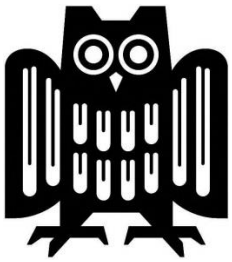
EXAMINING MEMORY PROCESSES UNDERLYING INTRUSIVE TRAUMA MEMORIES

—

THE IMPACT OF RETRIEVAL SUPPRESSION AND ASSOCIATIVE LEARNING



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CONTENTS

TABLE OF CONTENTS

INDEX OF FIGURES

INDEX OF TABLES

INDEX OF PUBLICATIONS

This Doctoral thesis consists of two chapters (and, in addition, two chapters that represent a general introduction and discussion), which are submitted or in preparation for publication as 'Original Articles' in international peer-reviewed journals. The author of this dissertation is the first author of both articles. However, other authors also contributed to the work (listed in the table). Both articles are presented here in their original form, apart from changes in formatting (e.g. figure colors and labeling). References for both articles are provided at the end of this work.

Chapter II	Streb, M., Mecklinger, A., Anderson, M.C., Lass-Hennemann, J., & Michael, T. (submitted). Memory control ability predicts reduced posttraumatic stress disorder symptoms after analogue trauma.
Chapter III	Streb, M., Conway, M. A., & Michael, T. (in preparation). Conditioned responses to trauma reminders: How durable are they over time and does imaginal trauma exposure reduce them?

INTRODUCTION

I INTRODUCTION

Traumatic events are one of the major threats to mental health all over the world. In Germany between 21% and 24% of the general population have encountered at least one traumatic event in their life (Hauffa et al., 2011; Perkonigg, Kessler, Storz, & Wittchen, 2000). In the aftermath of such an event, most survivors suffer from such symptoms as distressing intrusive memories or dreams of the event, physiological hyperarousal, emotional numbing, and avoidance of trauma reminders (McFarlane, 1988; Shalev, 1992). The majority of trauma survivors recover spontaneously within a few weeks after the traumatic event (see Figure I-1; Bonanno, 2005), however, for a significant number of them, these symptoms persist for several years (Bonanno, 2005; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; Perkonigg et al., 2000). If the symptoms persist for more than one month and lead to clinically significant distress or impairment, this symptom complex is referred to as Posttraumatic Stress Disorder (PTSD; for diagnostic criteria see Appendix, Table VI-1; American Psychiatric Association, 2013).

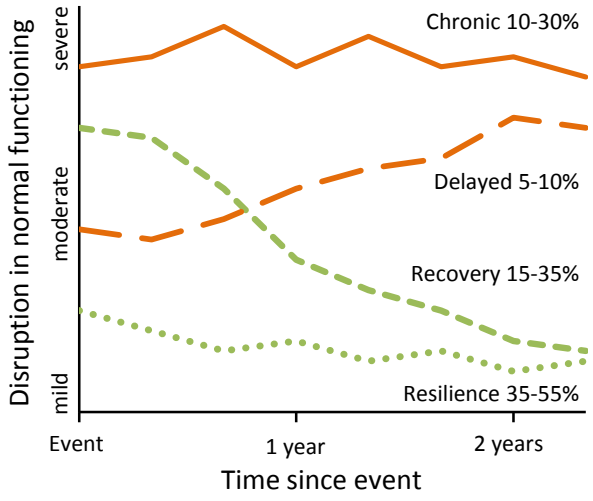

Figure I-1: Prototypical trajectories of disruption in normal functioning during the 2-year period following a traumatic event (adapted from Bonanno, 2005).

The prevalence rates of PTSD in Germany vary from 1% to 3% (Hauffa et al., 2011; Jacobi et al., 2014; Spitzer et al., 2009). PTSD has, when compared to other mental and physical disorders, a particularly strong negative impact on quality of life and is associated with high levels of disability and work loss (Alonso et al., 2004). Considerable effort is therefore invested in understanding its etiology and refining the available intervention techniques. There is a broad consensus among researchers in the field that intrusive memories of the traumatic event are of crucial relevance to understanding PTSD and thus for the development of more efficient intervention techniques (Brewin, 2014; Ehlers, 2015; Foa, Steketee, & Rothbaum, 1989). Nevertheless, the memory mechanisms which cause the constant involuntary retrieval of distressing trauma memories are not sufficiently understood. To address this issue, the aim of this work is the examination of memory mechanisms underlying the development and treatment of intrusive trauma memories.

In the following, I will first outline known risk factors for the development of PTSD, including neural abnormalities. Next, I will describe the typical characteristics of intrusive memories of traumatic events. I will then introduce well-established memory models that form the basis of our understanding of intrusive trauma memories and how memory is affected by stress. Next, I will provide an overview on research investigating memory control processes and discuss their relevance for PTSD. Thereafter, I will describe memory processes that are supposed to underlie the automatic recall of intrusive trauma memories in PTSD. After that, I will provide an overview of theory-guided intervention techniques to alleviate PTSD. Thereafter, I will evaluate different methodological approaches to study memory mechanisms underlying intrusive trauma memories. I will then provide evidence that a deficient ability to voluntarily suppress memory retrieval is a potential cognitive risk

factor for developing intrusive trauma memories (Chapter II: Memory Control and Intrusive Trauma Memories). Further on, I will provide evidence that associative learning is crucially involved in the automatic retrieval of intrusive trauma memories, and discuss whether this learning process mediates the therapeutic effects of one of the most effective intervention techniques for PTSD (i.e. imaginal exposure; Chapter III: Conditioned Responses to Trauma Reminders). Finally, I will summarize and discuss these findings and their implications with respect to ways of explaining intrusive trauma memories and intervention methods, consider limitations, and suggest an outlook and directions for future research.

1 RISK FACTORS FOR POSTTRAUMATIC STRESS DISORDER

As people differ greatly in how they are affected by traumatic events and how long they suffer from intrusive memories and posttraumatic stress (see Figure I-1; Bonanno, 2005), considerable effort has been made to understand which factors put people at risk for developing chronic PTSD. A growing number of pre-trauma risk factors have been shown to be associated with later PTSD (Brewin, Andrews, & Valentine, 2000; DiGangi et al., 2013; Ozer, Best, Lipsey, & Weiss, 2008; Schmidt, Kaltwasser, & Wotjak, 2013). Pre-trauma risk factors include social, educational, and intellectual disadvantages, female gender, history of psychiatric disorders, family history of psychopathology, and prior trauma or life adversity (Brewin et al., 2000; DiGangi et al., 2013; Ozer et al., 2008). Specifically, recent meta-analyses indicate that women are more likely to develop PTSD as compared to men (Brewin et al., 2000; DiGangi et al., 2013; Ozer et al., 2008). Several studies have revealed that lower pre-trauma intelligence increases the vulnerability for PTSD symptoms (Betts, Williams, Najman, Bor, & Alati, 2012; Breslau, Lucia, & Alvarado, 2006; Koenen, Moffitt, Poulton,

Martin, & Caspi, 2007; Macklin et al., 1998). Problematic coping styles like rumination (Nolen-Hoeksema & Morrow, 1991) and avoidance (Gil & Caspi, 2006; Lengua, Long, & Meltzoff, 2006) have been found to be predisposing risk factors for PTSD. Furthermore, pre-trauma personality factors like neuroticism (Engelhard, van den Hout, & Kindt, 2003; Knezevic, Opacic, Savic, & Priebe, 2005; Parslow, Jorm, & Christensen, 2006) and trait anxiety (McNally et al., 2011; Weems et al., 2007) have also been found to predict later PTSD. A number of studies have indicated that pre-trauma psychopathology is a predictor for developing PTSD after trauma (e.g. Heinrichs et al., 2005; Lengua et al., 2006; Orr et al., 2012). As well, a variety of psychophysiological factors have been associated with subsequent PTSD, including startle reactivity (Orr et al., 2012; Pole et al., 2009), and salivary cortisol (Heinrichs et al., 2005; van Zuiden et al., 2011). Finally, a lack of social support (Koenen et al., 2007; Lengua et al., 2006) as well as lower socioeconomic status (Koenen et al., 2007) are pre-trauma risk factors for PTSD. In addition to these cognitive and environmental risk factors, particular characteristics of brain structures have been found to be associated with PTSD.

1.1 NEURAL ABNORMALITIES IN POSTTRAUMATIC STRESS DISORDER

Recent neuroimaging findings indicate that particular abnormalities in brain structure and functioning are associated with to an enhanced vulnerability for developing PTSD. Over the last several years, a number of structural and functional abnormalities have been identified in patients with PTSD (e.g. Francati, Vermetten, & Bremner, 2007; Karl et al., 2006; Pitman et al., 2012; Rauch, Shin, & Phelps, 2006; Smith, 2005). Most of these studies, however, were conducted after the traumatic event, comparing PTSD patients to trauma-exposed or non-

trauma-exposed healthy controls, which means the majority of these results do not distinguish abnormalities that reflect predisposing vulnerability factors from those that are a consequence of the trauma. To deal with this issue, Admon, Milad, and Hendler (2013) have reviewed neuroimaging studies, using genetic, environmental, twin, and prospective methods, and have proposed a model of neural abnormalities in PTSD that distinguishes between predisposing and acquired factors (see Figure I-2).

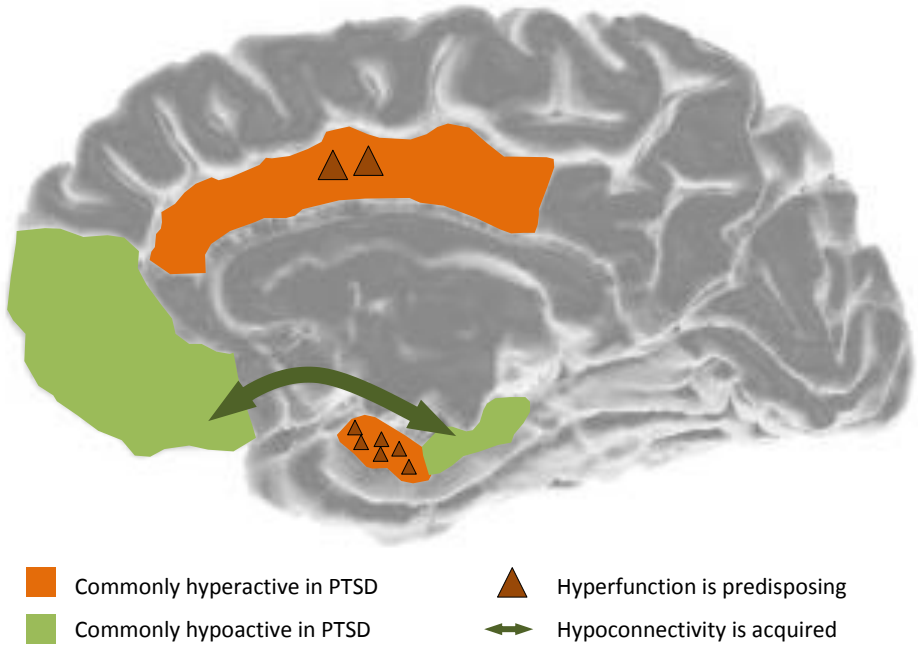

Figure I-2: Neural abnormalities in posttraumatic stress disorder (PTSD).

Orange areas mark the amygdala and dorsal anterior cingulate cortex (dACC). Green areas mark the hippocampus and medial prefrontal cortex, including the ventromedial prefrontal cortex (vmPFC), dorsomedial prefrontal cortex (dmPFC), and orbitofrontal cortex (OFC; adapted from Admon, Milad, et al., 2013).

They suggest that abnormal structure and heightened responsivity to negatively valenced stimuli of the amygdala and dorsal anterior cingulate cortex (dACC) represent predisposing abnormalities and thus constitute neural vulnerability factors for developing PTSD. This is in line with a number of neuroimaging studies observing heightened amygdala and dACC

activation in PTSD patients (e.g. Francati et al., 2007; Karl et al., 2006; Pitman et al., 2012; Rauch et al., 2006; Smith, 2005). As the amygdala and dACC have been found to mediate the generation and expression of fear (Graham & Milad, 2011; Phelps & Ledoux, 2005; Shin & Liberzon, 2010), these predisposing factors may lead to enhanced fear responses to traumatic events and prevent functional coping. On the other hand, reduced volume of brain regions in the medial prefrontal cortex (i.e. rostal anterior cingulated cortex, rACC; ventromedial prefrontal cortex, vmPFC; orbitofrontal cortex, OFC) seem to reflect changes in brain structure that are acquired along with the development of PTSD (Kasai et al., 2008; Sekiguchi et al., 2013). Furthermore, reductions in functional and structural connectivity between the vmPFC and the hippocampus may accompany the development of PTSD following a traumatic event (Admon, Leykin, et al., 2013; Admon et al., 2009). As these structures have been linked to the ability to extinguish conditioned fear responses (see section I-5.4; Hartley, Fischl, & Phelps, 2011; Milad et al., 2009; Milad et al., 2005; Milad et al., 2007; Rauch et al., 2005), structural and functional changes of these areas may represent acquired neural abnormalities that lead to reduced inhibition of conditioned fear responses.

Nevertheless, each of the factors described above accounts for a relatively small amount of variance (Admon, Milad, et al., 2013; Brewin et al., 2000), leading to the conclusion that the factors which determine who will and will not develop PTSD after trauma have not yet been fully revealed. As the vast majority of researchers from the field agree that intrusive memories of the traumatic event are of crucial relevance in PTSD, examining intrusive trauma memories may increase our understanding of this disorder and lead to more efficient intervention techniques (e.g. Brewin, Dalgleish, & Joseph, 1996; Ehlers & Clark, 2000; Foa et al., 1989).

2 INTRUSIVE MEMORIES OF TRAUMATIC EVENTS

Involuntary memory retrieval is a very common phenomenon after traumatic events. This retrieval, which is very distressing, typically consists of brief sensory fragments of the event (Ehlers, Hackmann, & Michael, 2004; Michael, Ehlers, Halligan, & Clark, 2005). Intrusions can include all sensory modalities, including bodily sensations, however, the most frequently intrusive memories occur in the form of visual images (Ehlers et al., 2002; Hackmann, Ehlers, Speckens, & Clark, 2004; Michael, Ehlers, Halligan, et al., 2005). Intrusive trauma memories are often very vivid and emotional, so that trauma survivors are in many cases not aware that they are experiencing a memory and instead report the impression that the event is happening in the here and now (Bremner, Krystal, Southwick, & Charney, 1995; Brewin et al., 1996; Hackmann et al., 2004; Michael, Ehlers, Halligan, et al., 2005; Van der Kolk & Fisler, 1995). Furthermore, unlike ordinary autobiographical memories, intrusive trauma memories often lack contextual information that would normally associate the sensory memory with a corresponding time and place (Brewin, Gregory, Lipton, & Burgess, 2010). Even though trauma survivors frequently describe intrusive trauma memories as “coming out of the blue”, they are actually triggered by a wide range of internal and external stimuli (Ehlers & Clark, 2000; Ehlers et al., 2004; Hackmann et al., 2004). Often these stimuli show sensory similarity to stimuli that have been encountered before or during the traumatic experience (Michael, Ehlers, Halligan, et al., 2005) and bear no meaningful relationship to the traumatic event (Ehlers et al., 2002). The retrieval of traumatic memories is typically under limited voluntary control, leading PTSD patients to develop other strategies to prevent their occurrence, e.g. avoiding stimuli with the potential to trigger trauma memories (Brewin, 2001; Brewin et al., 1996; Michael, Ehlers, Halligan, et al., 2005). Contemporary

models of PTSD assume that the way memories of traumatic experiences are encoded, represented, and retrieved can explain intrusive memories (Brewin, 2001; Conway & Pleydell-Pearce, 2000; Ehlers & Clark, 2000; Foa et al., 1989). Understanding general human memory functions is therefore crucial to our understanding of intrusive trauma memories.

3 MODELS OF HUMAN MEMORY

As most researchers from the field agree that intrusive memories play a key role in our understanding of PTSD (e.g. Brewin et al., 1996; Ehlers & Clark, 2000; Foa et al., 1989), uncovering the underlying mechanisms should provide further insights for identifying people at risk and for the development of more efficient intervention techniques. In order to understand how intrusive trauma memories occur, the essential models of human memory first need to be examined. Contemporary memory models which form the basis of current models of PTSD will therefore be described in the following section.

3.1 TAXONOMY OF HUMAN MEMORY SYSTEMS

A variety of information is stored in human memory. We remember our 18th birthday, know that Berlin is the capital of Germany, and know how to ride a bicycle. This spectrum of different types of information is unlikely to be represented in only a single memory system. There is a broad consensus among researchers that our memory can be subdivided into *declarative* (explicit) and *nondeclarative* (implicit) memory (see Figure I-3; Squire, 2004; Squire & Zola, 1996).

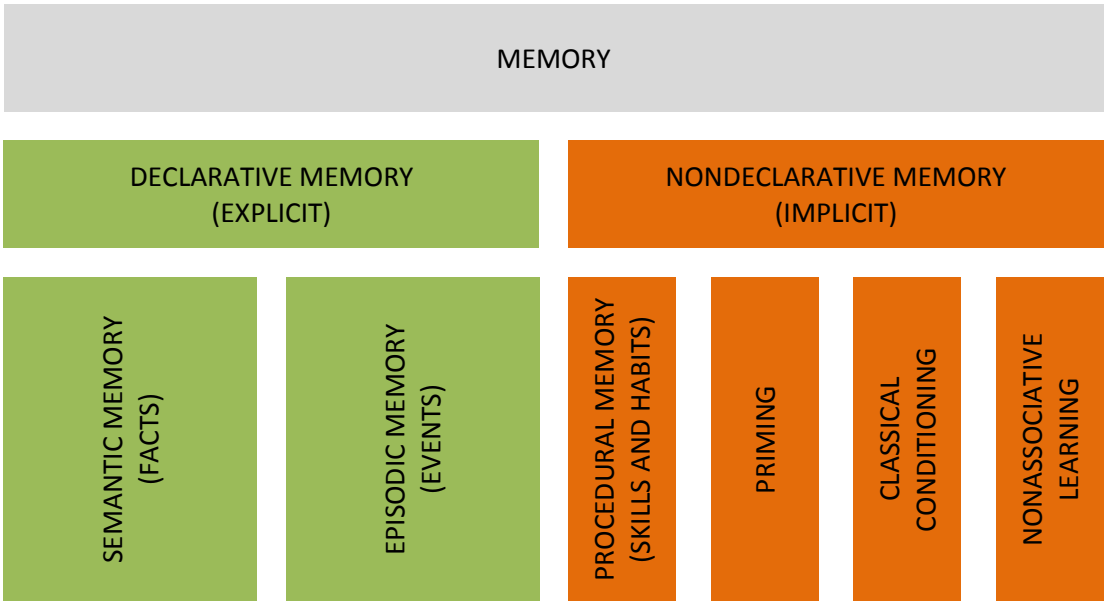

Figure I-3: A taxonomy of long-term memory system organization.

While declarative memories are thought to be consciously accessible, nondeclarative memory representations allow only limited conscious access (adapted from Squire, 2004).

Declarative memories are accessible for conscious retrieval and include *semantic memories* (i.e. memories of facts), as well as *episodic memories* (i.e. memories of personal experiences; Schacter & Tulving, 1994; Squire, 2004; Squire & Zola, 1996). Declarative memory is essentially associative, as it relates different memory components (e.g. words and objects; Mayes, Montaldi, & Migo, 2007). The neural correlate of this process can be found in various parts of the neocortex (e.g. lateral prefrontal cortex, LPFC; Levine et al., 2004; Ofen et al., 2007) projecting to the medial temporal lobes (e.g. hippocampus; Eichenbaum, 2001; parahippocampal formation; Ofen et al., 2007).

Nondeclarative memories form a heterogeneous collection of all memory representations that do not require involvement of consciousness (Squire & Zola, 1996). These include *procedural memory* (e.g. knowing how to ride a bicycle), *priming* (i.e. a change in the ability to identify, produce, or classify a stimulus as a result of prior encounter with the same or a

related stimulus), *classical conditioning* (i.e. a learning process in which a neutral stimulus comes to elicit a specific response after being repeatedly paired with another stimulus that elicits the response), *nonassociative learning* (i.e. a change in the response to a stimulus due to repeated exposure; e.g. habituation and sensitization; Squire & Zola, 1996). In contrast to declarative memory, none of these kinds of nondeclarative memory representations is thought to be primarily mediated by the hippocampus, instead, the brain areas thought to mediate these memory functions are also quite heterogeneous (Eichenbaum, 2001): While the neural correlate of procedural memory has been found in the striatum, priming is supposed to be mediated by areas in the neocortex, the amygdala is involved in emotional responses to classical conditioning, while the cerebellum is the basis of motoric reactions, and nonassociative learning is based on reflex pathways (Squire, 2004).

3.2 AUTOBIOGRAPHICAL MEMORY

Another important concept that has been considered in models of PTSD is called *autobiographical memory*. According to Conway (2005), autobiographical memory is memory for the events in the individual's life, so that, this concept overlaps to some extent with episodic memory (see section I-3.1). Conway (2003, p. 219) states, however, that episodic memories constitute short-term fragments of experiences, whereas "A uniquely human […] memory system represents conceptually organized autobiographical knowledge that provides a context or setting for episodic memories […] this system controls the output of the episodic system by directly inhibiting/activating it and by selecting and modifying the cues used to access it."

