*n* = 25)												
Training session 1	0.85	1.68	1.23	1.48	0.77	1.59	-0.33	0.65	-0.08	0.90	0.17	1.03
Training session 2	0.23	0.83	0.85	1.28	0.69	1.49	0.25	0.87	0.50	1.31	0.42	1.38
Training session 3	0.15	1.07	0.15	1.34	0.38	1.61	0.00	0.74	-0.25	0.62	0.00	1.21
Training session 4	0.62	1.50	0.85	1.14	0.69	1.18	-0.17	0.83	-0.33	0.65	0.00	0.95
Training session 5	0.58	1.31	0.75	1.21	0.67	1.15	-0.17	0.39	-0.25	0.62	-0.33	0.98
Training session 6	0.17	0.94	0.33	1.15	0.33	1.07	0.00	0.45	0.00	0.45	0.45	0.82

Notes. Δ = post-training scores minus baseline scores.

Table B.2

Group Characteristics for Additional Measures in the Intention-to-treat Sample (n = 33)

	Training Condition											
	Cognitive Control						Placebo					
	Baseline (n = 17)		Post (n = 14)		Follow-up (n = 13)		Baseline (n = 16)		Post (n = 15)		Follow-up (n = 12)	
Variable	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
PCL-5 total	45.59	17.04	42.79	19.80	40.77	17.03	41.00	16.07	35.33	18.92	28.50	16.28
PCL-5 Avoidance	5.24	2.54	4.71	3.12	3.85	3.05	5.31	2.50	4.20	2.83	2.58	2.75
PCL-5 Arousal/Reactivity	12.88	5.34	13.29	6.01	12.77	5.69	10.75	5.09	10.07	5.68	8.67	5.21
PCL-5 Thoughts/Feelings	15.06	7.22	13.93	7.01	13.54	7.18	14.31	7.03	12.07	7.35	10.33	7.15
CAPS total score 1-20	38.47	7.86	-	-	31.69	10.27	33.44	9.70	-	-	22.75	13.54
CAPS Avoidance	4.59	1.54	-	-	3.54	1.81	4.38	1.02	-	-	2.75	2.30
CAPS Arousal/Reactivity	11.06	2.28	-	-	10.00	2.74	8.81	2.61	-	-	5.92	3.60
CAPS Thoughts/Feelings	13.00	4.37	-	-	9.46	4.77	11.19	4.76	-	-	8.33	5.79
RIQ Suppression	9.53	3.64	10.64	2.47	10.85	3.13	11.13	2.87	9.47	3.44	8.50	2.97
RIQ Rumination	10.71	4.98	10.07	4.98	10.08	5.14	11.29	5.35	8.47	4.70	8.00	5.20
RIQ Dissociation	2.59	2.03	3.07	1.86	3.08	2.18	3.00	1.75	2.73	1.62	2.25	1.36

Notes. PCL-5 = PTSD checklist for DSM-5, CAPS = Clinician administered PTSD Scale for DSM-5, RIQ = Response to Intrusions Questionnaire.