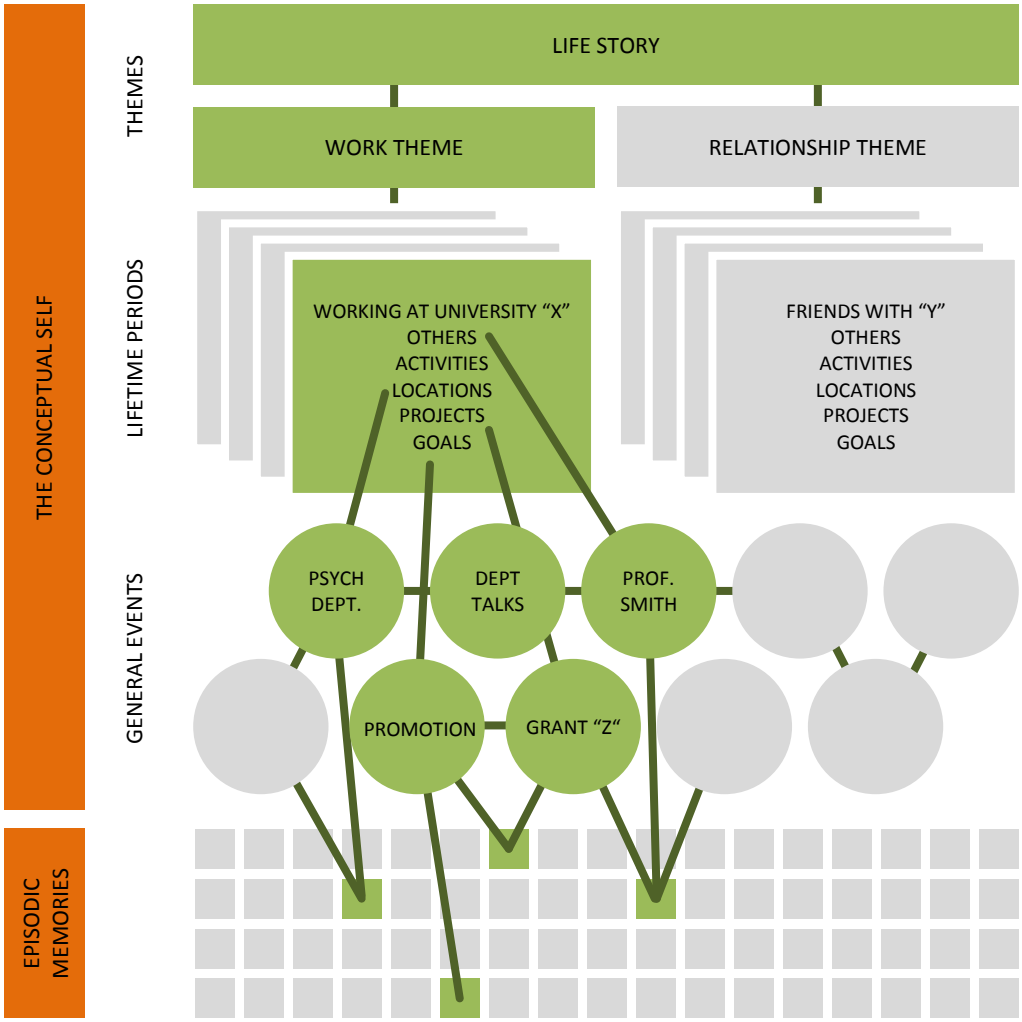

Figure I-4: The knowledge structures within autobiographical memory (adapted from Conway, 2005).

In his model, Conway (2005) argues that the autobiographical knowledge base is structured hierarchically (see Figure I-4): An overall life story is linked to several *global themes*, e.g. "work" or "personal relationships". These themes are divided according to the time period in which they occurred (e.g. "When I was a PhD student"). These lifetime periods include several *general events* containing more specific information about individuals, institutions, or activities involved in them (e.g. "Prof. Smith", "psychology department", or "department talks"). These general events also exist at a relatively abstract level, but can lead to specific episodic memories (e.g. "Prof. Smith's last department talk at the psychology department")

that provide detailed perceptual information (e.g. “the expression on Prof. Smith’s face when he ended his last talk”). Conway (2005) further postulates the existence of the *working self*, a central control process that controls access to the autobiographical knowledge base. The working self can manipulate memory cues that activate memory representations in the autobiographical knowledge base, and thus can control both encoding and retrieval of specific episodic memories (Conway, 2005).

3.3 STRESS-RELATED CHANGES IN MEMORY FUNCTIONS

Memory functions are affected by stress in several ways (Roozendaal, McEwen, & Chattarji, 2009). In addition to preparing the individual for coping with an acute danger or threat, another function of stress is to establish long-term adaptive responses (McEwen, 1998). Memories for emotionally arousing or stressful experiences are often very detailed and vivid (Dolcos, Denkova, & Dolcos, 2012; Mather, 2007; Mather & Sutherland, 2011; Roozendaal et al., 2009) and are more resistant to being forgotten over time (Ritchey, Dolcos, & Cabeza, 2008). However, these studies have focused on memory for individual items, thereby neglecting memory for contextual or relational information (i.e. associative memory). With regard to stress-related alterations in associative memory, the results are less clear: Some studies find enhanced memory for contextual or relational information (D'Argembeau & Van der Linden, 2005; Doerksen & Shimamura, 2001; MacKay & Ahmetzanov, 2005), while others find impaired memory for this kind of information (Cook, Hicks, & Marsh, 2007; Kensinger, Garoff-Eaton, & Schacter, 2007; Kensinger & Schacter, 2006; Pierce & Kensinger, 2011) or no differences (Mather, Gorlick, & Nesmith, 2009). What follows will

describe various explanations which have been put forward to resolve these contradictory findings.

Mather (2007) has outlined an object-based framework that predicts when arousal enhances memory binding and when it impairs it, thereby building on the findings that focused attention is required for binding features of objects together (Treisman, 1999) and that emotional stimuli have the potential to attract attention (Eastwood, Smilek, & Merikle, 2001; Fox, Russo, Bowles, & Dutton, 2001). She has proposed that an attentional focus, as is typically observed with emotionally arousing stimuli (Schimmack & Derryberry, 2005), enhances within-object binding, and thus enhances memory of associated within-object features (e.g. color of the object). As the attentional focus, however, is limited solely to the emotional object, it does not promote memory binding with other objects or contextual features and can even impair the creation of these associations. Contextual memory for within-stimulus details should therefore be enhanced due to emotional arousal, while contextual memory for those between stimuli should be impaired.

Recently, Chiu, Dolcos, Gonsalves, and Cohen (2013) have emphasized the critical role of underlying memory representations of an item and contextual memories in this context. Specifically, they propose that studies showing memory enhancement with emotional arousal tend to involve stimulus properties that are perceptual or conceptual, and thus can be "unitized" to be represented as a single item. In contrast, relational memory representations, such as contextual information or information about relationships to other stimuli, are thought to be impaired due to emotional arousal. The neural basis for the differential impact of emotion on these memory representations is supposed to be found in the hippocampus:

Several findings indicate that relational memory representations strongly depend on the hippocampus, while item memory is largely independent of hippocampal involvement (Cohen, Poldrack, & Eichenbaum, 1997; Cohen et al., 1999; Diana, Yonelinas, & Ranganath, 2008; Konkel & Cohen, 2009; Konkel, Warren, Duff, Tranel, & Cohen, 2008). There is also evidence that the interaction between the amygdala and the hippocampus during high levels of stress can lead to reduced hippocampal functioning (for reviews see Lupien & Lepage, 2001; Radley & Morrison, 2005; Sapolsky, 2004). Following Chiu et al. (2013), stress-related impairments in hippocampal functioning should cause deficits in relational memory, while leaving memory for (unitized) items unimpaired. Assuming that is true, impaired encoding of relational information during traumatic events may create memory representations that lack contextual information, potentially leading to vividly remembered fragments of the traumatic events without contextual information, as well as to the extensive recollection of trauma memories typically observed in PTSD.

Since, the majority of trauma survivors recover quickly after traumatic events, they must therefore be able to control this automatic retrieval of trauma memories, indicating that the ability to control memory retrieval may help in recovering from traumatic events. The following paragraphs will discuss research which examines these memory control processes and their effects on memory representations, as well as implications for intrusive trauma memories.

4 MEMORY CONTROL AND INTRUSIVE TRAUMA MEMORIES

As traumatic events are highly aversive, one obvious reaction after such events is to try to exclude them from awareness. It has been proposed that active control processes can be engaged to inhibit either memory encoding or retrieval of unwanted memories and that this inhibition leads to a reduced likelihood of that memory being retrieved again, a process called motivated forgetting (Anderson & Hanslmayr, 2014). Even though this is a rather controversial issue, as some researchers claim that suppressing a thought actually *increases* its tendency to occur again (Purdon, 1999; Wegner, 1994; Wegner, Schneider, Carter, & White, 1987; Wenzlaff & Wegner, 2000), there is growing evidence for successful motivated forgetting (Anderson & Hanslmayr, 2014). To reduce the likelihood of subsequent memory retrieval, inhibitory control can be engaged either during memory encoding or retrieval. On the one hand, inhibiting memory encoding may prevent the consolidation of memory traces. Stopping memory retrieval, on the other hand, may decrease the subsequent accessibility of a memory by preventing the automatic process of retrieving an associated memory as a reaction to a cue. The following section will discuss various approaches to investigating these different aspects of motivated forgetting and how they may relate to intrusive trauma memories.

4.1 DIRECTED FORGETTING

Whether people can voluntarily forget recently encountered information when they are instructed to do so, has often been studied by means of the directed forgetting procedure

(Bjork, 1972, 1989). Two variants of this paradigm have been established: item-method directed forgetting and list-method directed forgetting.

In item-method directed forgetting paradigms, participants are presented with a series of stimuli to study. After each stimulus they are instructed either to remember or to forget it. Participants are tested afterwards for all of the previously studied items. The to-be-forgotten stimuli are often less well remembered as compared to the to-be-remembered stimuli (Anderson & Hanslmayr, 2014). Item-method directed forgetting effects have been observed in recall and recognition tests, as well as in implicit memory tests (Basden, 1996; Basden, Basden, & Gargano, 1993; MacLeod & Daniels, 2000). These forgetting effects are usually explained by selective rehearsal, meaning that to-be-forgotten items are not further processed and thus are more likely to be forgotten than to-be-remembered items, which are actively rehearsed (Bjork, 1989). Nevertheless, Anderson and Hanslmayr (2014) have proposed that active inhibitory control processes may actually be involved in this process. This assumption is based on findings that the forget condition is more effortful than the remember condition (Fawcett & Taylor, 2008) and that it shares mechanisms with stopping a motor action (Fawcett & Taylor, 2010). Whether active inhibitory control processes are involved in this form of forgetting therefore remains an open issue.

In the list-method directed forgetting procedure, participants study an entire list of words and are subsequently instructed to remember or forget the whole list. Afterwards, participants study a second list and are subsequently instructed to remember the preceding list. After the second list, recall is tested. Participants typically recall fewer words from the first list when they were instructed to forget the list as compared with being instructed to remember it

(Anderson & Hanslmayr, 2014). Participants often recall more items from the second list when they have been instructed to forget the first list as compared with being instructed to remember it (Bäuml, Pastötter, & Hanslmayr, 2010). These effects have been reported for free recall, cued recall, and recognition tests (Anderson & Hanslmayr, 2014). There is also some evidence that active control mechanisms may be involved in this phenomenon, as brain oscillations and pupillary reactions indicate a higher cognitive load after the forget instruction as compared to the remember instruction (Bäuml, Hanslmayr, Pastötter, & Klimesch, 2008; Geiselman, Bjork, & Fishman, 1983).

As people differ in the ability to voluntarily forget, differences in directed forgetting could also be involved in determining to what extend people suffer from intrusive memories after traumatic events. To examine this relationship, Zwissler et al. (2012) assessed directed forgetting in trauma survivors. They found that PTSD patients showed reduced item-method directed forgetting as compared to trauma-exposed controls with no PTSD, indicating that memory control ability is reduced in trauma survivors with PTSD (for similar results see Cottencin et al., 2006). However, because directed forgetting was examined after the traumatic event, it remains unclear whether deficient directed forgetting constitutes a factor of vulnerability or a consequence of the disorder. Prospective studies are therefore needed to investigate, whether differences in memory control can predict later intrusive trauma memories.

4.2 RETRIEVAL-INDUCED FORGETTING

Another active mechanism that leads to forgetting has been found in the phenomenon of retrieval-induced forgetting (Anderson, Bjork, & Bjork, 1994). This phenomenon describes how the act of remembering can cause forgetting of related information in memory. Retrieval-induced forgetting is typically studied with the following paradigm: Participants study a list of items in which each item is associated with two other items (e.g. word-pairs: fruits – apple, fruits – orange). One of these associations is repeatedly practiced afterwards (e.g. given the retrieval cue fruits – a___), while the other is not repeated. Following this practice, a recall test for all items is completed. Typically, the non-practiced items (e.g. orange) are less well remembered than practiced items and are even impaired when compared to a control condition of stimuli that have not been studied before (e.g. fruits – b___). This impairment has been attributed to an inhibitory control mechanism that suppresses retrieval of the non-practiced item in order to reduce interference caused by competing memory traces (Anderson et al., 1994; Anderson & Spellman, 1995; Bäuml & Aslan, 2004).

However, the only study so far which has investigated retrieval-induced forgetting in trauma-survivors found no significant differences between participants with PTSD and participants without PTSD (Blix & Brennen, 2012), so it remains unclear whether the same inhibitory process is involved in suppressing trauma memories.

4.3 SUPPRESSION-INDUCED FORGETTING

Another active forgetting process that supposedly involves inhibitory control is retrieval suppression (Anderson & Green, 2001; Anderson & Hanslmayr, 2014). It refers to the process implemented when people are confronted with reminders of an unpleasant memory and try to exclude the unwanted memory from awareness. Anderson and Green (2001) proposed the existence of a cognitive control mechanism that is able to accomplish this by blocking retrieval of the unwanted memory. Analogous to stopping a reflexive motor action, retrieval suppression can prevent an unwanted memory from entering awareness (Anderson & Green, 2001).

To investigate suppression-induced forgetting, Anderson and Green (2001) developed the think/no-think (TNT) task. This task simulates situations where one is confronted with a reminder of an unwanted memory and tries to suppress its retrieval. Numerous studies using the TNT task have found that when memory retrieval is suppressed, participants are less able to subsequently recall that memory, even when they are instructed to do so (Anderson et al., 2004; Benoit, Hulbert, Huddleston, & Anderson, 2014; Küpper, Benoit, Dalgleish, & Anderson, 2014). This effect increases systematically with the number of times the no-think items are suppressed (Anderson & Green, 2001; Joormann, Hertel, Brozovich, & Gotlib, 2005; Joormann, Hertel, LeMoult, & Gotlib, 2009). Suppression-induced forgetting has been demonstrated as well for negatively valenced stimuli, including words and scenes (Depue, Curran, & Banich, 2007; Küpper et al., 2014; Lambert, Good, & Kirk, 2010; van Schie, Geraerts, & Anderson, 2013). As suppression-induced forgetting has also been observed when a novel cue is used to test memory retrieval, the general accessibility of that memory

trace seems to be affected (Anderson & Green, 2001; Anderson & Huddleston, 2012). This is taken as evidence for an active control process being involved in retrieval suppression (Anderson & Green, 2001; Anderson & Huddleston, 2012; for an alternative explanation see Tomlinson, Huber, Rieth, & Davelaar, 2009).

The electrophysiological correlate of this control process has been found in the N2 event-related potential (ERP) component, which had previously been linked to inhibition of a prepotent motor response (Bergström, de Fockert, & Richardson-Klavehn, 2009a, 2009b; Mecklinger, Parra, & Waldhauser, 2009; Waldhauser, Lindgren, & Johansson, 2012). The amplitude of this component is even able to predict whether a memory has been successfully suppressed or not, meaning that its probability of being recalled in a subsequent memory test is reduced (Mecklinger et al., 2009). Furthermore, there is evidence indicating that the neural mechanism underlying retrieval suppression is a down-regulation of mediotemporal lobe (MTL) activity, especially in the hippocampus, by control processes in the prefrontal cortex, especially the dorsolateral prefrontal cortex (dlPFC) and the ventrolateral prefrontal cortex (vlPFC; Anderson & Hanslmayr, 2014; Anderson et al., 2004; Benoit et al., 2014). These findings suggest that retrieval suppression is accomplished by a prefrontal inhibitory process that down-regulates recollection of episodic memories in the hippocampus.

It seems plausible therefore to assume that the same inhibitory processes involved in retrieval suppression during the TNT task is also involved in stopping the involuntary retrieval of traumatic memories after trauma. Indeed, a recent study assessing retrieval suppression in trauma survivors has found that traumatized participants with PTSD show deficits in suppressing retrieval of aversive images as compared to traumatized participants

without PTSD (Catarino, Kupper, Werner-Seidler, Dalgleish, & Anderson, 2015). Because it remains unclear, however, whether these deficits existed before the trauma and thus promoted PTSD development, or whether they are simply a consequence of the disorder, prospective studies are needed to examine whether deficient memory control ability is a pre-existing cognitive risk factor for the development of intrusive trauma memories and PTSD after a traumatic event.

4.4 AIMS OF STUDY 1: MEMORY CONTROL AND INTRUSIVE TRAUMA MEMORIES

This thesis aims to follow that line of research and investigate whether pre-trauma memory control ability can predict later intrusive memories and other PTSD symptoms. In addition, it examines whether neural correlates of inhibitory control processes found to be associated with retrieval suppression, along with the inhibition of a prepotent motor response, can also predict reduced intrusive trauma memories, and thus are likely to be involved in controlling their automatic retrieval, as well. As the concept of retrieval suppression is the most naturalistic analogue to situations in which a trauma exposed person is confronted with a potential memory cue of the traumatic event, examining this phenomenon in relation to intrusive trauma memories will provide the most relevant insights. The first study therefore examines the relationship between suppression-induced forgetting and its neural correlates to intrusive memories after traumatic events.

5 MEMORY PROCESSES UNDERLYING AUTOMATIC TRAUMA MEMORY RECALL

Intrusive trauma memories differ from other episodic memories in a number of qualities: Intrusions are triggered by a wide range of reminders and are under limited voluntary control (Halligan, Michael, Clark, & Ehlers, 2003). Whereas episodic memories usually are recognized as memories (Tulving, 1983), trauma survivors often are not aware that intrusions are memories of the traumatic event and instead experience them as happening in the "here and now" (Michael, Ehlers, Halligan, et al., 2005). There is broad consensus among researchers that dysfunctional encoding and/or retrieval of trauma memories can account for the occurrence of intrusive trauma memories (Brewin, 2001; Conway & Pleydell-Pearce, 2000; Ehlers & Clark, 2000; Foa et al., 1989). The following sections focus on memory mechanisms that have been suggested as involved in the development and occurrence of intrusive trauma memories.

5.1 DEFICIENT MEMORY INTEGRATION

Unlike ordinary autobiographical memories that are usually under voluntary control, memories of traumatic events often are retrieved unintentionally. It has been proposed that the extreme stress experienced during traumatic situations leads to memory representations that differ fundamentally from other autobiographical memory representations (Brewin, 2001; Brewin et al., 1996; Ehlers & Clark, 2000). Research on autobiographical memories in non-traumatized participants indicates that autobiographical events are usually incorporated into an autobiographical memory knowledge base (Conway & Pleydell-Pearce, 2000), and

that this elaboration in turn facilitates intentional retrieval and, more importantly, allows the inhibition of automatic retrieval triggered by associated memory cues (Conway & Pleydell-Pearce, 2000). In PTSD patients, however, this elaboration seems to fail, preventing an appropriate control of the automatic retrieval of trauma memories (Brewin, 2001; Ehlers & Clark, 2000).

Several findings indicate that during emotionally arousing events encoding of relational information is impaired (see section I-3.3; Bremner et al., 1995; Lupien & Lepage, 2001; Metcalfe & Jacobs, 1998). During high levels of stress the interaction between the hippocampus and the amygdala can lead to a decline in hippocampal functioning (Bremner et al., 1995; Lupien & Lepage, 2001; Metcalfe & Jacobs, 1998; Radley & Morrison, 2005; Sapolsky, 2004). Reduced hippocampal activity in turn leads to deficient binding of individual features of the experience into a coherent memory, which produces memory representations that are less accessible to voluntary memory retrieval. This explanation can account for why trauma survivors sometimes are not able to voluntarily recall all contextual details of the traumatic event (Brewin, 2001). Activity in the amygdala, however, is generally enhanced as stress increases, leading to the formation of strong conditioned responses (Pitman, Shalev, & Orr, 2000). In concert, these reactions may bring about memory representations that can easily be triggered by cue-driven retrieval and at the same time are less accessible to inhibitory control mechanisms (Brewin, 2001; Conway & Pleydell-Pearce, 2000). These findings correspond to the clinical observations of PTSD patients experiencing involuntary intrusive trauma memory retrieval that is triggered by trauma-associated stimuli and can hardly be controlled voluntarily.

5.2 ENHANCED PERCEPTUAL PRIMING

To trigger a traumatic memory, trauma-associated stimuli first need to be perceived. A lowered perceptual threshold in PTSD patients may contribute to the extensive retrieval of traumatic memories and this may be due to perceptual priming (Ehlers & Clark, 2000).

The perception and identification of a stimulus is improved when that stimulus has been encountered before. Participants typically show lower perceptual identification thresholds for repeated stimuli, and are both more accurate and faster in identifying repeated stimuli as compared to new stimuli (Schacter, Dobbins, & Schnyer, 2004; Tulving & Schacter, 1990). This form of nondeclarative memory has been referred to as perceptual priming. Despite severe impairments in explicit memory tests that require conscious recollection of previously encountered information, amnestic patients often show unimpaired perceptual priming effects (Hamann & Squire, 1997). Furthermore, while explicit memory typically declines over time (Wickelgren, 1972), perceptual priming effects are very stable over time (Musen & Treisman, 1990; Tulving, Schacter, & Stark, 1982), and have even been reported after a delay of 48 weeks (Cave, 1997). Perceptual priming can also occur for stimuli that are perceptually similar to a previously encountered stimulus (Cooper, Schacter, Ballesteros, & Moore, 1992; Seamon et al., 1997), and is not impaired when attention is divided (Kellogg, Newcombe, Kammer, & Schmitt, 1996) or the stimuli are irrelevant during encoding (Szymanski & MacLeod, 1996).

Based on these findings, Ehlers and Clark (2000) have suggested that perceptual priming is especially pronounced during traumatic situations, which leads to a lowered threshold for stimuli that were perceived during trauma. As perceptual priming can also occur for

perceptually similar stimuli, stimuli that only bear some similarity to those present during the trauma should also have lower perceptual thresholds in the aftermath of a traumatic event. Perceiving potential trauma reminders in neutral environments would, in turn, lead to a higher probability of trauma memories being retrieved.

Perceptual priming effects for traumatic events have recently been investigated by means of experimental analogue paradigms. Healthy participants were presented with traumatic and neutral picture stories, and then subsequently given a test of implicit memory. In this test they had to identify blurred versions of neutral visual stimuli that were presented during the picture stories. Stimuli originally presented in the traumatic picture stories showed enhanced perceptual priming effects (i.e. higher identification rates) as compared to those presented during the neutral picture stories (e.g., Arntz, de Groot, & Kindt, 2005; Ehlers, Mauchnik, & Handley, 2012; Ehlers, Michael, Chen, Payne, & Shan, 2006; Holz, Lass-Hennemann, Streb, Pfaltz, & Michael, 2014; Michael & Ehlers, 2007). This enhanced perceptual priming effect was also shown to predict intrusive memories of the traumatic picture stories in the following week (Ehlers et al., 2012; Ehlers et al., 2006; Michael & Ehlers, 2007).

An enhanced perceptual priming effect for trauma-related stimuli has also been found in a study of trauma survivors (Kleim, Ehring, & Ehlers, 2012). Participants with PTSD had a higher likelihood of identifying blurred trauma-related pictures as compared to general threat pictures or neutral pictures, whereas trauma survivors without PTSD did not show these perceptual priming effects. This processing advantage for trauma-related pictures also predicted PTSD symptoms at six-month follow-up assessments. Other studies employing a number of different paradigms to examine perceptual priming in trauma survivors have also

found specific perceptual priming effects only in those participants that later developed PTSD (Amir, Leiner, & Bomyea, 2010; Michael, Ehlers, & Halligan, 2005).

5.3 PERCEPTUAL MEMORY PROCESSING

Roediger (1990) has suggested that memory performance benefits from the extent to which cognitive operations at retrieval recapitulate those engaged during encoding. If, therefore, a memory's encoding was mainly data-driven (i.e. primarily encoding perceptual features rather than conceptual information), its memory representation will be more accessible to data-driven recall, whereas, if a memory is encoded semantically it will be more accessible to semantic retrieval. Support for this hypothesis comes from neuroimaging studies indicating that the cortical activity during encoding of a stimulus is reinstated when the stimulus is subsequently retrieved (Danker & Anderson, 2010; Dewhurst & Knott, 2010; Johnson & Rugg, 2007).

In building on this framework, Ehlers and Clark (2000) have suggested that data-driven processing during traumatic situations facilitates data-driven recall and thus puts people at risk for experiencing intrusive memories when confronted with trauma reminders. To test whether data-driven processing of traumatic events predicts subsequent PTSD symptoms, peri-traumatic data-driven processing was assessed via questionnaires in survivors of motor vehicle accidents (Ehring, Ehlers, & Glucksman, 2008) and assault survivors (Halligan et al., 2003). In line with the hypothesis, data-driven processing did predict PTSD severity six months later, however, these studies rely on retrospective ratings and thus provide no evidence for a causal relationship between data-driven processing during trauma and subsequent intrusive memories. To address this issue, Halligan, Clark, and Ehlers (2002)

instructed healthy participants to engage in either data-driven processing or conceptual processing while they were watching traumatic film footage. Additionally, pre-experimental cognitive processing styles and cognitive processing during film presentation were assessed via questionnaires. Contrary to the hypothesis, the instructions had little influence on cognitive processing during film presentation, but participants who reported more data-driven processing during film presentation, as well as more habitual data-driven processing subsequently developed more intrusive memories of the traumatic film. Kindt, van den Hout, Arntz, and Drost (2008) have been able to show that participants who were instructed to engage in data-driven processing in the aftermath of viewing a traumatic film had more intrusive trauma memories as compared to participants that were instructed to engage in conceptual processing. Furthermore, performing a distracting verbal task that interferes with conceptual processing (i.e. counting backwards in sevens) during trauma film presentation leads to more frequent intrusive trauma memories as compared to performing no additional task during film presentation (Bourne, Frasquilho, Roth, & Holmes, 2010), which supports the importance of perceptual processing for the development of intrusive trauma memories.

5.4 FEAR CONDITIONING

Another memory mechanism that is supposedly involved in the formation of intrusive trauma memories is fear conditioning. According to the fear conditioning approach, the traumatic event can be seen as an unconditioned stimulus (UCS) that triggers unconditioned responses (UCR) such as intense fear and arousal. Through spatial and temporal contiguity, this UCR becomes associated with neutral stimuli that are present during trauma (conditioned stimuli, CS). Subsequently, these CSs can trigger reactions similar to the

original emotional and physiological reactions to the trauma (conditioned responses, CRs; see also Brewin et al., 1996; Ehlers & Clark, 2000; Foa et al., 1989; Keane, Zimering, & Caddell, 1985). According to this framework, intrusive trauma memories can be considered as CRs that are triggered by trauma-associated stimuli (CSs; Foa et al., 1989; Keane et al., 1985; Rothbaum & Davis, 2003). Individual differences in the ease with which these associations are acquired and how durable they are over time (i.e. conditionability), as well as how likely they are to be transferred to similar stimuli (i.e. generalization), should therefore determine whether PTSD symptoms persist. The concept of enhanced conditionability assumes that people differ in their disposition to develop CRs when confronted with a traumatic event and/or to show reduced extinction learning of theses CRs (Orr et al., 2000). In line with this account, PTSD patients show enhanced CRs during acquisition and extinction as compared to trauma survivors without PTSD (Blechert, Michael, Vriends, Margraf, & Wilhelm, 2007; Orr et al., 2000). Lommen, Engelhard, Sijbrandij, van den Hout, and Hermans (2013) have been able to show that reduced extinction learning before a traumatic event predicts subsequent PTSD symptom severity. Wegerer, Blechert, Kerschbaum, and Wilhelm (2013), using short aversive film clips as UCSs, have also shown that reduced extinction learning (as indexed by valence ratings and SCRs) predicted subsequent intrusive memories of the aversive film clips, thus providing further evidence for associative learning being involved in the development of intrusive trauma memories.

Nevertheless, fear conditioning paradigms often lack ecological validity, as the procedure is rather artificial and does not resemble the typical time course of a traumatic event. Furthermore, the studies mentioned above only assessed conditioned responses and

conditioned intrusive memories immediately after the acquisition procedure, which leaves open the critical question of whether these conditioned reactions remain stable over time.

5.5 AIMS OF STUDY 2: CONDITIONED RESPONSES TO TRAUMA REMINDERS

To fill this gap, the second aim of this thesis is to examine the temporal stability of conditioned responses to trauma reminders. As conditioned associations are thought to account for intrusive trauma memories, this is a crucial precondition. Furthermore, this study aims to extend the previous findings from rather artificial laboratory paradigms to more naturalistic conditions that resemble more closely the complexity of real-life trauma and thus provide higher ecological validity.

6 TREATMENT APPROACHES FOR POSTTRAUMATIC STRESS DISORDER

With increasing understanding of the underlying mechanisms of PTSD, effective treatment methods have been developed. The next section will give an overview of the treatment methods currently available and discuss their supposed underlying functional mechanisms.

As changes in the hormones and neurotransmitters have been reported in PTSD patients, several drug therapies have been used to treat PTSD, including tricyclic antidepressants, anticonvulsants and mood stabilizers (e.g. carbamazepine), benzodiazepines, monoamino oxidase inhibitors, and specific serotonin reuptake inhibitors (SSRIs; Friedman & Schnurr, 1995; Sutherland & Davidson, 1994). A recent meta-analysis found significant superiority to placebo only for SSRIs (Hoskins et al., 2015), however, the reported effect sizes were relatively low when compared to psychological treatments (Bisson et al., 2007; Hoskins et

al., 2015). Psychological treatments are therefore recommended over pharmacological treatments as the method of choice for PTSD therapy (Benedek, Friedman, Zatzick, & Ursano, 2009; Forbes et al., 2007; National Collaborating Centre for Mental Health, 2005).

A number of psychological treatments for PTSD have been developed, including trauma focused cognitive behavioral therapy (TFCBT; Foa, Rothbaum, Riggs, & Murdock, 1991; Foa et al., 1989), eye-movement desensitization and reprocessing (EMDR; Shapiro, 1991), various stress-management programs (Carlson, Chemtob, Rusnak, Hedlund, & Muraoka, 1998; Foa et al., 1991; Meichenbaum, 2007; Vaughan et al., 1994), supportive, non-directive therapy (Blanchard et al., 2003), hypnotherapy (Brom, Kleber, & Defares, 1989), psychodynamic therapy (Brom et al., 1989), and interpersonal therapy (Krupnick et al., 2008).

Several meta-analyses suggested that TFCBT and EMDR show the best treatment outcomes (Bisson et al., 2007; Bradley, Greene, Russ, Dutra, & Westen, 2005; Cloitre, 2009; Ehlers et al., 2010; Seidler & Wagner, 2006; Van Etten & Taylor, 1998; for contradictory results see Benish, Imel, & Wampold, 2008). Studies examining potential differences between these treatment methods have consistently found that they are equally effective (Bisson et al., 2007; Bradley et al., 2005; Forbes et al., 2007; Seidler & Wagner, 2006). Both methods are trauma-focused, which means that the patient confronts memories of the traumatic event, and this *imaginal exposure* to the traumatic event may be the relevant component underlying the beneficial effects of these treatments. Despite their effectiveness, however, relatively little is known about the processes underlying these intervention effects.

As described above, traumatic memory representations in people with PTSD can easily be triggered by trauma reminders and at the same time are less accessible to intentional retrieval and, more importantly, to inhibitory control mechanisms (see section I-3.2; Brewin, 2001; Conway & Pleydell-Pearce, 2000). This kind of memory representation is thought to result from a lack of hippocampal processing due to extreme stress during encoding (see section I-3.3; Bremner et al., 1995; Lupien & Lepage, 2001; Metcalfe & Jacobs, 1998; Radley & Morrison, 2005; Sapolsky, 2004), which leads to uncontrolled, conditioned responses such as physiological reactions and cue-driven retrieval of trauma memories (Brewin, 2001; Foa et al., 1989; Pitman et al., 2000).

Deliberately reactivating the trauma memory, including as many contextual details as possible (i.e. imaginal exposure), should therefore promote hippocampus-dependent binding with contextual information and thus enable conditioned responses to be inhibited voluntarily (Brewin, 2001; Ehlers & Clark, 2000). In line with this reasoning, Ehlers et al. (2012), employing an analogue design, were able to show that imaginal exposure after an analogue trauma led subsequently to a reduction in both intrusive memories and negative evaluative conditioning (i.e. a change in valence of a neutral stimulus due to its pairing with another negative stimulus). It remains unclear, however, whether imaginal exposure also influences conditioned reactions to neutral trauma-associated stimuli, such as physiological arousal, negative mood, and intrusive trauma memories.

6.1 SUBSIDIARY AIMS OF STUDY 2: CONDITIONED RESPONSES TO TRAUMA REMINDERS

In the light of the assumption that conditioned responses to trauma-associated stimuli should be alleviated by imaginal exposure, the second study additionally aimed to examine whether imaginal exposure to the traumatic event can reduce the number and intensity of intrusive trauma memories triggered by trauma-associated stimuli, as well as conditioned physiological reactions. According to this approach, when people reactivate their trauma memories voluntarily, this promotes memory integration and thus reduces conditioned reactions, such as emotional arousal and intrusive trauma memories.

7 METHODOLOGICAL PARADIGMS TO STUDY MEMORY PROCESSES UNDERLYING INTRUSIVE MEMORIES IN POSTTRAUMATIC STRESS DISORDER

To study the mechanisms underlying intrusive memories, different methodological paradigms have been developed, each of which presents its own advantages and drawbacks. Requirements for the implemented paradigms can vary widely depending upon the question being researched. The following section will discuss specific requirements for studying particular research questions and the sort of paradigms that can meet those requirements.

7.1 CLINICAL FIELD STUDIES

One common and obvious method for investigating intrusive trauma memories is to study people that have been exposed to a traumatic event. In these populations, different factors

can be assessed for trauma survivors immediately after the traumatic event and their potential to predict later intrusive memories can be evaluated (see the meta-analysis by Ozer et al., 2008). A substantial portion of our knowledge comes from such longitudinal studies. Michael, Ehlers, Halligan, et al. (2005), for example, examined assault survivors and found that subjective evaluations of the characteristics of intrusive memories after the assault could predict PTSD symptoms in a six-month follow-up better than mere intrusion frequency. Even though clinical field studies have a very high ecological validity, one shortcoming of many of these studies is that they rely on retrospective reports of the participants' experiences (Candel & Merckelbach, 2004). As retrospective reports are very vulnerable to subsequent biases, prospective studies are essential for drawing reliable conclusions about causality. It is, however, clearly unjustifiable to intentionally expose participants to real-life traumatic events. One way to circumvent this problem is by studying people who are very likely to experience a traumatic event (e.g. due to their profession). A sample of fire-fighters, for example, has been tested before and after trauma exposure to draw conclusions about potential pre-existing risk factors for PTSD (Bryant & Guthrie, 2005). Even though these paradigms have produced important insights, the trauma itself, its context, and the person's reactions during the trauma are not under experimental control in this design, thus making causal conclusions impossible. The only paradigms offering complete experimental control are analogue trauma studies.

7.2 ANALOGUE TRAUMA STUDIES

As it is clearly unethical to intentionally expose participants to a real-life traumatic event, researchers have tested different kinds of stressors that model important aspects of real-life

trauma and can cause similar memory phenomena without putting participants' mental health at any risk. A range of analogue paradigms has been developed to investigate memory processes relevant to intrusive trauma memories. All involve exposing non-clinical participants to a laboratory equivalent of a traumatic event. Ehlers et al. (2006) exposed participants to picture stories describing traumatic events (e.g. somebody is killed by a housebreaker), using pictures of the international affective picture system (IAPS; Lang, Bradley, & Cuthbert, 2008), and successfully induced intrusive memories. This picture story paradigm has the advantage of allowing neutral picture stimuli to be presented during the analogue trauma, so that perceptual priming for these trauma-associated stimuli could be assessed subsequently (see section I-5.2). Because, however, the picture stories are still relatively mild stressors, the typically observed number of intrusive memories is relatively low, and the resemblance to traumatic events is limited.

Another promising approach for inducing analogue trauma under experimentally controlled conditions is the trauma film paradigm (for a review see Holmes & Bourne, 2008). By presenting to healthy participants a short film clip (ca. 10 min) depicting traumatic events (e.g. a car accident or a homicide), intrusive memories, negative mood, distress, and other analogues of PTSD symptoms can reliably be induced (Brewin & Saunders, 2001; Halligan et al., 2002; Laposa & Alden, 2006). As aversive film clips can cause relatively high emotional arousal (Schaefer, Nils, Sanchez, & Philippot, 2010), the trauma film paradigm has considerable ecological validity. By assessing cognitive variables before film presentation, potential pre-existing risk factors can be examined by correlating them with subsequent intrusive memories and analogue PTSD symptoms. Additionally, stimuli that are present during the trauma and might later function as trauma reminders are also under

experimental control and thus can systematically be manipulated in order to study their potential to trigger later PTSD symptoms.

In order to enhance the participants' immersion in the traumatic situation, virtual reality environments have been implemented recently (Dibbets & Schulte-Ostermann, 2015; Scheel et al., 2012). This method can induce intrusive memories at frequencies comparable to those observed in the trauma film paradigm (Dibbets & Schulte-Ostermann, 2015). As well, these paradigms allow participants to interact with the environment to a certain extent. Although this enhances the sense of being involved in the event (Dibbets & Schulte-Ostermann, 2015), it also diminishes experimental control of the situation, and thus the ability to compare participants.

7.3 FEAR CONDITIONING STUDIES

As associative learning is presumed to be an important factor in the development of PTSD (e.g. Ehlers & Clark, 2000; Foa et al., 1989), differential fear conditioning paradigms are thought to mimic some of the basic features of traumatic events with a high degree of experimental control.

In these paradigms, one CS is paired with the UCS during the acquisition phase (CS+), while another CS is not paired with the UCS (CS-) and thus serves as a safety signal. Neutrally valenced picture stimuli are typically used as CSs and are paired with aversive stimuli (UCS) such as aversive noises or pictures, unpleasant electric stimulation, or air blasts (Kim & Jung, 2006; Sehlmeyer et al., 2009). In the following extinction phase, both CSs are presented without the UCS. The differential reactions to the CS+ and the CS- during

acquisition and/or extinction are used as indexes of conditionability (Duits et al., 2015; Lissek et al., 2005). Examining fear conditioning in trauma survivors showed that PTSD patients have enhanced CRs during acquisition and extinction as compared to trauma survivors without PTSD (Blechert et al., 2007; Orr et al., 2000). Reduced extinction learning before a traumatic event could even predict subsequent severity of PTSD symptoms (Lommen et al., 2013).

Because fear conditioning experiments can mimic only some aspects of a traumatic event and are unlikely to generate complex intrusive memories, Wegerer et al. (2013) developed a conditioned intrusion paradigm. In this paradigm they used short aversive film clips (25 s) as UCSs and paired them with neutral sounds (CSs). To model situations where one is exposed to potential trauma reminders, the CS sounds were presented again, faded in at intervals against a neutral background soundscape. This paradigm was able to successfully induce conditioned intrusive memories and demonstrated that conditionability of valance ratings and physiological arousal was associated with conditioned and spontaneous intrusive memories of the film clips. Even though this paradigm led to a significant advance in the ecological validity of fear conditioning as a model for PTSD, the paradigm is still somewhat artificial and does not depict the typical time course of a traumatic event.

7.4 METHODOLOGICAL PARADIGMS USED IN THIS THESIS

The research question addressed in Study 1, whether pre-trauma memory control can predict later intrusive trauma memories, clearly requires a prospective study design to make inferences about deficient memory control as a potential cognitive risk factor for PTSD. One

way to investigate this is by assessing memory control in participants who are very likely to be exposed to a traumatic event after the assessment. Field studies testing participants in high risk groups (e.g. fire fighters) often have the problem that prior traumatization is very likely among the group members, so that implementing such a field study design would have undermined the prospective character of the study. Furthermore, the diversity of traumatic events participants are exposed to in field studies leads to a great deal of uncontrolled variation in PTSD symptoms. This is especially disadvantageous, when between-subject factors are examined, as is necessary for investigating the current question. Paradigms using analogue traumatic events thus offer an efficient way to circumvent these problems. As the trauma film paradigm has been shown to cause a reasonable quality of intrusive memories without putting participants' mental health at risk, it was implemented to simulate real-life trauma in this study.

As Study 2 aimed to examine the question of whether conditioned responses to trauma reminders are involved in the development of intrusive trauma memories and their treatment, complete experimental control of stimuli present during the traumatic event is needed. Because this is impossible to achieve in a field study of traumatic events, the best method for investigating this is the trauma film paradigm. To control which stimulus associations are established during the traumatic event, the presentation of neutral sound stimuli was systematically manipulated during film presentation.

MEMORY CONTROL AND INTRUSIVE TRAUMA MEMORIES

II MEMORY CONTROL AND INTRUSIVE TRAUMA MEMORIES

Following the lines of research reviewed above, Study 1 aims to investigate pre-trauma retrieval suppression ability in relation to intrusive trauma memories and other PTSD symptoms. It is hypothesized that a deficit in the ability to suppress memory retrieval of unwanted memories constitutes a potential cognitive risk factor for developing intrusive trauma memories and other PTSD symptoms after a traumatic event. Furthermore, the neural control mechanisms underlying retrieval suppression (as indexed by the N2 ERP component) are expected to predict later intrusive trauma memories and other PTSD symptoms. In the following, the article based on Study 1 is presented in the original form in which it was submitted for publication (apart from changes in formatting).

STUDY 1: MEMORY CONTROL ABILITY PREDICTS REDUCED POSTTRAUMATIC STRESS DISORDER SYMPTOMS AFTER ANALOGUE TRAUMA

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1 ABSTRACT

Most trauma survivors suffer from intrusive reexperiencing in the aftermath of trauma. For survivors' well-being, it is key that these intrusions are controlled. Memory control can be exerted through retrieval suppression (RS). Poor RS, however, should be associated with persistent distressing intrusions and posttraumatic stress disorder (PTSD). This study tested the hypothesis that individual differences in RS ability predict intrusive reexperiencing after trauma. RS was examined with the think/no-think task (TNT) using behavioral and event related potential (ERP) measures. Twenty-four healthy participants watched a traumatic film after having performed the TNT task. Intrusion frequency, intrusion distress and other PTSD-like symptoms from the trauma film were measured with an electronic diary and the Impact of Event Scale (IES-R). In line with our hypothesis, behavioral measures of RS ability predicted reduced distress ratings for intrusions (r = -.53, p < .01). Further ERP markers of RS (a fronto-centrally distributed N2) predicted reduced distress ratings of intrusions (r = -.45, p < .05) and reduced scores on the IES-R (r = -.49, p < .01). Participants with lower RS ability exhibited PTSD-like symptoms after analogue trauma, suggesting that deficient memory control is a potential risk factor for developing PTSD.

2 INTRODUCTION

In the aftermath of trauma, most trauma survivors suffer from intrusive memories of the traumatic event. While intrusive memories decline for some trauma survivors in the months after the trauma, others continuously suffer from them and develop posttraumatic stress disorder (PTSD; Michael, Ehlers, Halligan, et al., 2005). Although unwanted and highly distressing memories are an integral feature of PTSD, neither the presence nor the frequency of spontaneous trauma memories in the immediate aftermath of trauma is a good predictor of chronic PTSD (McFarlane, 1988; Shalev, 1992). However, the distress that accompanies such initial intrusions is a powerful predictor of persistent PTSD (Michael, Ehlers, Halligan, et al., 2005). As intrusions in PTSD seriously undermine emotional well-being and cognitive functioning, PTSD is often considered a memory disorder (Brewin, 2011). Naturally, traumatized people are highly motivated to prevent trauma memories from spontaneously coming to mind, as they wish to reduce the distress and distraction they cause. Recent research indicates that retrieval suppression (RS) is a cognitive control mechanism that keeps unwanted memories at bay (Anderson & Hanslmayr, 2014). However, the ability to inhibit memory retrieval varies substantially across people (Levy & Anderson, 2008, 2012), and thus it may offer an explanation why some people recover spontaneously after traumatic events, whereas others continuously suffer from extensive retrieval of trauma memories. Indeed, a recent ambulatory monitoring study has established that PTSD patients report remembering or reliving the traumatic event on average 22 times per week (Pfaltz, Michael, Meyer, & Wilhelm, 2013), highlighting the difficulties they have in controlling unwanted memories. Thus, a deficit in retrieval suppression may contribute to intrusive reexperiencing in PTSD. Accordingly, when people encounter reminders to a recently experienced trauma,

nearly everyone will experience memories intruding into their mind (Levy & Anderson, 2008); but people who have strong retrieval suppression ability can eliminate these memories from awareness, and their tendency to intrude again in the future. On the other hand, people with a deficit in retrieval suppression will not be able to accomplish this, and will, as a result, keep experiencing intrusive memories. As a matter of fact, a recent study investigating the ability to suppress retrieval of aversive images in traumatized subjects with and without PTSD shows that retrieval suppression is compromised in PTSD patients (Catarino et al., 2015). Although this study links PTSD to retrieval suppression deficits, it cannot answer the question whether deficits in retrieval suppression result from PTSD or instead serve as a risk factor for its development.

To study retrieval suppression of unwanted memories in the laboratory, Anderson and Green (Anderson & Green, 2001) developed the think/no-think (TNT) task. In this paradigm, people are repeatedly prompted with cues to previously learned memories and asked to either retrieve the memory ("think" trials), or to stop its retrieval ("no-think" trials). Numerous studies have found that no-think items are more poorly recalled on subsequent memory tests, an effect termed suppression-induced forgetting (Anderson & Green, 2001; Anderson & Huddleston, 2012; Anderson et al., 2004). Recent neuroimaging studies found negative coupling between the right dorsolateral prefrontal cortex (dlPFC) and the hippocampus, indicating that a control process supported by the dlPFC down-regulates activity in the hippocampus to stop retrieval (Benoit & Anderson, 2012; Gagnepain, Henson, & Anderson, 2014). An electrophysiological correlate of this putative control process was found in a fronto-centrally distributed N2 component, a negative-going ERP component which is consistently larger during retrieval suppression than during retrieval (Bergström et

al., 2009b; Bergström, Velmans, de Fockert, & Richardson-Klavehn, 2007; Depue et al., 2007; Mecklinger et al., 2009; Waldhauser et al., 2012). Importantly, a larger N2 deflection during retrieval suppression predicts greater suppression-induced forgetting (Mecklinger et al., 2009). A correlation has also been demonstrated between the TNT N2 and the N2 observed in a motor stopping task (Mecklinger et al., 2009), indicating that retrieval suppression and motor stopping similarly recruit general response inhibition mechanisms. Critically, these general control processes may also be involved in inhibiting involuntary retrieval of traumatic memories. Thus, measuring variation in the N2 during retrieval suppression may provide an important window into individual differences in the underlying neural mechanisms that determine which people are vulnerable to persistent intrusive memories in the aftermath of trauma.

Therefore, we hypothesize that a deficit in memory control, as indexed by behavioral and ERP estimates of retrieval suppression, is a potential risk factor for extensive intrusive reexperiencing in PTSD. People who are good at retrieval suppression should also be more capable of limiting the accessibility of traumatic memories. To test this hypothesis, it is necessary to employ a prospective design that assesses retrieval suppression ability *before* a traumatic event occurs, and then examine how variation in this ability predicts response to the subsequent trauma. Such a prospective design is, naturally, very difficult to realize in clinical samples. A way to circumvent this problem is to use an analogue paradigm: The trauma film paradigm provides a prospective experimental tool for investigating intrusive memories in the laboratory. In this paradigm, healthy participants watch a traumatic film clip and are asked to record their intrusive memories of the film over the following days (Holmes & Bourne, 2008). To test our hypotheses we used a prospective design, combining the TNT

procedure and the trauma film paradigm. We first used the TNT procedure to estimate participants' general retrieval suppression ability (using neutral word stimuli) with behavioral (suppression-induced forgetting) and ERP (N2) measures. After having performed the TNT, participants watched a traumatic and a neutral film clip. Analogue PTSD symptoms after the trauma film were measured both with an electronic diary and with the Impact of Event Scale (IES-R, a clinical standard questionnaire assessing PTSD symptoms: intrusive reexperiencing, avoidance, hyperarousal). We expected that participants with high retrieval suppression ability (as indexed by behavioral and ERP estimates) would show fewer intrusions than would participants with low retrieval suppression ability (Hypothesis 1). Because the distress caused by intrusions is known to strongly predict chronic PTSD and because participants (and patients in general) should be more motivated to inhibit distressing intrusions than non-distressing ones, we predicted that participants with low retrieval suppression ability (as indexed by behavioral and ERP estimates) would show more distressing intrusions (Hypothesis 2). Finally, we examined how well retrieval suppression ability (as indexed by behavioral and ERP estimates) predicts PTSD-like symptoms in general as measured with the IES-R (Hypothesis 3).

3 METHOD

3.1 PARTICIPANTS

Twenty-four non-psychology students (12 female, age ranged from 18 to 32 years, M = 24.7, SD = 4.20) were recruited on the campus of Saarland University and participated in exchange for 76 Euros. All participants had normal or corrected-to-normal vision, were

native German speakers, right-handed, reported no history of neurological or psychiatric disorders, and gave informed consent. The research was approved by the Department of Psychology Ethics Committee of Saarland University. The electroencephalogram (EEG) data of three participants were excluded due to recording errors.[1]

3.2 THINK/NO-THINK TASK

Eighty-four weakly related neutrally valenced word pairs were composed (60 critical items and 24 filler items). Words were selected from a German standardized data base (Melinger & Weber, 2006). The selection of the final experimental word pairs was guided by a rating procedure. In this procedure words with orthographical and phonological similarities were excluded and only pairs with weak semantic relationship were included. Each word pair comprised a cue (left hand) and a response (right hand) word and was presented in the center of a 100 Hz computer display on a white background, using E-Prime 2.0 software (Psychology Software Tools Inc., Sharpsburg, USA). The critical pairs were rotated across experimental conditions (baseline, think, no-think) and across subjects.

The TNT task consisted of four phases: Training, Practice, Think/No-Think, and Final Recall. The Training phase had three stages. First, each word pair was presented for 3400 ms (ISI: 600 ms). Second, participants overtly recalled the response to the cues, which were shown for up to 4000 ms, or until response. Following a 600 ms ISI, the correct response appeared for 1000 ms. This procedure was repeated until participants recalled at least 50% of

[1] All statistical analyses of behavioral data showed the same pattern of results for the complete and the reduced dataset without the three excluded participants. Behavioral results are reported for the complete sample.

the critical responses. Third, we presented each cue one more time for up to 3300 ms (ISI: 1100 ms) to assess which responses had been learned.

During Practice, all participants were trained on the TNT task, using the previously learned filler items. They were instructed to covertly recall the responses for cues presented in green (think condition), but to block out all thoughts of the associated responses for cues presented in red (no-think condition). Moreover, participants were instructed to not try to generate distracting thoughts in order to not think about the No-Think items but rather to control memory by simply suppressing retrieval (known as a "direct suppression" instruction; see Benoit & Anderson, 2012; Bergström et al., 2009b; LeMoult, Hertel, & Joormann, 2010). Think and no-think trials alternated pseudo-randomly. Each cue was on screen for 3000 ms (ISI: 1000 ms) — timings identical to the actual Think/No-Think phase. After the first half of the Practice phase a questionnaire was administered verbally to help identify any covert rehearsal of no-think items and allow the experimenter to give feedback to the participant to correct this problem (Bulevich, Roediger, Balota, & Butler, 2006).

After practice, the critical Think/No-Think phase was split into five blocks. In each block, participants saw each cue of the think and no-think pairs twice. Within a block, a given cue was only repeated once all other cues had been presented. Thus, each critical item was retrieved or suppressed ten times. A short break (45s) separated each block. After the second block the questionnaire that was administered during Practice was administered again to avoid any covert rehearsal of no-think items.

In the final test phase, participants were given cue words and asked to recall the associated response words — irrespective of prior instructions. The cues were presented for a

maximum of 3300 ms (ISI: 1100 ms). Cues were presented in block randomized format, with each block of 6 trials containing two items from each of the Think, No-think, and Baseline conditions, presented in random order.

3.3 ANALOGUE TRAUMA

All participants saw two film clips (one neutral and one traumatic) in pseudo-randomized order. The neutral film consisted of neutral scenes (11 min) from the movie *Three Colors: Blue* directed by Krzysztof Kieslowski (1993; Schaefer et al., 2010). The traumatic film consisted of neutral and violent scenes (11 min) from the movie *Irreversible* by Gaspar Noé (2002; Nixon, Nehmy, & Seymour, 2007; Qin, Hermans, van Marle, Luo, & Fernandez, 2009; Verwoerd, Wessel, & De Jong, 2010). After watching each film clip, an adapted version of the Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988) was administered, assessing how participants felt while watching the preceding film. Thereafter, participants were asked to rate how strongly each film caused physiological arousal on a 5-point scale going from "very slightly or not at all" to "extremely."

3.4 ASSESSMENT OF INTRUSIVE REEXPERIENCING AND ANALOGUE POSTTRAUMATIC STRESS DISORDER SYMPTOMS

During the five days following film presentation, participants documented every intrusive film memory, using an iPod Touch (4^{th} gen., Apple Inc., Cupertino, USA) running Forms VI (Pendragon Software Corporation, Chicago, USA). The frequency of intrusive memories was determined by summing up their number from the neutral and the traumatic film

separately. For each memory, participants rated how distressing it was on a 10-point scale going from “not at all” to “extremely”. These ratings were averaged for the neutral and the traumatic film separately.

Six days after film presentation, every participant completed the Impact of Event Scale - Revised (IES-R; German translation; Maercker & Schützwohl, 1998; Weiss, Wilson, & Keane, 2004), a 22-item questionnaire assessing PTSD symptoms. Every item (e.g. “Things I saw or heard suddenly reminded me of it”) was rated on a 5-point scale spanning from “not at all” to “extremely”.

3.5 PROCEDURE

Participants were run individually, following written informed consent. On the first day, they were interviewed to exclude any axis I disorder (5th ed.; DSM-5;American Psychiatric Association, 2013) or prior traumatic experience. The following day, participants performed the TNT task. During this task EEG was recorded. On the third day, participants watched the traumatic and the neutral film. Intrusions were documented over the following five days. Six days after film presentation participants completed the IES-R and were fully debriefed.

3.6 STATISTICAL ANALYSIS OF BEHAVIORAL MEASURES

Performance data of the TNT task were analyzed using a mixed-design analysis of variance (ANOVA), with Response Condition (think, no-think, baseline) as within-subject factor and counterbalancing of items through each condition (three levels) as between-subject factor. To assess individual differences, we calculated a score for each participant’s retrieval

suppression ability by subtracting recall of no-think items from baseline items. Thus, participants with enhanced retrieval suppression ability had higher scores. This measure was z-normalized within that participant's counterbalancing group to control for differences in the memorability between items (Anderson et al., 2004; Levy & Anderson, 2012).

Correlation analyses focused on the association between behavioral and ERP estimates of retrieval suppression in the TNT task and intrusion measures (i.e. intrusions frequency and distress in the electronic diaries and the IES-R score). Pearson correlations were calculated.

3.7 ELECTROPHYSIOLOGICAL RECORDING AND PREPROCESSING

Subjects were seated in an electrically shielded room. While performing the TNT task, the electroencephalogram (EEG) was continually recorded from the scalp using a 72-channel active-electrode system (Biosemi Inc., Amsterdam, The Netherlands) with 64 standard 10-20 electrode positions, 6 EOG channels (2 x VEOG, 1 x HEOG, 1 x REOG as the average of all 6 channels referenced to averaged mastoids) and 2 mastoid reference channels. Absolute electrode offsets were kept below 30 mV, which is appropriate for this type of electroencephalogram amplifier. The EEG was recorded continuously in the DC to 128 Hz frequency range and A-D converted with 24 bit resolution at a sampling rate of 512 Hz. Continuous EEG data was re-referenced off-line from the Common Mode Sense (CMS) electrode to averaged mastoids and then filtered with a digital low-pass filter set to 30 Hz. Stimulus locked epochs were extracted between 200 ms pre until 1600 ms post onset of a given cue word. Epoched data was corrected for eye movement artefacts using the revised aligned-artefact average procedure suggested by Croft and Barry (Croft & Barry, 2000) by

means of hierarchical multiple linear regression using the vertical, horizontal, and radial EOG, using the data of an EOG calibration sequence included at the beginning of the experiment to allow for reliable estimations of the regression coefficients. The method for statistical control of artifacts (Junghöfer, Elbert, Tucker, & Rockstroh, 2000) was then used for further editing and artefact rejection. This procedure detects individual channel artifacts, detects global artifacts, replaces artifact-contaminated sensors with spline interpolation statistically weighted on the basis of all remaining sensors, and computes the variance of the signal across trials to document the stability of the averaged waveform. The rejection of artifact-contaminated trials and sensor epochs relies on the calculation of statistical parameters for the absolute measured scalp potential amplitudes over time, their standard deviation over time, the maximum of their gradient over time (first temporal derivative), and the determination of boundaries for each of these three parameters. Baseline correction was calculated from 200 ms before stimulus onset to stimulus onset. Finally, clean data epochs were averaged for each participant and for each think or no-think trial.

3.8 ERP STATISTICAL ANALYSIS

ERP waveforms for think and no-think trials were quantified by measuring the mean amplitudes in two time windows (180-240 ms, 350-450 ms). Selection of these time windows was based on visual inspection and previous ERP research (Mecklinger et al., 2009). Statistical analysis of the ERP data was based on the following electrodes: frontal (F3, Fz, F4), central (C3, Cz, C4), and parietal (P3, Pz, P4). To quantify individual differences, ERPs to no-think items were subtracted from ERPs to think items. Thus, subjects with higher negativity for no-think items, had numerically larger scores. These

measures were z-normalized within each counterbalancing condition (as described above). Scores from FCz recording site were used for the correlational analyses, as the ERP subtraction measures in both time windows were largest at this recording site.

4 RESULTS

4.1 SUPPRESSION-INDUCED FORGETTING WAS OBSERVED

We found significant suppression-induced forgetting effects in the TNT task, as no-think items were more poorly recalled than were baseline items (Figure II-1; $F(1, 21) = 7.16$, $p = .01$, $\eta_p^2 = .254$).[2]

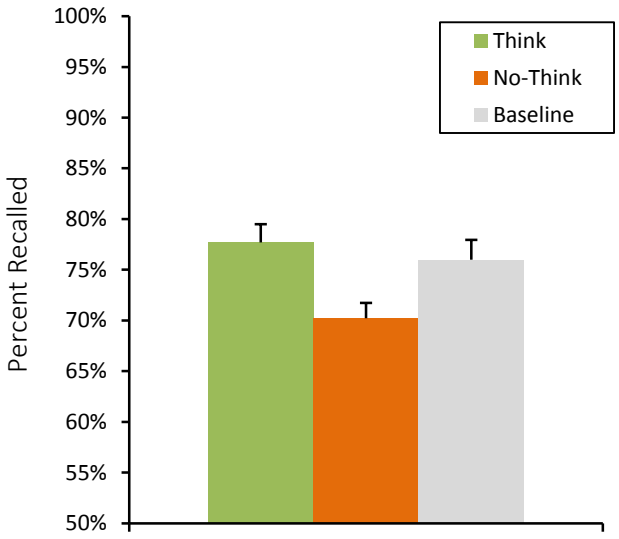

Figure II-1: Cued recall rates for previously learned word pairs.

Recall was reduced in the no-think condition compared to the baseline condition and the think condition. Error bars represent the standard error following Cousineau-Morey corrections for within-subject designs (Cousineau, 2005; O'Brien & Cousineau, 2014).

[2] The two-way ANOVA with Response Condition (think, no-think, baseline) as within-subject factor and counterbalancing of items through each condition (three levels) as between-subject factor revealed a main effect of Response Condition ($F(2, 42) = 5.34$, $p = .009$, $\eta_p^2 = .203$). No main effect for counterbalancing of items was observed ($F(2, 21) = 1.08$, $p = .36$, $\eta_p^2 = .093$). Also no significant interaction between the two factors was observed ($F(4, 42) = 1.71$, $p = .17$, $\eta_p^2 = .151$).

This indicates that participants were able to suppress memory retrieval successfully, which led to reduced ability to recall the memory. No-think recall was also lower than think recall ($F(1, 21) = 12.60$, $p = .002$, $\eta_p^2 = .375$). No significant difference was found between think recall and baseline recall ($F(1, 21) = 0.34$, $p = .57$, $\eta_p^2 = .033$). As the baseline recall rate was relatively high, this may be due to ceiling effects.

Grand average ERPs revealed pronounced differences between the think and no-think conditions (Figure II-2A). The first ERP effect consisted of an enhanced early negativity (~200 ms) that was larger in the no-think condition than in the think condition. As apparent from Figure II-2B, the early negativity to no-think trials had a broad bilateral distribution and co-occurred with a positive (P2) deflection to think trials. The largest differences between think and no-think trials emerged at frontal and central sites (Bergström et al., 2009a; Mecklinger et al., 2009, for similar results). The early negativity was followed by a second negative going component with a similar fronto-central maximum that peaked around 400 ms. As it resembled the N2 component related to motor stopping in previous studies (Mecklinger et al., 2009), it will be referred to as the N2 effect in the following. Notably, the N2 was larger for no-think than for think trials, indicating that it reflects a process relevant for retrieval suppression.

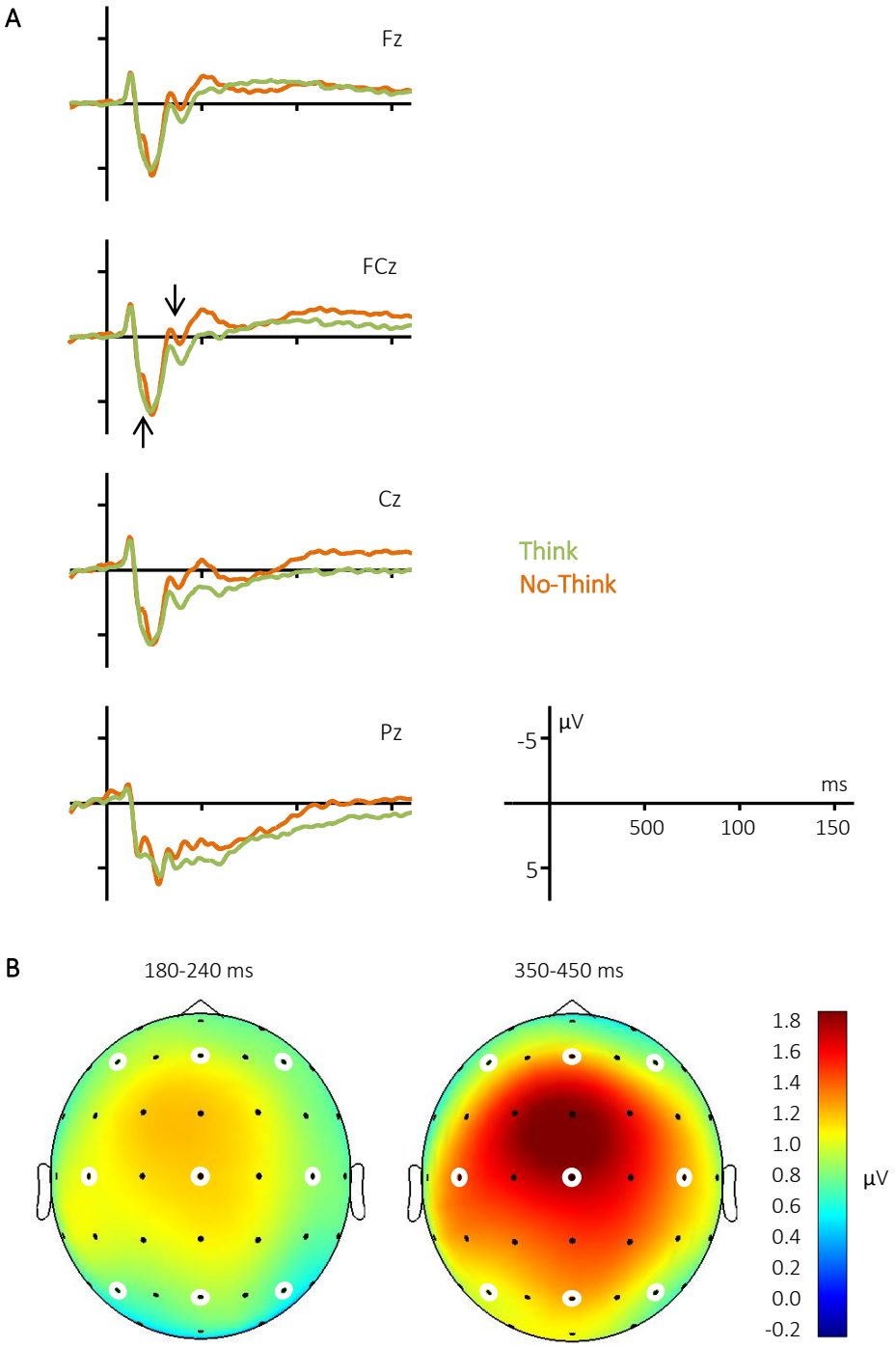

Figure II-2: ERP analysis of the think/no-think task.

(A) Grand average ERPs for the think and no-think condition during the think/no-think phase for all word pairs depicted at the Fz, FCz, Cz, and Pz recording sites. Arrows illustrate the early negativity and the N2 components. **(B)** Topographic maps showing the scalp distributions of the ERP differences between think and no-think Items. Grand average difference waves were computed by subtracting the no-think condition from the think condition. The electrodes used for statistical analyses are highlighted in white.

4.2 BOTH ENHANCED EARLY NEGATIVITY AND N2 COMPONENTS DURING RETRIEVAL SUPPRESSION PREDICTED LATER SUPPRESSION-INDUCED FORGETTING

A global ANOVA with the factors Response Condition (think, no-think), Time Window (180-240 ms, 350-450 ms), Region (frontal, central, parietal) and Laterality (left, middle, right) yielded significant interactions between Response Condition, Time Window, Region, and Laterality, ($F(4, 80) = 5.40$, $p = .001$, $\eta_p^2 = .213$), Response Condition, Time Window, and Region ($F(2, 40) = 5.59$, $p = .007$, $\eta_p^2 = .218$), Response Condition, Time Window, and Laterality ($F(2, 40) = 8.25$, $p = .001$, $\eta_p^2 = .292$). This suggests that the ERPs in both time windows and response conditions differed in the three regions and the three levels of the laterality factor.

Follow-up repeated measures ANOVAs with the factors Response Condition, Region and Laterality performed for each time window revealed a main effect of Response Condition ($F(1, 20) = 7.89$, $p = .01$, $\eta_p^2 = .283$), in the early time window (180-240 ms), reflecting an enhanced and broadly distributed early negativity for no-think compared to think trials.

In the second time window (350-450 ms), follow up analyses revealed a main effect of response condition ($F(1, 20) = 11.20$, $p = .003$, $\eta_p^2 = .359$) and significant interactions between Response Condition and Region ($F(2, 40) = 6.16$, $p = .005$, $\eta_p^2 = .235$), Response Condition and Laterality ($F(2, 40) = 7.74$, $p = .001$, $\eta_p^2 = .279$) and Response Condition, Region and Laterality ($F(4, 80) = 5.89$, $p = .001$, $\eta_p^2 = .228$).

Post-hoc analyses conducted to break down these interactions revealed significant response type effects at all 9 laterality by region combinations with largest effect sizes at the middle

(ω^2 = 0.34) and right (ω^2 = 0.36) central sites and smallest effect sizes at left frontal (ω^2 = 0.13) and left central (ω^2 = 0.18) recording sites.

In a complementary analysis, we explored whether the early negativity and the N2 predicted individual differences in retrieval suppression. The early negativity was positively correlated with suppression-induced forgetting at the level of individual participants. The larger the amplitude differences of the early negativity between the think and no-think conditions the larger the suppression-induced forgetting (r = .57, p = .007). The same correlation pattern was obtained for the N2 difference measure (r = .48, p = .03; Figure II-3A), indicating that both ERP components may reflect processes relevant for suppression-induced forgetting.

4.3 THE TRAUMATIC FILM WAS AVERSIVE AND LED TO PTSD-LIKE SYMPTOMS

Participants reported that they experienced significantly more negative emotions and higher physiological arousal during presentation of the traumatic film as compared to the neutral film (negative emotions: $t(23) = 11.36$, p = .001, d = 2.32; arousal: ($t(23) = 12.60$, p = .001, d = 2.57).

Furthermore, participants reported significantly more intrusive reexperiencing of the traumatic film than of the neutral film (traumatic: M = 4.0, SD = 2.9; neutral: M = 0.2, SD = 0.4; $t(23) = 6.55$, p = .001, d = 0.06). Critically, those intrusions associated with the traumatic film were rated as significantly more distressing than those associated with the neutral film (traumatic: M = 4.0, SD = 2.4; neutral: M = 0.0, SD = 0.0; $t(23) = 8.34$, p = .001, d = 1.95). This indicates that the traumatic film successfully induced PTSD-like intrusions.

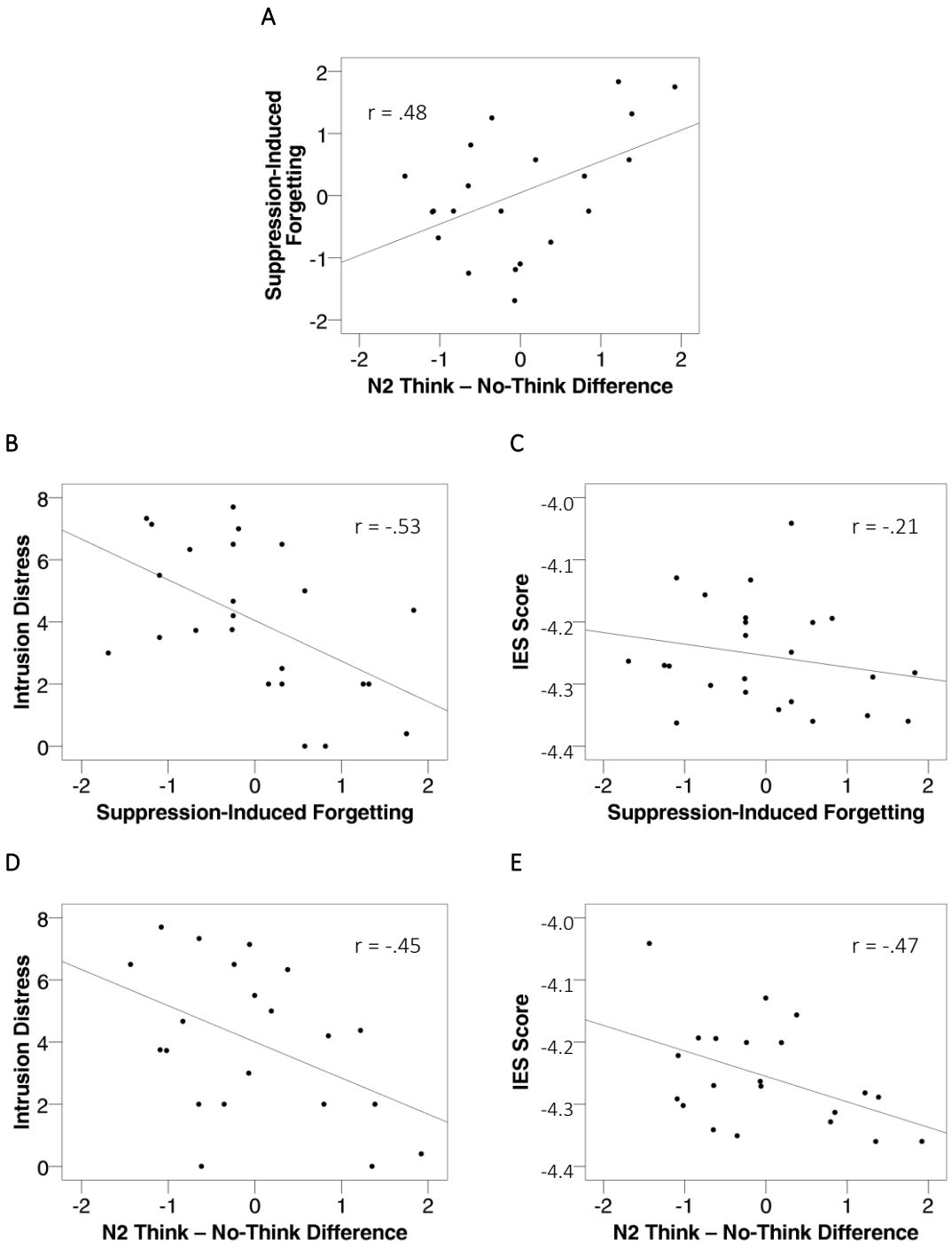

Figure II-3: Correlations between suppression-induced forgetting and analogue PTSD symptoms.

(A) The positive correlation between suppression-induced forgetting (baseline recall – no-think recall) and the N2 difference (N2 think – N2 no-think). **(B)** The negative correlation between suppression-induced forgetting and distress ratings for intrusive reexperiencing measured by the electronic diary. **(C)** The non-significant correlation between suppression-induced forgetting and the Impact of Event Scale -Revised (IES-R). **(D)** The negative correlation between the N2 difference and distress ratings for intrusive reexperiencing measured by the electronic diary. **(E)** The negative correlation between the N2 difference and IES-R scores. All ERP measures for the correlational analyses were taken from the FCz recording site.

4.4 BETTER RETRIEVAL SUPPRESSION ABILITY PREDICTED LOWER INTRUSION DISTRESS AND ANALOGUE PTSD SYMPTOMS

In line with our hypothesis, increased suppression-induced forgetting predicted reduced distress for intrusive memories in the electronic diary (r = -.53, p = .008; Figure II-3B). However, there was not a reliable correlation between suppression-induced forgetting and overall intrusion frequency in the electronic diary (r = .14, p = .52) or between suppression-induced forgetting and the IES-R score (r = -.21, p = .33; Figure II-3C).

Paralleling the analysis of behavioral indices, we examined whether the N2, which in the present and in previous studies (Mecklinger et al., 2009) has been related to behavioral measures of retrieval suppression, predicted intrusion distress and frequency. Indeed, an enhanced N2 to no-think items significantly predicted reduced distress during intrusive memories (r = -.45, p = .04; Figure II-3D) and also reduced IES-R scores (r = -.47, p = .03; Figure II-3E). As for the behavioral data, there was no significant correlation between the N2 and overall frequency intrusions of the traumatic film (r = .08, p = .74).

5 DISCUSSION

Most people experience intrusive memories in the aftermath of a traumatic event. While intrusive memories decline for some trauma survivors, others continuously suffer from them. In the present study, we investigated whether deficits in the ability to suppress memory retrieval may be one cause for such persisting intrusions. In particular, we examined whether behavioral and ERP measures of retrieval suppression ability predicted individual differences in intrusive reexperiencing (intrusion frequency and intrusion distress) and

PTSD-like symptoms (as measured with the IES) after an analogue trauma. In line with our hypotheses, we found that behavioral and ERP correlates of retrieval suppression ability predicted the distress caused by intrusive memories of a traumatic film. In detail, participants with low retrieval suppression ability reported more distress caused by intrusive memories than did participants with high retrieval suppression abilities. Furthermore, individual differences in the N2, the ERP correlates of retrieval suppression, predicted analogue PTSD symptoms, as measured with the IES. Thus, our results are in line with previous findings linking PTSD with retrieval suppression deficits (Catarino et al., 2015) and memory control deficits (Zwissler et al., 2012). Extending these findings, our study is the first to show that deficits in retrieval suppression ability were linked to intrusive memories in a prospective design, indicating that pre-existing deficits in memory control ability may constitute a risk factor for the development of PTSD. This corresponds with recent research indicating that patients with PTSD show impaired response inhibition (Aupperle, Melrose, Stein, & Paulus, 2012).

Replicating earlier findings, retrieval suppression in the TNT task was reflected by greater negative going ERPs at fronto-central electrode sites. The first ERP difference between think and no-think trials emerged in the time window from 180-240 ms. This finding is in line with previous studies on retrieval suppression that found a similar early ERP difference between think and no-think trials (Bergström et al., 2009a; Mecklinger et al., 2009; Waldhauser et al., 2012). As proposed by Bergström et al. (2009a) this early effect may reflect the detection of the need to control memory retrieval. A possible neural generator of this component lies in the frontal lobe, including the right inferior frontal gyrus, as indicated by a recent dipole source localization study (Chen et al., 2012). Notably, in the present

study, differences in this time window predicted suppression-induced forgetting, meaning that the differential processing of think and no-think trials in this time window may be relevant for the effectiveness of retrieval suppression.

We further found an N2 component between 350 and 450 ms over frontal and central electrodes that was enhanced for no-think items compared to think items. Replicating earlier findings (Mecklinger et al., 2009), differences between think and no-think items in this time window predicted later suppression-induced forgetting. Our findings indicate that this ERP component reflects processes related to active suppression of memory traces. The early negativity and the N2 may index different component processes of inhibitory control, such as detecting the need for cognitive control and the active suppression of unwanted memories (Bergström et al., 2009a, 2009b; Mecklinger et al., 2009; Waldhauser et al., 2012).

Building on previous research linking the N2 with retrieval suppression and motor suppression (Mecklinger et al., 2009), we wanted to examine whether this ERP component is also relevant for controlling intrusive trauma memories. Indeed, an enhanced N2 was related to less distressing intrusive reexperiencing and less severe analogue PTSD symptoms. This indicates that the N2 component not only reflects processes relevant for suppressing retrieval of simple word pairs in laboratory settings, as in the TNT task, but also for controlling unwanted memories after a real-life traumatic experience, leading to less distressing intrusive reexperiencing. By showing that the N2 correlated with memory control measures in both laboratory and more naturalistic settings, our results support the view, that retrieval suppression in both situations relies on the same mechanisms (Anderson & Hanslmayr, 2014; Anderson et al., 2004; Catarino et al., 2015; Depue et al., 2007; Küpper et al., 2014).

Surprisingly, we did not find a reliable relationship between the reported overall frequency of intrusive memories of the traumatic film and either the behavioral or the ERP correlates of retrieval suppression in the TNT task. This finding is in line with the study of Wessel, Overwijk, Verwoerd, and de Vrieze (2008), who also did not find a relationship between retrieval suppression in the TNT paradigm and intrusion frequency after a traumatic film. However, this is in contrast to previous findings linking successful retrieval suppression with a decline of intrusions of the associated responses during the TNT task itself (Benoit et al., 2014; Levy & Anderson, 2012). One explanation for the missing association between retrieval suppression and intrusion frequency in the current study relates to motivational issues: Our participants were not, in fact, instructed to suppress intrusive memories of the film, making the engagement of suppression uncertain. Anderson and Hanslmayr (2014) recently argued that to effectively suppress a memory, it is necessary to have a strong motivation to do so. In the laboratory this motivation is achieved by experimental instructions. In the trauma film procedure, we assumed that the negative affect of an aversive memory would supply motivation to engage in spontaneous suppression. However, participants may only have suppressed the truly distressing intrusions from the traumatic film, limiting the number of intrusions affected by inhibition. This may have attenuated distress associated with those intrusions, while making effects on intrusion frequency more difficult to measure. If these lines of reasoning were correct, one would predict that intrusions with high distress ratings (that participants would have been naturally motivated to suppress) would be less frequent in participants with high retrieval suppression ability compared to those with low retrieval suppression ability. An additional analysis examining

the number of highly distressing intrusions in both groups, confirmed this assumption.[3] Subjects with high suppression-induced forgetting scores had fewer highly distressing intrusions than subjects with low suppression-induced forgetting scores. A second explanation for the missing association is that retrieval suppression after the traumatic film may have primarily reduced the vividness of memories by degrading access to upsetting details, leaving overall access to the events intact. Indeed, Küpper et al. (2014) found that in a pictorial TNT task memory for details of upsetting images was reduced very effectively after no-think trials, even when the image itself could be recalled (see also Noreen & MacLeod, 2013; Stephens, Braid, & Hertel, 2013). Similarly, in the current study, even though intrusion frequencies did not reliably decline during our measurement period, effective suppression of upsetting details of the traumatic memories may have reduced distress.

In summary, the present findings suggest that deficient retrieval suppression is not a consequence of traumatic experiences but rather a potential risk factor for the development of distressing intrusive reexperiencing after traumatic events. People with good retrieval suppression abilities had less distressing intrusions and fewer PTSD-like symptoms. As such, the present data support the idea that prospectively measuring and recognizing poor retrieval suppression may help to identify people unlikely to recover on their own after a traumatic event and to guide appropriate intervention approaches to prevent them from developing PTSD (Dunn, Billotti, Murphy, & Dalgleish, 2009; Joormann et al., 2005; Peterson, Klein, Donnelly, & Renk, 2009). Indeed, if retrieval-suppression is a general

[3] Participants with high and low retrieval suppression ability were divided into two groups, based on a median split of their suppression-induced forgetting score. Subjects with high suppression-induced forgetting scores had a significantly reduced frequency of highly distressing intrusions (distress rating of 6 to 10) compared to subjects with low suppression-induced forgetting scores ($t(22) = 1.95$, $p = .03$ (1-sided), $d = 0.83$).

ability that spans both laboratory and trauma settings, as indicated here, it suggests that training retrieval suppression with laboratory methods may be a promising method for improving people's ability to cope with intrusive memories in the aftermath of trauma.

CONDITIONED RESPONSES TO TRAUMA REMINDERS

III CONDITIONED RESPONSES TO TRAUMA REMINDERS

Study 2 aimed to examine the temporal stability of conditioned responses to trauma reminders. As conditioned associations are thought to account for the occurrence of intrusive trauma memories, such temporal stability is a crucial precondition. Furthermore, this study extends previous findings from rather artificial fear conditioning paradigms to more naturalistic conditions which more closely resemble the complexity of a real-life trauma and thus attains higher ecological validity. Following the assumption that conditioned responses to trauma-associated stimuli should be alleviated by imaginal exposure, a second aim of this study is to examine whether imaginal exposure to the traumatic event can reduce the number and intensity of intrusive trauma memories that are triggered by trauma-associated stimuli, along with conditioned physiological responses to these stimuli. In the following, the article based on Study 2 is presented in the original form in which it was prepared for publication (apart from changes in formatting).

STUDY 2: CONDITIONED RESPONSES TO TRAUMA REMINDERS: HOW DURABLE ARE THEY OVER TIME AND DOES IMAGINAL TRAUMA EXPOSURE REDUCE THEM?

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1 ABSTRACT

Intrusive memories of traumatic events — a hallmark symptom of posttraumatic stress disorder — are triggered by stimuli perceptually similar to stimuli that have been encountered in the context of the traumatic event. Models of PTSD assume that conditioned associations between neutral stimuli and traumatic events play an important role in PTSD, and that imaginal exposure has the effect of reducing these associations. This study aims to examine whether conditioned associations lead to intrusive trauma memories and how they are affected by imaginal exposure. Forty-eight healthy females watched a neutral film and a traumatic film containing neutral sounds, and on the following day were randomly allocated to imaginal exposure to either the traumatic film (treatment condition) or the neutral film (control condition). Intrusive memories were monitored for one week. Participants repeatedly completed a memory triggering task, in order to assess how durable conditioned intrusive memories, anxiety, and physiological reactions (skin conductance level, heart rate) are over time. Trauma-associated sounds elicited intrusive memories and anxiety when presented directly after film presentation, as well as one and seven days later. Furthermore, enhanced conditionability predicted later spontaneous trauma intrusions. This study therefore provides evidence for the assumption that intrusive trauma memories can be

explained by conditioned responses to neutral stimuli encountered during the trauma and that these effects are stable over time. No evidence was found for conditioned physiological reactions or for the hypothesis that imaginal exposure has the effect of reducing conditioned reactions. Implications for PTSD and its treatment are discussed.

2 INTRODUCTION

Intrusive memories of traumatic events are a hallmark symptom of posttraumatic stress disorder (PTSD; American Psychiatric Association, 2013). These memories consist of vividly experienced thoughts, images, and perceptions that cause immense distress (Michael, 2000; Michael, Ehlers, Halligan, et al., 2005). Unlike ordinary autobiographical memories, intrusive trauma memories are involuntarily retrieved and lack contextual information (Ehlers et al., 2004). Intrusive memories are triggered by stimuli perceptually similar to stimuli that have been encountered in the context of the traumatic event (Brewin et al., 1996; Foa et al., 1989). These stimuli do not necessarily have a meaningful relationship to the traumatic event (Ehlers et al., 2004). Furthermore, intrusive memories are often experienced as if they are actually happening (Hackmann et al., 2004).

Contemporary models of PTSD assume that intrusive memories can be explained by the way memories of traumatic experiences are encoded, represented, and retrieved (Brewin, 2001; Conway & Pleydell-Pearce, 2000; Ehlers & Clark, 2000; Foa et al., 1989). Ehlers and Clark (2000) have proposed that the cue-driven retrieval of trauma memories, initiated by perceptually similar cues, is due to strong perceptual priming and associative learning for trauma-related stimuli. According to this model, temporal co-occurrence causes neutral

stimuli to become associated with the aversive experience of the traumatic event and subsequently have the potential to trigger intrusive reexperiencing of the trauma, including memories, emotions, and physiological arousal (see also Foa et al., 1989; Keane et al., 1985). Thus, intrusive memories in PTSD can be regarded as conditioned reactions (CR) and triggers can be seen as conditioned stimuli (CS) that predict a traumatic event (unconditioned stimulus, UCS; Foa et al., 1989; Keane et al., 1985; Rothbaum & Davis, 2003). Furthermore, perceptual priming is thought to lower the perceptual threshold for these conditioned stimuli, which increases their probability of being recognized and acting as triggers for conditioned reactions and cue-driven retrieval of trauma memories.

It has been proposed that, in general, this cue-driven retrieval is inhibited as soon as episodic memories are integrated into the autobiographical memory system (Conway, 2005; Conway & Pleydell-Pearce, 2000). This system is regarded as a representation of conceptually organized autobiographical knowledge, regulated by a central control process, the working self, which controls the retrieval and encoding of episodic memories (Conway, 2003, 2005). Based on this model, Ehlers and Clark (2000) have suggested that poor memory integration of the traumatic experience in PTSD patients leads to insufficient inhibition of cue-driven retrieval of trauma memories. This corresponds to findings from cognitive neuroscience which suggests that stress-related alterations in brain functioning are responsible for the uncontrolled stimulus-driven retrieval in PTSD (Brewin, 2001; Elzinga & Bremner, 2002). Specifically, stress leads to enhanced activation in the amygdala during the traumatic event (Pitman et al., 2000; Shin, Rauch, & Pitman, 2006). As the amygdala is involved in fear conditioning, enhanced activation reinforces the acquisition of conditioned fear reactions (Davis & Whalen, 2001; LeDoux, 2000). On the other hand, there is evidence that the

interaction between the amygdala and the hippocampus during high levels of stress can lead to reduced hippocampal functioning, which in turn leads to impaired contextual and relational memory representations (for reviews see Bremner et al., 1995; Lupien & Lepage, 2001; Metcalfe & Jacobs, 1998; Radley & Morrison, 2005; Sapolsky, 2004). This deficient contextual integration is also thought to reduce voluntary control of memory retrieval and — more importantly — the inhibition of automatic cue-driven memory retrieval (Brewin, 2001; Ehlers & Clark, 2000).

According to this model of PTSD, memory integration should lead to a reduction of conditioned reactions and intrusive memories triggered by trauma-related stimuli. Indeed, clinical efficacy studies show that intervention techniques which focus on trauma memories and include a verbalization of the traumatic experience (e.g. memory elaboration or imaginal exposure) provide the best therapeutic outcomes (Bisson et al., 2007). It is not clear, however, whether this memory integration actually leads to a reduction of the memory processes supposedly underlying intrusive memories (i.e. perceptual priming and associative learning).

The first study examining the memory mechanisms underlying the effects of trauma memory integration treatment was conducted by Michael and Ehlers (2007). They presented traumatic and neutral picture stories to healthy participants and subsequently administered questions designed to promote remembering the traumatic experience and integrating it into participants' other autobiographical memories (e.g. whether the picture stories reminded them of things that had happened in their own lives). As expected, participants showed reduced intrusive memories after this memory elaboration as compared to a control group

that completed a series of cognitive tasks unrelated to the picture stories instead of the elaboration task. They also found that perceptual priming was reduced in the memory elaboration group. Using a similar design, Ehlers et al. (2012) investigated the effects of memory elaboration and imaginal exposure on perceptual priming, associative learning, and intrusive memories after traumatic picture stories. They found that both interventions were able to reduce the frequency of subsequent intrusive trauma memories and negative evaluative conditioning effects (i.e. the change in valence of a stimulus due to its paring with another negative or positive stimulus). Furthermore, memory elaboration also lowered perceptual priming effects for trauma-related stimuli. Taken together, these findings support the assumption that embedding the trauma memory into autobiographical memories leads to reduced intrusive trauma memories and that perceptual priming and associative learning are involved in this treatment effect. These results therefore provide evidence for the assumption that memory integration leads to a normalization of both the lowered perceptual threshold and conditioned negative evaluations for trauma-related stimuli that trigger conditioned reactions and trauma memories. These studies did not, however, include a direct measurement of conditioned reactions (e.g. intrusive memories, anxiety) to trauma-related stimuli, so whether associative learning is involved in the reduction of intrusive trauma memories after memory integration remains an open issue.

There is growing evidence for the important role associative learning plays in the development and maintenance of PTSD (Duits et al., 2015). Orr et al. (2000) investigated fear conditioning in PTSD patients and trauma-exposed participants without PTSD using a differential fear conditioning paradigm. Neutral visual stimuli were used as CS and either paired with an electrical stimulus as UCS or not. During acquisition, PTSD patients showed

larger differential skin conductance (SC), heart rate (HR) and electromyogram responses to the CS+ (stimulus paired with the UCS) versus the CS- (stimulus not paired with the UCS) compared to trauma-survivors without PTSD. When CS+ and CS- were subsequently repeatedly presented without being followed by the UCS (extinction), only PTSD patients continued to show differential SC responses to CS+ versus CS-. Delayed extinction in PTSD patients compared to trauma-exposed or healthy control groups has also been found in larger heart rate responses (Peri, Ben-Shakhar, Orr, & Shalev, 2000), startle responses (Norrholm et al., 2011), and subjective ratings of valence and US-expectancy (Blechert et al., 2007). In a prospective study of soldiers who were tested before and after their deployment, reduced extinction learning was found to be a pre-trauma vulnerability factor for PTSD symptom severity (Lommen et al., 2013). Taken together, these findings indicate that conditioned reactions to trauma reminders play an important role for the development of intrusive reexperiencing.

One limitation, however, of fear conditioning experiments is their relatively poor ecological validity. The UCSs implemented to simulate a traumatic event in the laboratory are electrical stimulation or aversive noises (Duits et al., 2015; Lissek et al., 2005). These stimuli are suitable for investigating conditioned fear reactions, but allow no inferences about complex intrusive trauma memories as they are observed after real-life trauma. Because of these shortcomings Wegerer et al. (2013) have recently developed the conditioned intrusion paradigm. In this paradigm, neutral sounds are either paired with short aversive film clips (CS+) or presented alone (CS-). Subsequently, the CS+ when presented again while embedded in a neutral background soundscape triggered intrusive memories, and induced anxiety and physiological arousal (as indexed by SC levels). Furthermore, conditionability of

subjective valence ratings and fear reactions in this task was associated with later ambulatory intrusive memories, which indicates that fear conditioning is involved in the development of intrusive trauma memories. This paradigm was an important step toward investigating fear conditioning in a more naturalistic laboratory setting, yet its ecological validity is still limited, as the repeated presentation of the CS+ paired with the UCS that is interrupted by inter-trial intervals and CS- presentations is quite artificial and does not resemble the typical time course of a traumatic event. Furthermore, conditioned intrusive memories and fear reactions were only assessed directly after the acquisition phase, so it remains unclear whether the associated responses are stable over time.

A more naturalistic laboratory analogue of traumatic experiences is the trauma film paradigm. In this paradigm healthy participants are exposed to a stressful film (typical duration: 8-12 min), depicting traumatic events, such as actual or threatened death and serious physical injuries. Over the following days, participants keep a diary to document their intrusive memories of the presented film. Several studies verify that this paradigm can cause intrusive memories that are analogous to intrusive trauma memories in PTSD (for a review see Holmes & Bourne, 2008), so that the trauma film paradigm provides an experimental tool for investigating memory processes underlying PTSD with high ecological validity.

In order to examine how stable conditioned responses to trauma reminders are over time, and how they are affected by imaginal memory exposure, we combined the conditioned intrusions paradigm from Wegerer et al. (2013) with the standard trauma film paradigm. Specifically, neutral sounds were repeatedly presented during either a traumatic film clip

(CS+) depicting interpersonal violence or a neutral control film (CS-) depicting neutral social interactions. To test whether trauma-associated sounds (CS+) trigger traumatic memories and increase anxiety, the memory triggering task developed by Wegerer et al. (2013) was performed after film presentation. To examine how durable these conditioned responses are over time, we implemented the memory triggering task again one day and one week after presenting the film. To study whether fear conditioning plays a role in the therapeutic effects of imaginal exposure, one day after seeing the film, participants were instructed to imagine and verbalize either the events of the traumatic or neutral film, following Ehlers' (1999) rational for imaginal exposure.

Our design has the advantage of using the well-established standard trauma film paradigm that is known to reliably induce analogue trauma intrusions and allows experimental control of which neutral stimuli are present during the analogue trauma, as in a fear conditioning paradigm. It therefore enables the investigation of associative learning during traumatic events in one of the most natural ways possible. Additionally, by having participants repeatedly perform the memory triggering task after the traumatic film, we are able to assess whether conditioned intrusive memories remain stable over a longer time span and how they are impacted by the therapeutic intervention of imaginal exposure.

This experimental analogue study had two main aims: (1) Investigating associative learning for intrusive memories and conditioned fear in a traumatic context and (2) testing whether associative learning processes are involved in the therapeutic effects of imaginal exposure on subsequent intrusive trauma memories. The following hypotheses were examined:

Hypothesis 1: It was expected that neutral sound stimuli repeatedly presented during a traumatic film (CS+), would lead, when presented again in a neutral context, to more intense intrusive memories, more anxiety, and greater physiological arousal (as indexed by enhanced skin conductance levels and heart rates) as compared to neutral stimuli that were originally presented during a neutral film (CS-). This effect was expected to be observed directly after film presentation (t1), on the following day (t2, t3), and one week after film presentation (t4).

Hypothesis 2: Furthermore, enhanced conditionability, as assessed by differential conditioned reactions (CS+ minus CS-) directly after film presentation (t1), was expected to predict the intensity of subsequent ambulatory intrusive trauma memories and Impact of Event Scale (IES-R) scores.

Hypothesis 3: Imaginal exposure to the traumatic film was expected to reduce the differential conditioning effects (CS+ minus CS-) on intrusive memories, anxiety, and physiological arousal directly after imaginal exposure (t3) and six days later (t4) as compared to imaginal exposure to the neutral film.

Hypothesis 4: Furthermore, imaginal exposure to the traumatic film was expected to lead to reduced spontaneous intrusive memories on subsequent days and reduced IES-R scores as compared to imaginal exposure to the neutral film.

3 METHOD

3.1 PARTICIPANTS

Forty-eight female non-psychology students (mean age: 23.8, range 19-34 years) were recruited on the campus of Saarland University and participated in exchange for 56 Euros. Only female participants were included because of gender differences in affective self-reports and physiological responses to emotional stimuli (Bianchin & Angrilli, 2012; Bradley, Codispoti, Sabatinelli, & Lang, 2001; Kring & Gordon, 1998), and because the prevalence of PTSD is higher among women (Perkonigg et al., 2000). All participants had normal or corrected to normal vision, were native German speakers, reported no history of neurological or psychiatric disorders or past traumatic experience, and gave informed consent. The research was approved by the Department of Psychology Ethics Committee of Saarland University.

3.2 ANALOGUE TRAUMA AND INTRUSION CONDITIONING

All participants saw two film clips (one neutral and one traumatic) in pseudo-randomized order. The neutral film was a compilation of neutral scenes (11 min) from the movie “Three Colors: Blue” directed by Krzysztof Kieslowski (1993). The traumatic film consisted of neutral and violent scenes (11 min) from the movie “Irreversible” by Gaspar Noé (2002). During presentation of each film clip one of two neutral sounds with a duration of 5 s (sound A: clock ticking, sound B: sound of a passing train) was presented every minute (11 times) to serve as conditioned stimuli (CS; see Figure III-1). The CS sounds were assigned to CS+ (i.e., sound that was presented during the aversive film clip and serves as danger signal) and

CS- (i.e., sound that was presented during the neutral film clip and served as safety signal), pseudo-randomized across participants. After watching each film clip, an adapted version of the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) was administered, assessing how participants felt while watching the preceding film. Participants were subsequently asked to rate how strongly the preceding film caused physiological arousal on a 5-point scale going from "very slightly or not at all" to "extremely".

3.3 MEMORY TRIGGERING TASK

The memory triggering task was designed to simulate situations of everyday life in which trauma survivors experience intrusive memories that are triggered by CSs (Wegerer et al., 2013). Following a 1 min physiological baseline measurement, participants were informed that they would then be presented with a background soundscape via headphones while they let their mind wander freely.

The soundscapes were of 3 min duration and featured various people talking with neither content nor language identifiable. In the *CS+ cue condition*, the CS+ sound (clock ticking or train passing) was faded in six times with 5 s duration during sound-scape presentation (see Figure III-1). In the *CS- cue condition*, the CS- sound was faded in six times with 5 s duration. In the *no-cue condition*, no sound cues were faded in. In both the CS+ and the CS- cue conditions, sound cues were presented subtly but perceptibly at the same points in time (at 15 s, 45 s, 75 s, 105 s, 135 s, 165 s from soundscape onset). The order of cue conditions was counterbalanced across participants (including all six permutations).

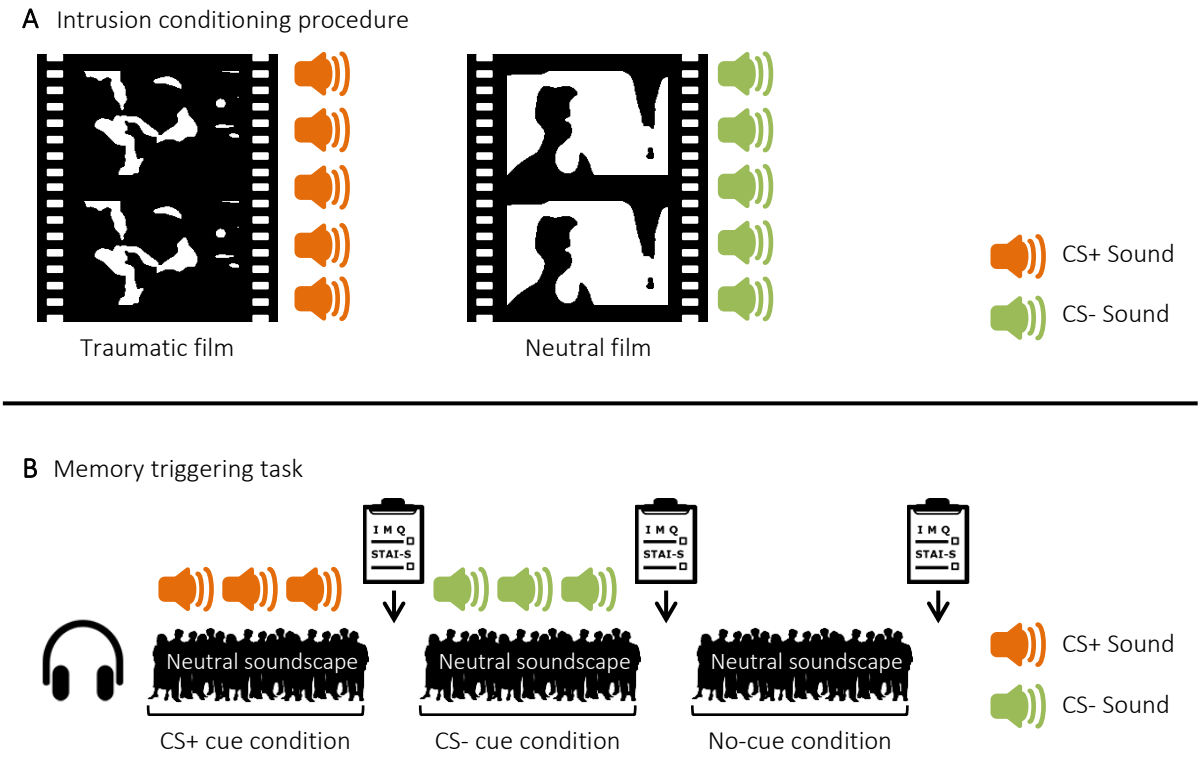

Figure III-1: Schematic depiction of the conditioned-intrusions paradigm.

(A) Intrusion conditioning procedure with traumatic and neutral film scenes as unconditioned stimuli (UCS) and neutral sounds as conditioned stimuli (CS+ and CS-). **(B)** Memory triggering task. Neutral soundscape with faded in CS+ sounds (CS+ cue condition) CS- sounds (CS- cue condition), or no additional sound faded in (no-cue condition); IMQ: Intrusive Memory Questionnaire; STAI-S: STAI state anxiety scale. (modified from Wegerer et al., 2013)

Following each 3 min soundscape presentation, participants filled in the STAI state questionnaire (Laux, Glanzmann, Schaffner, & Spielberger, 1981) and the Intrusive Memory Questionnaire (IMQ; Ehring, Fuchs, & Kläsener, 2009; Michael, 2000; Zetsche, Ehring, & Ehlers, 2009). The IMQ was adapted to assess frequency and duration (in seconds) as well as distress (visual analogue scale going from “0 = not at all” to “100 = extremely”) during the preceding soundscape. Intrusions were defined as spontaneous involuntary memories that could include thoughts, pictures, noises, and emotions. Participants first completed the IMQ with regard to intrusive memories of the traumatic film. To make sure that only trauma-related memories were included in this assessment, the IMQ was subsequently administered

again with regard to neutral memories. Only the version assessing trauma-related memories was used for data analysis. To obtain a more reliable score for intrusive trauma memories, we additionally calculated an index of intrusive trauma memories by building a composite score of the IMQ by standardizing (*z*-transformation) and summing all single items for the traumatic film (For purposes of better illustration the composite scores were transformed into T-scores.)

The three soundscapes from the memory triggering task were presented before film presentation (t0) without subsequent questionnaires to habituate participants to the stimuli and to examine potential pre-experimental differences between the cue conditions. The memory triggering task was assessed at four different measurement points in time (see Figure III-2): (t1) after film presentation, (t2) before imaginal exposure (one day after film presentation), (t3) after imaginal exposure, (t4) at follow-up session (one week after film presentation).

3.4 IMAGINAL EXPOSURE

On the day following film presentation, participants were asked to imagine and verbalize one of the two previously seen film clips (neutral or traumatic). The treatment group was asked to imagine the traumatic film and the control group was asked to imagine the neutral film. The instructions were modeled on imaginal exposure (Ehlers, 1999). Participants were asked to close their eyes and imagine the respective film clip as vividly as they could. Participants were encouraged to remember as much detail as possible and recall their original feelings and thoughts. They were asked to remember the action of the film in chronological order.

The exposure lasted from 3 to 20 min (M = 7.98, SD = 3.59). The imaginal exposure session was audio recorded and each participant was rated by two independent persons regarding how well they followed the instructions on a rating scale going from 1 to 10 (inter-rater reliability: r = .70, p < .001). Participants had an average compliance score of M = 6.66 (SD = 1.33), indicating that they had followed the instructions.

3.5 ASSESSMENT OF AMBULATORY INTRUSIVE MEMORIES AND THE IMPACT OF EVENT SCALE

During the seven days following film presentation, participants documented every intrusive film memory, using an iPod Touch (4th gen., Apple Inc., Cupertino, USA) running Forms VI (Pendragon Software Corporation, Chicago, USA). The frequency of intrusive memories was determined by summing up their frequency for the neutral and the traumatic film separately. For each memory, participants stated its duration (in seconds) and rated how distressing it was on a 10-point scale going from “not at all” to “extremely”. These ratings were averaged for the neutral and the traumatic film separately (Michael & Ehlers, 2007; Pfaltz et al., 2013).

Seven days after film presentation, every participant completed the Impact of Event Scale (IES-R; German translation; Maercker & Schützwohl, 1998; Weiss et al., 2004), a 22-item questionnaire assessing PTSD symptoms. Every item (e.g. “Things I saw or heard suddenly reminded me of it”) was rated on a 5-point scale spanning from “not at all” to “extremely”. The instructions of IES-R were adapted to assess only symptoms relating to the traumatic film.

3.6 PROCEDURE

The study took place at the laboratories of the Department of Clinical Psychology and Psychotherapy of the Saarland University. Participation included three appointments: film presentation session (day 1), imaginal exposure session (day 2), and follow-up session (day 8; see Figure III-2). Participants were assigned randomly to one of the two imaginal exposure conditions (*treatment condition* with imaginal exposure to the traumatic film or *control condition* with imaginal exposure to the neutral film).

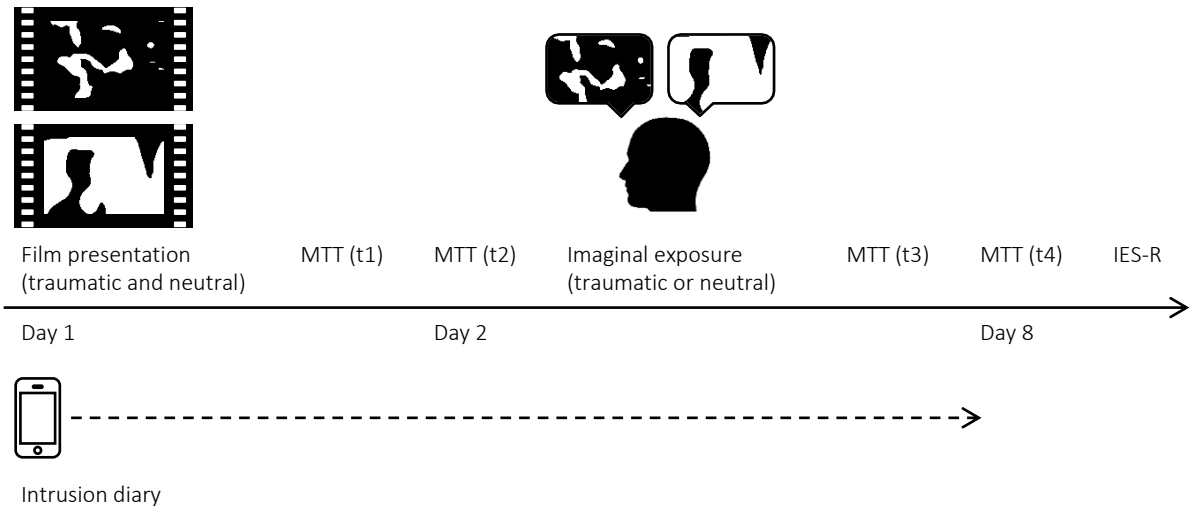

Figure III-2: Study design overview.

All participants watched a traumatic and a neutral film including neutral sounds. During the memory triggering task (MTT) the neutral sounds from the film were presented again to trigger intrusive memories and conditioned fear. It was administered at four points of measurement (t1: after film presentation, t2: one day after film exposure, before Imaginal exposure, t3: after imaginal exposure, t4: one week after film exposure). On the following day, participants were instructed to imagine and verbalize either the traumatic film (treatment condition) or the neutral film (control condition). One week after film presentation, participants completed the Impact of Event Scale (IES-R). Participants documented every intrusive memory during the week following film exposure (intrusion diary).

Film presentation session (Day 1). After their arrival at the laboratories, participants were led to the experiment room, and electrodes for physiological measurements (electrocardiogram, skin conductance) were attached (as described in detail in: III3.7 Apparatus and Physiological Recording). Participants were subsequently presented with the

three soundscapes of the memory triggering task (t0; CS+ cue condition, CS- cue condition, no-cue condition). This was done in order to assess whether the three conditions had pre-experimental differences in their potential to trigger physiological reactions. Afterwards, each participant saw the two film clips (neutral and traumatic). After presentation of both film clips, participants completed the first run of the memory triggering task (t1) to assess conditioned reactions to the film-associated sounds directly after the films. Participants were reminded to record spontaneous intrusive memories with the electronic diary during the following week before they left the laboratory.

Imaginal exposure session (Day 2). On the following day, participants returned to the laboratory. Electrodes for physiological measurements were again attached, and participants completed the second run of the memory triggering task (t2) to determine whether conditioned reactions to the film-associated sounds were still present one day after film exposure. Afterwards, they were instructed to complete an imaginal exposure either to the traumatic film (treatment condition) or to the neutral film (control condition). After the imaginal exposure, participants completed the third run of the memory triggering task (t3) to examine the immediate effects of imaginal exposure on conditioned reactions to the film-associated sounds and left the laboratory.

Follow-up session (Day 8). Seven days after film presentation, participants returned to the laboratory for the last time. They turned in the electronic diary, electrodes for physiological measurements were again attached, and they completed a final run of the memory triggering task (t4) to see whether conditioned reactions to the film-associated sounds were still observable one week after film presentation. Afterwards, participants completed an adapted

version of the IES-R, received 56 Euros for their participation, and were offered to ask questions about the design and goals of the study.

3.7 APPARATUS AND PHYSIOLOGICAL RECORDING

Participants were seated in an electrically shielded room. Stimulus presentation and behavioral data acquisition were controlled by E-Prime 2.0 (Psychology Software Tools, Inc., Pittsburg, PA, USA). Acoustic stimuli were presented via shielded headphones at a constant volume across participants. To measure heart rate, a standard lead-II electrocardiogram (ECG) with two Ag/AgCl electrodes was used to collect a raw ECG signal with an ActiveTwo amplifier (BioSemi, Amsterdam, The Netherlands) at a sampling rate of 2048 Hz. R-waves were identified automatically by ANSLAB (Wilhelm and Peyk, 2012) and edited manually for artifacts, false positives or non-recognized R-waves and transformed into instantaneous heart rates (HR). To measure skin conductance levels (SCL), two Ag/AgCl electrodes filled with isotonic electrode gel were attached to the proximal part of the palm of the participants' non-dominant hand (with an alternating current of 1 mA synchronized with the sampling frequency passed between the electrodes). The raw signal of electrodermal activity was cautiously collected using an ActiveTwo amplifier (BioSemi, Amsterdam, The Netherlands) at a sampling rate of 2048 Hz and decimated to 25 Hz before further analysis. It was then manually edited for artifacts, smoothed using a 1 Hz low-pass filter.

3.8 STATISTICAL ANALYSES

Memory triggering task. For each run of the memory triggering task (t0, t1, t2, t3, t4), mean SCL and HR were calculated as the average across the whole phase (3 min) of each condition (CS+ cue condition, CS- cue condition, no-cue condition). Before the actual experiment, a habituation phase (t0) was completed, additionally examining potential pre-experimental differences in physiological reactions to the three cue conditions. No such differences were observed (see Table III-3).

To examine the differential conditioning effects on intrusive memories and state anxiety, repeated measures analyses of variance (ANOVA) were calculated separately for each point of measurement (t1, t2, t3, t4[4]) and each outcome measure (IMQ, STAI state anxiety) with the cue condition as the within-participant factor (CS+ cue condition, CS- cue condition, no-cue condition). To examine the differential conditioning effects on physiological measures, repeated measures analyses of covariance (ANCOVA) were calculated separately for each point of measurement (t1, t2, t3, t4[4]) and each outcome measure (HR, SCL) with cue condition as the within-participant factor (CS+ cue condition, CS- cue condition, no-cue condition). To account for baseline differences, the respective physiological baseline measurement was included as a covariate.

Individual estimates of conditionability were calculated as the differential reaction to CS+ versus CS- separately for each outcome measure (IMQ, STAI state anxiety, HR, SCL) of the

[4] As the two experimental groups (treatment group, control group) did not differ at point of measurement t3 and t4 with regard to all outcome variables of the MTT, the data of both groups were collapsed for this analysis.

MTT directly after film presentation (t1). These indices of conditionability were correlated with subsequent ambulatory intrusions (frequency, duration, distress) and the IES-R score.[5]

Individual *t*-tests examined differences between the treatment condition and the control condition in the differential conditioning scores (CS+ minus CS-) of each outcome measure (IMQ, STAI state anxiety, HR, SCL) separately for the two post-treatment points of measurement (t3, t4).

Ambulatory intrusive memories and Impact of Event Scale. Individual *t*-tests were used to examine differences between the treatment condition and the control condition in the frequency of intrusive trauma memories after imaginal exposure, as well as their duration and distress ratings. A *t*-test was used to compare the IES-R scores of the treatment condition and the control condition.

The alpha level for all analyses was set to .05 and significant main or interaction effects of ANOVAs were further explored using *t*-tests. For all ANOVAs and *t*-tests, effects sizes are reported partial eta squared (η_p^2) or Cohen's *d*, respectively. When the sphericity assumption was violated in ANOVAs, the Greenhouse-Geisser correction for repeated measures was applied with nominal degrees of freedom being reported. Due to missing values, degrees of freedom varied across analyses.

All statistical analyses were calculated using IBM SPSS Statistics 22 (IBM Corp., Armonk, NY, USA).

[5] As the two experimental groups (treatment group, control group) did not differ at day 7 with regard to IES-R scores, the data of both groups were collapsed for this analysis.

4 RESULTS

4.1 VALIDITY OF THE FILM MATERIAL

Participants reported significantly more negative emotions and higher subjective physiological arousal during presentation of the traumatic film as compared to the neutral film (see Table III-1). Participants also showed significantly enhanced physiological arousal as indexed by elevated skin conductance levels (SCL) and heart rate (HR) during presentation of the traumatic film as compared to the neutral film (see Table III-1).

Table III-1: Emotional and physiological reactions to the two film clips and ambulatory intrusive memories of the film clips.

	Reactions to the film clips		
	Traumatic film	**Neutral film**	**Interferential statistics**
	M (SD)	*M (SD)*	
PANAS – Positive	11.72 (4.86)	9.74 (5.27)	$t(46) = 2.47$, $p < .05$, $d = 0.36$
PANAS – Negative	24.02 (7.73)	5.60 (5.31)	$t(46) = 14.99$, $p < .001$, $d = 2.19$
Subjective arousal	2.35 (1.06)	0.73 (0.89)	$t(47) = 10.78$, $p < .001$, $d = 1.56$
SCL	8.865 (0.861)	8.690 (0.817)	$t(43) = 4.11$, $p < .001$, $d = 0.62$
HR	77.01 (13.69)	72.07 (11.58)	$t(42) = 4.78$, $p < .001$, $d = 0.73$

Note: PANAS – Positive: PANAS score for positive affect; PANAS – Negative: PANAS score for negative affect; Subjective arousal: subjective arousal rating after film presentation ("To what extent did the film cause physiological reactions (faster heartbeat, sweating etc.)?", scale 0 – 100; 0 = not at all, 100 = extremely); SCL: skin conductance level given as ln(1 + SCL) in µS; HR: heart rate given as beats per minute.

4.2 VALIDITY OF IMAGINAL EXPOSURE

During the first three minutes of imaginal exposure, the treatment group showed marginally significant elevated skin conductance levels as compared to the control group (see Table III-2). The treatment group furthermore showed significantly elevated heart rates as compared to the control group. This indicates enhanced physiological arousal in the treatment group as a reaction to remembering the trauma memories when compared to the

group that remembered the neutral film. Furthermore, duration and compliance ratings for the treatment group were higher than for the control group (see Table III-2).

Table III-2: Physiological reactions, duration, and compliance for imaginal exposure.

	Imaginal exposure		
	Treatment group (trauma exposure)	**Control group (neutral exposure)**	**Interferential statistics**
	M (SD)	*M (SD)*	
SCL	2.361 (0.696)	2.067 (0.564)	$t(43) = 1.73$, $p = .09$, $d = 0.51$
HR	90.77 (17.76)	83.62 (14.36)	$t(42) = 2.90$, $p = .006$, $d = 2.90$
Duration	532.73 (151.19)	393.71 (101.28)	$t(46) = 3.74$, $p = .001$, $d = 1.10$
Compliance score	7.29 (1.28)	6.04 (1.09)	$t(46) = 3.63$, $p = 001.$, $d = 1.07$

Note: SCL: skin conductance level given as ln(1 + SCL) in µS; HR: heart rate given as beats per minute; Interferential statistics for baseline-corrected measures; Duration: duration of exposure session given as seconds; Compliance score: averaged score from two independent persons rating how well participants followed the instructions (scale: 1 - 10) .

4.3 HYPOTHESIS 1: CONDITIONED INTRUSIVE MEMORIES AND CONDITIONED FEAR

Intrusive Memory Questionnaire. As expected, responses to the IMQ (including subjective intrusive trauma memory frequency and duration as well as distress through intrusive trauma memories) differed significantly by condition in the memory triggering task, comprised of neutral soundscapes with CS+, CS-, or no faded in sound cues at all points of measurement (t1: post-film, t2: pre-treatment, t3: post-treatment, t4: follow-up; see Table III-3). As the planned comparisons revealed, at all points of measurement participants reported more numerous, longer, and more distressing memories of the traumatic film during the CS+ cue condition as compared to the CS- and the no-cue condition (all ts(47) > 2.06, ps < .05, ds > 0.60; see Table III-3). The CS- cue condition, in turn, did not differ from the no-cue condition with regard to frequency, duration, or level of distress of memories of the traumatic film at all points of measurement (all ts(47) < 1.30, ps > .20, ds < 0.38; see Table

III-3). This means that participants showed differential conditioning effects for conditioned trauma memories and that these effects were still observable one day and one week after film presentation.

State anxiety. As expected, STAI state anxiety differed significantly by condition in the memory triggering task at all points of measurement (t1, t2, t3, t4; see Table III-3). As planned comparisons revealed, participants reported more state anxiety during the CS+ condition than during the CS- and the no-cue condition for all points of measurement (all *t*s(47) > 2.78, *p*s < .03, *d*s > 0.81; see Table III-3). The CS- cue condition, in turn, did not differ from the no-cue condition with regard to state anxiety at all points of measurement (all *t*s(47) < 1.68, *p*s > .10, *d*s < 0.49; see Table III-3). This means that participants showed differential conditioning effects for state anxiety and that these effects were still observable one day and one week after film presentation.

Skin conductance level. Contrary to our hypothesis, no significant differences between the three cue conditions (CS+ cue condition, CS- cue condition, no-cue condition) in SCL during the memory triggering task were observed at all points of measurement (see Table III-3). These findings indicate that, counter to our hypothesis, no differential conditioning effects for skin conductance level were present.

Heart rate. Contrary to our hypothesis, no significant differences between the three cue conditions (CS+ cue condition, CS- cue condition, no-cue condition) in HR during the memory triggering task were observed for all points of measurement (see Table III-3). These findings indicate that, counter to our hypothesis, no differential conditioning effects for heart rate were present.

Table III-3: Results from intrusive memories, state anxiety, SCL, and HR during the memory triggering task after film presentation (t0, t1, t2, t3, t4).

	Memory triggering task			
	CS+ condition	**CS- condition**	**No-cue condition**	**Interferential statistics**
	M (SD)	*M (SD)*	*M (SD)*	
Day 1: Physiological baseline measurement (t0)				
SCL	1.68 (0.71)	1.65 (0.69)	1.67 (0.73)	$F(2, 90) = 0.64$, $p = .53$, $\eta_p^2 = .01$
HR	73.82 (10.95)	74.03 (11.44)	73.87 (11.32)	$F(1.6, 72.4) = 0.93$, $p = .40$, $\eta_p^2 = .02$
Post-film measurement (t1)				
IMQ – Score	75.12 (30.40)[a]	58.92 (21.44)[b]	56.88 (24.12)[b]	$F(2, 94) = 15.65$, $p < .001$, $\eta_p^2 = .25$
IMQ - Frequency	4.49 (2.91)[a]	2.77 (2.09)[b]	2.56 (2.56)[b]	$F(2, 94) = 17.57$, $p < .001$, $\eta_p^2 = .27$
IMQ - Duration	26.61 (39.83)[a]	9.32 (18.00)[b]	7.35 (18.64)[b]	$F(1.5, 71.0) = 12.87$, $p < .001$, $\eta_p^2 = .22$
IMQ - Distress	36.77 (30.24)[a]	18.79 (25.03)[b]	19.31 (24.58)[b]	$F(2, 94) = 3.96$, $p < .05$, $\eta_p^2 = .08$
State anxiety	48.21 (13.90)[a]	45.02 (13.16)[b]	44.54 (11.88)[b]	$F(1.7, 78.5) = 8.53$, $p < .01$, $\eta_p^2 = .15$
SCL	2.11 (0.71)	2.11 (0.73)	2.12 (0.71)	$F(2, 86) = 1.69$, $p = .19$, $\eta_p^2 = .04$
HR	71.76 (10.71)	71.85 (10.61)	72.88 (11.17)	$F(2, 90) = 0.17$, $p = .85$, $\eta_p^2 = .01$
Day 2: Pre-treatment measurement (t2)				
IMQ – Score	62.55 (29.30)[a]	41.96 (18.04)[b]	40.13 (16.67)[b]	$F(2, 94) = 29.36$, $p < .001$, $\eta_p^2 = .39$
IMQ - Frequency	3.28 (2.70)[a]	1.40 (1.62)[b]	1.10 (1.39)[b]	$F(1.6, 76.6) = 26.43$, $p < .001$, $\eta_p^2 = .36$
IMQ - Duration	32.39 (46.19)[a]	15.14 (46.19)[b]	13.83 (28.21)[b]	$F(1.5, 71.0) = 12.87$, $p < .001$, $\eta_p^2 = .22$
IMQ - Distress	36.77 (30.24)[a]	18.79. (25.03)[b]	19.31 (24.58)[b]	$F(2, 94) = 15.21$, $p < .001$, $\eta_p^2 = .24$
State anxiety	40.23 (12.18)[a]	36.08 (10.04)[b]	35.81 (9.70)[b]	$F(1.3, 62.5) = 10.98$, $p < .01$, $\eta_p^2 = .19$
SCL	1.61 (0.74)	1.62 (0.69)	1.60 (0.69)	$F(2, 90) = 0.93$, $p = .40$, $\eta_p^2 = .02$
HR	78.46 (13.62)	77.85 (13.60)	78.03 (13.62)	$F(2, 92) = 0.02$, $p = .99$, $\eta_p^2 < .01$
Post-treatment measurement (t3)				
IMQ – Score	61.62 (25.83)[a]	46.44 (19.44)[b]	45.09 (20.71)[b]	$F(1.7, 81.9) = 21.42$, $p < .001$, $\eta_p^2 = .31$
IMQ - Frequency	3.08 (2.09)[a]	1.78 (1.79)[b]	1.46 (1.53)[b]	$F(2, 94) = 16.44$, $p < .001$, $\eta_p^2 = .26$
IMQ - Duration	26.85 (36.05)[a]	9.60 (16.98)[b]	12.35 (28.89)[b]	$F(1.5, 69.7) = 15.49$, $p < .001$, $\eta_p^2 = .25$
IMQ - Distress	36.35 (31.54)[a]	26.75 (30.04)[b]	24.06 (25.37)[b]	$F(2, 94) = 6.88$, $p < .01$, $\eta_p^2 = .13$
State anxiety	42.25 (11.50)[a]	39.92 (11.24)[b]	38.81 (10.93)[b]	$F(1.8, 83.5) = 9.39$, $p < .001$, $\eta_p^2 = .17$
SCL	2.11 (0.72)	2.09 (0.73)	2.09 (0.74)	$F(2, 90) = 0.27$, $p = .76$, $\eta_p^2 = .01$
HR	74.67 (12.35)	74.37 (12.85)	75.09 (12.57)	$F(1.3, 60.9) = 0.81$, $p = .45$, $\eta_p^2 = .02$
Day 7: Follow-up measurement (t4)				
IMQ – Score	45.27 (16.32)[a]	32.70 (9.01)[b]	33.32 (10.18)[b]	$F(1.7, 78.1) = 22.68$, $p < .001$, $\eta_p^2 = .33$
IMQ - Frequency	2.21 (1.95)[a]	0.81 (1.28)[b]	0.67 (0.97)[b]	$F(1.4, 67.5) = 27.91$, $p < .001$, $\eta_p^2 = .37$
IMQ - Duration	9.15 (11.52)[a]	2.23 (3.47)[b]	3.19 (5.15)[b]	$F(1.3, 60.2) = 14.73$, $p < .001$, $\eta_p^2 = .24$
IMQ - Distress	18.13 (23.73)[a]	6.50 (12.94)[b]	9.25 (19.39)[b]	$F(2, 94) = 6.94$, $p < .01$, $\eta_p^2 = .13$
State anxiety	35.71 (10.97)[a]	33.77 (9.82)[b]	33.96 (9.11)[b]	$F(1.4, 66.6) = 4.74$, $p < 05.$, $\eta_p^2 = .92$
SCL	1.47 (0.64)	1.45 (0.65)	1.48 (0.64)	$F(2, 98) = 0.46$, $p = .63$, $\eta_p^2 = .01$
HR	77.10 (12.28)	76.71 (12.12)	76.49 (12.22)	$F(1.8, 77.4) = 0.18$, $p = .83$, $\eta_p^2 < .01$

Note: IMQ Score: composite scores of the IMQ in T-scores; state anxiety: assessed by STAI state; SCL: skin conductance level given as ln(1 + SCL) in µS; HR: heart rate given as beats per minute. As the two experimental groups (treatment group, control group) did not differ at point of measurement t3 and t4, data from both groups were collapsed for this analysis. a, b, different superscripts indicate that the conditions differed from each other at $p < .05$ in post hoc tests.

4.4 HYPOTHESIS 2: CONDITIONABILITY AND AMBULATORY INTRUSIVE MEMORIES

To examine whether conditionability of intrusive memories (IMQ), state anxiety (STAI-S), and physiological arousal (SCL, HR) can predict later intrusive trauma memories and IES-R scores, conditionability scores were calculated (CS+ minus CS-) separately for each variable.

Conditionability of intrusive memories (IMQ) was significantly correlated with the frequency, duration, and distress of subsequent ambulatory trauma intrusions (all *r*s > .33, *p*s < .05; see Table III-4), indicating that the specific conditioned reactions to trauma-associated cues (CS+) were predictive of later intrusive memories in everyday life.

No correlations, however, were observed for conditionability of state anxiety and physiological arousal (SCL, HR), or for the IES-R scores (see Table III-4).

Table III-4: Correlations between conditionability (as indexed by differential effects on IMQ, STAI-S, HR, SCL) and ambulatory intrusive trauma memories and IES-R scores.

	Ambulatory intrusive trauma memories			**Impact of Event Scale**
	Frequency	**Duration**	**Distress**	**IES-R score**
	r (*p*)	*r* (*p*)	*r* (*p*)	*r* (*p*)
Conditionability (CS+ minus CS-)				
IMQ – Score	**.39** (**.006**)	**.33** (**.02**)	**.46** (**.001**)	.18 (.22)
State anxiety	.12 (.42)	-.03 (.84)	.22 (.13)	.23 (.11)
SCL	-.02 (.92)	-.12 (.42)	.02 (.92)	-.10 (.54)
HR	.09 (.54)	.08 (.58)	.12 (.41)	.11 (.45)

Note: All scores constitute differential conditioning scores (CS+ minus CS-) from the memory triggering task; IMQ Score: composite scores of the intrusive memory questionnaire for trauma intrusions in T-scores; state anxiety: assessed by STAI state anxiety scale; SCL: skin conductance level given as ln(1 + SCL) in µS; HR: heart rate given as beats per minute.

4.5 HYPOTHESIS 3: EFFECTS OF IMAGINAL EXPOSURE ON CONDITIONED INTRUSIVE MEMORIES AND FEAR

Contrary to our hypotheses, the two exposure conditions did not differ with regard to differential conditioning effects for the IMQ (composite score, frequency, duration, and distress of traumatic intrusions), STAI-S, SCL, or HR at both points of measurement after imaginal exposure (t3, t4; see Table III-5).

Taken together, these findings indicate that in this study imaginal exposure to the traumatic film had no beneficial effects on differential conditioning as compared to imaginal exposure to the neutral film.

4.6 HYPOTHESIS 4: EFFECTS OF IMAGINAL EXPOSURE ON AMBULATORY INTRUSIVE MEMORIES AND IES-R SCORES

Counter to our hypothesis, the treatment group did not differ with regard to ambulatory intrusive trauma memories (assessed with electronic diary) when compared to the control group (see Table III-6). Furthermore, no significant difference between the two treatment groups was found in the Impact of Event Scale score and its subscales (see Table III-6).

Taken together, these findings indicate that in this study, imaginal exposure to the traumatic film had no beneficial effects on intrusive trauma memories and the impact of the traumatic film as compared to imaginal exposure to the neutral film.

Table III-5: Group differences in differential conditioning scores of intrusive memories, state anxiety, SCL, and HR during the memory triggering task before (t2) and after imaginal exposure (t3, t4).

	Differential conditioning in the memory triggering task		
	Treatment group (trauma exposure)	**Control group (neutral exposure)**	**Interferential statistics**
	M (SD)	*M (SD)*	
Day 2:			
Pre-treatment measurement (t2)			
IMQ – Score	20.70 (30.93)	20.48 (17.64)	$t(36.5) = 0.03$, $p = .98$, $d = 0.01$
IMQ - Frequency	1.77 (2.75)	2.00 (1.62)	$t(46) = 0.35$, $p = .73$, $d = 0.10$
IMQ - Duration	22.08 (45.50)	12.50 (16.61)	$t(29.0) = 0.97$, $p = .34$, $d = 0.36$
IMQ - Distress	14.71 (27.89)	21.25 (26.09)	$t(46) = 0.84$, $p = .41$, $d = 0.24$
State anxiety	3.58 (5.68)	4.71 (10.56)	$t(46) = 0.46$, $p = .65$, $d = 0.14$
SCL	-0.02 (0.30)	-0.01 (0.19)	$t(46) = 0.19$, $p = .85$, $d = 0.06$
HR	0.73 (3.18)	0.50 (2.73)	$t(46) = 0.26$, $p = .79$, $d = 0.08$
Post-treatment measurement (t3)			
IMQ – Score	15.91 (25.59)	14.44 (16.46)	$t(46) = 0.24$, $p = .81$, $d = 0.07$
IMQ - Frequency	1.15 (2.57)	1.46 (2.13)	$t(46) = 0.46$, $p = .65$, $d = 0.14$
IMQ - Duration	23.33 (34.39)	11.17 (12.86)	$t(29.3) = 1.62$, $p = .11$, $d = 0.60$
IMQ - Distress	7.38 (28.23)	11.83 (21.28)	$t(46) = 0.62$, $p = .54$, $d = 0.18$
State anxiety	1.83 (7.18)	2.83 (4.16)	$t(36.9) = 0.59$, $p = .56$, $d = 0.19$
SCL	0.005 (0.13)	0.043 (0.17)	$t(45) = 0.86$, $p = .40$, $d = 0.26$
HR	-0.53 (2.15)	1.13 (8.68)	$t(46) = 0.91$, $p = .37$, $d = 0.27$
Day 7:			
Follow-up measurement (t4)			
IMQ – Score	12.22 (18.53)	12.92 (15.32)	$t(46) = 0.14$, $p = .89$, $d = 0.04$
IMQ - Frequency	1.38 (2.16)	1.42 (1.35)	$t(46) = 0.08$, $p = .94$, $d = 0.02$
IMQ - Duration	7.50 (13.63)	6.33 (11.03)	$t(46) = 0.33$, $p = .75$, $d = 0.10$
IMQ - Distress	10.25 (22.18)	13.00 (27.71)	$t(46) = 0.38$, $p = .71$, $d = 0.11$
State anxiety	1.13 (4.10)	2.75 (7.11)	$t(46) = 0.97$, $p = .34$, $d = 0.29$
SCL	-0.007 (0.19)	0.058 (0.183)	$t(44) = 1.19$, $p = .24$, $d = 0.36$
HR	0.61 (1.96)	0.16 (3.00)	$t(44) = 0.61$, $p = .55$, $d = 0.18$

Note: All scores constitute differential conditioning scores (CS+ minus CS-) from the memory triggering task; IMQ Score: composite scores of the intrusive memory questionnaire for trauma intrusions in T-scores; IMQ Frequency: number of intrusive memories; IMQ duration: duration of intrusive memories; IMQ distress: distress elicited by intrusive memories; state anxiety: assessed by STAI state anxiety scale; SCL: skin conductance level given as ln(1 + SCL) in µS; HR: heart rate given as beats per minute.

Table III-6: Results for ambulatory intrusive memories and the Impact of Event Scale (IES-R) for treatment and control group separately.

	ANOVA		
	Treatment group (trauma exposure)	**Control group (neutral exposure)**	**Interferential statistics**
	M (SD)	*M (SD)*	
Pre-treatment ambulatory trauma intrusions			
Frequency	3.88 (4.48)	3.96 (4.88)	$t(46) = 0.06$, $p = .95$, $d = 0.02$
Duration	245.54 (899.50)	118.58 (179.92)	$t(46) = 0.68$, $p = .50$, $d = 0.20$
Distress	3.90 (2.42)	4.18 (2.94)	$t(46) = 0.37$, $p = .72$, $d = 0.11$
Post-treatment ambulatory trauma intrusions			
Frequency	5.08 (5.44)	4.08 (4.42)	$t(46) = 0.70$, $p = .49$, $d = 0.21$
Duration	335.42 (984.49)	145.08 (390.59)	$t(46) = 0.88$, $p = .38$, $d = 0.26$
Distress	2.92 (2.36)	3.04 (2.20)	$t(46) = 0.18$, $p = .86$, $d = 0.05$
Impact of Event Scale (IES-R)			
IES-R score	-3.33 (0.85)	-3.39 (0.85)	$t(46) = 0.23$, $p = .82$, $d = 0.07$
Intrusions	9.67 (6.50)	8.54 (5.09)	$t(46) = 0.67$, $p = .51$, $d = 0.19$
Hyperarousal	2.96 (3.01)	3.29 (3.67)	$t(46) = 0.34$, $p = .73$, $d = 0.10$
Avoidance	11.08 (8.11)	9.26 (7.73)	$t(46) = 0.80$, $p = .43$, $d = 0.23$

Note: Frequency: frequency of intrusive memories; Duration: subjective duration of intrusive memories; Distress: distress-rating for intrusive memories; IES-R-Score: Values represent diagnostic values according to the following formula: IES-R Score = -0.02 × Intrusions + 0.07 × Avoidance + 0.15 × Hyperarousal – 4.36 by Maercker and Schützwohl (1998).

5 DISCUSSION

This study reveals that associative learning contributes to spontaneous intrusive memories after an analogue trauma. Our findings support the assumption that conditioned associations between neutral stimuli and traumatic events play an important role in the development of intrusive memories of trauma. We found no evidence for the hypothesis that the effects of imaginal exposure work to reduce these associations. From a methodological perspective, we made it possible to study associative learning in the standard trauma film paradigm by experimentally controlling neutral sound stimuli (CSs) encountered during film presentation

(UCS). These sound stimuli subsequently elicited intrusive memories and anxiety when presented again after film presentation, but also when presented again one or seven days after film presentation. Our work therefore opens up new possibilities for studying triggers of intrusive memories of trauma, which could enhance our understanding of PTSD.

In line with hypothesis 1, intrusive memories and state anxiety were highest when trauma-associated sound cues were presented during a neutral background soundscape (CS+ cue condition) as compared to the same soundscape when sound cues associated with a neutral film (CS- cue condition) or no additional sound cues (no-cue condition) were presented. Our findings therefore are in line with a previous fear conditioning study, which demonstrated that presenting acoustic, conditioned trauma reminders during a neutral background soundscape can trigger intrusive memories and anxiety (Wegerer et al., 2013). Furthermore, the pattern of results observed was not only found directly after film presentation (t1), but remained stable until the following day (t2, t3) and was still present seven days after film presentation (t4). It is clear that conditioned stimuli retain their potential to trigger intrusive memories and anxiety for a timespan of at least one week, which is a very important extension of previous findings, as Wegerer et al. (2013) only investigated conditioned memories and state anxiety directly after the conditioning procedure. The observed temporal stability of conditioning effects is in line with contemporary models of PTSD proposing that intrusive memories can be explained by associative learning processes (Brewin, 2001; Ehlers & Clark, 2000; Foa et al., 1989; Keane et al., 1985; Rothbaum & Davis, 2003). Only if conditioned reactions to trauma reminders are temporally stable, can they account for intrusive memories that recur stable over several months or even years, as it is typically reported in PTSD patients.

Surprisingly, peripheral physiological indicators of arousal (SCL, HR) during the memory triggering task did not confirm hypothesis 1. SCL and HR for the three cue conditions did not differ significantly at any point of measurement (t1, t2, t3, t4). Both groups showed significantly enhanced physiological parameters during the traumatic film clip as compared to the neutral film clip. During the memory triggering task, however, no significant differences were observed, indicating that, when presented again in a neutral context (CS+ cue condition), trauma-associated stimuli did not lead to enhanced physiological arousal as compared to neutral-associated stimuli (CS- cue condition) or the neutral context alone (no-cue condition). This stands in contrast to a number of previous studies showing enhanced physiological reactivity to trauma reminders in trauma exposed participants (for a review see Pole, 2007). Nevertheless, our findings are partly in line with the findings of Wegerer et al. (2013), who used the same memory triggering task in a fear conditioning paradigm. They also found no SCL differences between the CS+ cue condition and the CS- condition, as well as no differences between the CS- and the no-cue condition. In contrast to our results, however, they reported significant differences in SCL between the CS+ and the no-cue condition, indicating that trauma-associated stimuli led to increased physiological arousal. The absence of this effect in the current study may be due to lower contingency of the CS+, as the CS+ stimuli were presented once per minute during the film clips and did not take the timing of the events depicted into account. This may have reduced the strength of conditioned physiological fear reactions as compared to the fear conditioning paradigm used in the study by Wegerer et al. (2013). Future studies should improve contingency for neutral stimuli in the trauma film paradigm by presenting the CS+ sounds immediately preceding

the most aversive moments of a traumatic film, which would increase the likelihood of conditioned fear reactions with regard to physiological parameters, as well.

In line with hypothesis 2, the conditionability of intrusive memories (as indexed by the IMQ) was correlated with the frequency, duration, and distress of subsequent ambulatory trauma intrusions (assessed by means of the electronic diary): participants who acquired stronger differential conditioned intrusive trauma memories were more likely to experience ambulatory intrusive trauma memories on the days following the analogue trauma. This finding indicates that the conditionability of intrusive memories is related to the spontaneous occurrence of such memories, underlining the important role of conditioned reactions in the development of intrusive memories of trauma. No correlations, however, were observed for conditionability of state anxiety and physiological arousal, which may again be due to limited contingency caused by relatively low temporal precision and separation of the CSs and UCSs (see above). Furthermore, no significant correlations between indices of conditionability and the IES-R scores were observed. As the IES-R originally was constructed to assess the impact of real-life trauma, interindividual variance in our sample of healthy participants was limited. As a certain degree of variance is needed to find correlations, the low variation in IES-R scores in the current study may have led to the non-significant correlation.

Contrary to hypothesis 3, the treatment group showed neither a stronger reduction of intrusive trauma memories nor reduced state anxiety in the memory triggering task after imaginal exposure as compared to the control group. These findings indicate that imaginal exposure in our study had no influence on conditioned reactions to trauma-associated

stimuli. This is counter to current models of PTSD, which assume that imaginal exposure should reduce conditioned reaction to trauma reminders (Brewin, 2001; Ehlers & Clark, 2000; Foa et al., 1989; Keane et al., 1985; Rothbaum & Davis, 2003). As conditioned intrusive trauma memories and anxiety were still observable one week after film presentation, the acquired associations may have been too robust to be impacted by a single imaginal exposure session. In the treatment of PTSD, patients usually receive multiple sessions including imaginal exposure (Ehlers, Clark, Hackmann, McManus, & Fennell, 2005), and the intervention in our study may have been too weak to cause any effects on associated responses. Future studies should examine whether implementing more sessions of imaginal exposure leads to significant reductions in conditioned trauma responses.

In contrast to hypothesis 4, the treatment group showed no reduction in ambulatory intrusive trauma memories on the days following imaginal exposure as compared to the control group. This is in contrast to findings from clinical samples showing that therapeutic interventions, including imaginal exposure, show significant reductions in PTSD symptoms (Bisson et al., 2007) and especially intrusive memories (Hackmann et al., 2004; Speckens, Ehlers, Hackmann, & Clark, 2006). As there was a relatively fast decline in intrusive trauma memories for both groups on the days following film presentation, floor effects may account for these findings. On the days following exposure sessions, participants in both groups had already reported fairly low numbers of intrusions, which may have allowed no further improvement through imaginal exposure. Furthermore, the treatment group did not have significantly reduced IES-R scores as compared to the control group. This may be due to the broad time-window covered by the questionnaire: subjects were asked to complete the IES-R with regard to the whole week following the trauma film, so the initial reactions to the film

may have disguised potential beneficial effects in the treatment group. The IES-R may index the initial reaction to the trauma film rather than differential effects of the imaginal exposure. Future studies should therefore more carefully separate initial reactions to the trauma film from reactions to imaginal exposure for example by instructing participants to complete the IES-R solely with regard to the days following imaginal exposure or by separating film presentation and imaginal exposure by a longer period of time.

Another explanation for the missing effects of imaginal exposure may be found in the relatively short assessment period of intrusive memories and PTSD symptoms after the imaginal exposure. As in clinical samples, intrusive memories usually decrease only gradually over several weeks following imaginal exposure (Ehlers et al., 2005; Hackmann et al., 2004; Speckens et al., 2006). Indeed, the only analogue study showing a reduction of intrusive memories by imaginal exposure also assessed intrusive memories over a longer period of time (one month after imaginal exposure) as compared to the current study (Michael & Ehlers, 2007). Thus, future studies investigating the effects of imaginal exposure should examine intrusive memories for longer periods of time.

Yet another reason for the missing effects of imaginal exposure could be due to a potential side effect of the memory triggering task. The MTT was modeled to simulate an everyday-life situation in which trauma reminders are encountered and trigger intrusive memories (Wegerer et al., 2013), however, as participants in the MTT were confronted with the CS+ without a following UCS, it could also be regarded as an extinction learning phase. According to this view, before our actual intervention, participants would already have passed through two sessions of extinction learning. Some interventions for PTSD suggest

that exposing PTSD patients to trauma reminders promotes extinction of conditioned responses to these stimuli (Ehlers & Clark, 2000; Ehlers et al., 2005), so that repeatedly presenting CS+ stimuli during the MTT may have fostered extinction learning and overlaid the therapeutic effects of the imaginal exposure in our study. Assessing the MTT solely at follow up session could circumvent this shortcoming in future studies.

One limitation of our study is that we used an analogue design, so that it is not clear to what extent our results can be transferred to traumatic events in real life. Even though the film used in our study was very aversive, it is still a relatively mild stressor compared to traumatic events. Hence, the intrusive memories reported by our participants are not equivalent to intrusive memories after real-life trauma. As well, the frequency of intrusive memories in our sample was fairly small when compared to trauma exposed samples (Michael, Ehlers, Halligan, et al., 2005). With regard to intrusive memories, there may be only limited room for improvement in analogue trauma studies such as ours. Exposing participants to stronger stressors should, of course, lead to more intrusive memories, but ethical considerations set inevitable limits on the intensity of laboratory stressors.

A further limitation of the current study is that the sample was comprised of women only. We decided to include only women for several reasons: first, previous studies have observed significant gender differences in affective self-reports and physiological responses to emotional stimuli (Bianchin & Angrilli, 2012; Bradley et al., 2001; Kring & Gordon, 1998), so that including both genders would have added systematic variance to our outcome measures. Second, the prevalence of PTSD is higher among women (Perkonigg et al., 2000), so we expected the traumatic film clip to have a larger impact on women than on men. As

we were interested in the memory processes underlying PTSD and its intervention methods and not in gender differences in this study, we decided on a study that only included women. Future studies should extend our findings to both genders.

In summary, our experiment demonstrated that presenting neutral sound stimuli during a traumatic film leads to conditioned intrusive responses to these stimuli that remain stable over a time period of at least one week. Furthermore, the conditionability of intrusive trauma memories predicted later spontaneous intrusions of trauma memories. Our study therefore provides evidence for the assumption that intrusive trauma memories can at least partially be explained by conditioned responses to neutral stimuli that have been encountered during the trauma, however, no evidence was found for the hypothesis that imaginal trauma exposure has the effect of reducing these associations. Future research should further examine the role of associative learning for imaginal exposure to promote enhancements of this clinical intervention for PTSD patients.

GENERAL DISCUSSION

IV GENERAL DISCUSSION

The global aim of this thesis was to examine the mechanisms underlying intrusive memories after traumatic events. As recent findings suggest that deficits in the ability to voluntarily inhibit memory retrieval are related to PTSD symptom severity (Catarino et al., 2015), the studies included in this work tested whether deficits in retrieval suppression constitute a potential cognitive risk factor that leads to an increase in intrusive memories after traumatic events. Furthermore, these studies investigated whether the same neural process that mediates retrieval suppression (Mecklinger et al., 2009) is also associated with fewer trauma memories.

Since current research indicates that conditioned responses to trauma reminders are associated with intrusive trauma memories (Wegerer et al., 2013), another aim of this thesis was to further examine the role of these conditioned responses in the development and maintenance of intrusive trauma memories. Specifically, the temporal stability of conditioned reactions was investigated. An additional aim of this thesis was to test whether conditioned responses are reduced after imaginal exposure, as has been suggested by current models of PTSD (Brewin, 2014; Ehlers, 2015).

In what follows, I will first give a short summary of the research questions and interpretations of both studies. Next, I will discuss the results from the broader perspective of current memory models and models of PTSD. Further on, I will consider limitations and caveats of the studies conducted and provide an outlook and directions for future research. Finally, I will summarize the major findings and end with concluding remarks.

1 SUMMARY

1.1 STUDY 1: MEMORY CONTROL AND INTRUSIVE TRAUMA MEMORIES

Study 1 was designed to test whether pre-existing deficits in memory control constitute a potential cognitive risk factor for intrusive memories after traumatic events, and whether the neural processes underlying memory control are also involved in controlling intrusive trauma memories. Suppression-induced forgetting, our index of memory control, was found to be predictive of subjective distress experienced during intrusive memories of a traumatic film. Furthermore, the neural correlate of the inhibitory control process which is supposed to underlie suppression-induced forgetting (i.e. N2 ERP component) also predicted a reduction in the degree of distress of intrusive memories, as well as a reduction in other analogue PTSD symptoms. These findings indicate that the pre-existing ability to suppress memory retrieval is beneficial for recovering from intrusive memories after traumatic events. Furthermore, the findings indicate that the same inhibitory control process that was found to mediate retrieval suppression and stopping a prepotent motor response is also involved in controlling the automatic retrieval of intrusive trauma memories.

1.2 STUDY 2: CONDITIONED RESPONSES TO TRAUMA REMINDERS

Study 2 aimed to investigate whether conditioned responses to trauma-associated stimuli are stable over time and whether they are affected by imaginal exposure. Indeed, intrusive memories and subjective fear as a reaction to trauma-associated stimuli were observed and remained stable over the entire assessment period of one week, providing further evidence for the assumption that associative learning plays a crucial role in the development and

maintenance of intrusive memories after traumatic events. Furthermore, conditionability of subjective indices did predict subsequent ambulatory intrusive memories, however, physiological parameters assessing emotional arousal as a reaction to the trauma reminders did not show these effects. Moreover, imaginal exposure had no impact on conditioned responses to trauma-associated stimuli or intrusive trauma memories.

2 DISCUSSION FROM THE PERSPECTIVE OF CURRENT MODELS IN THE FIELD

The findings of the two studies have already been discussed in chapters II and III. I will next consider the results of both studies more broadly with regard to contemporary memory models and models of PTSD.

2.1 STUDY 1: MEMORY CONTROL AND INTRUSIVE TRAUMA MEMORIES

In replication of earlier findings, retrieval suppression in the TNT task led to a decline in the cued recall of suppressed words (no-think condition) relative to previously studied but not additionally processed words (baseline condition). Furthermore, it was also possible to replicate the ERP components previously observed to mediate retrieval suppression (i.e. early negativity, N2; Bergström et al., 2009a; Mecklinger et al., 2009; Waldhauser et al., 2012). In this study, differences in N2 predicted suppression-induced forgetting, an extension of previous results. Our findings indicate that these ERP components reflect inhibitory control processes, such as detecting the need for cognitive control and the active suppression of unwanted memories, so they are in line with inhibitory control accounts of

suppression-induced forgetting (Anderson & Green, 2001; Anderson & Hanslmayr, 2014; Anderson & Huddleston, 2012; Anderson et al., 2004).

2.1.1 ERP CORRELATES OF RETRIEVAL INHIBITION

In Study 1, attempts to suppress memory retrieval in the think/no-think task were reflected by greater negative going ERP amplitudes at fronto-central electrode sites. In line with previous findings (Bergström et al., 2009a; Mecklinger et al., 2009; Waldhauser et al., 2012), the first ERP difference between think and no-think trials occurred in the time window from 180-240 ms. Bergström et al. (2009a) found that differences in this component predicted interindividual differences in suppression-induced forgetting, which indicates that it resembles a process involved in inhibiting the memory trace. The second ERP difference was an N2 component from 350-450 ms that was enhanced for no-think items as compared to think items, which also corresponds to earlier studies (Bergström et al., 2009b; Bergström et al., 2007; Depue et al., 2007; Mecklinger et al., 2009; Waldhauser et al., 2012). Differences between think and no-think items in the N2 predicted later suppression-induced forgetting, replicating findings from Mecklinger et al. (2009). Furthermore, Mecklinger et al. (2009) found that this N2 component was correlated with the N2 elicited by stopping a prepotent motor response, indicating that it may resemble a general inhibitory control mechanism. Prior work using a motor stopping task has suggested that the neural generator of the N2 is located in the prefrontal cortex: ventral and dorsolateral PFC (Lavric, Pizzagalli, & Forstmeier, 2004) or right inferior frontal gyrus (Chen et al., 2012). This is in line with brain areas found to be involved in inhibition of a prepotent motor response (Aron, Robbins, & Poldrack, 2004) and in retrieval suppression (Anderson & Hanslmayr, 2014).

Previous studies have found that retrieval suppression is also accompanied by a significant reduction in the parietal episodic memory effect between 500 and 600 ms (Bergström et al., 2009a; Bergström et al., 2007; Hanslmayr, Leipold, Pastotter, & Bauml, 2009; Mecklinger et al., 2009). Since this component is thought to reflect conscious recollection in reaction to a memory cue (Rugg & Curran, 2007), it's reduction is most likely to reflect a down-regulation of recollection activity in the hippocampal-parietal network as a consequence of successful suppression (Anderson & Hanslmayr, 2014; Depue et al., 2007). More convincing evidence for this effect is that it only occurs when participants suppress the memory directly, instead of using thought substitution (i.e. retrieving another associated stimulus) as a strategy to avoid remembering the target (Bergström et al., 2009a). As modulations in the parietal episodic memory effect have not predicted successful retrieval suppression in previous studies (Bergström et al., 2007; Hanslmayr, Leipold, & Bauml, 2010), and as we were especially interested in inhibitory control processes underlying retrieval suppression, the parietal episodic memory component was not included in the analysis of this study.

Taken together, the ERP data from Study 1 support previous findings on ERP correlates of inhibitory control processes potentially underlying suppression-induced forgetting effects. Early negativity and N2 may index different processes relevant for retrieval suppression, such as detecting the need for cognitive control and the active suppression of unwanted memories, whereas the reduction of the parietal episodic memory effect most likely resembles the consequence of successful retrieval inhibition (Bergström et al., 2009a, 2009b; Mecklinger et al., 2009; Waldhauser et al., 2012).

2.1.2 EFFECTS OF ATTENTION AND ENCODING

The think/no-think task was specifically designed to examine the effects of suppressing memory retrieval and thus carefully separated suppression of memory retrieval from potential inhibitory processes during encoding (Anderson & Green, 2001). While this separation is relatively easy to manage for neutral stimuli, several effects need to be considered regarding emotionally arousing stimuli. As emotional stimuli affect attention and motivation, the way they are encoded differs from the encoding of neutral stimuli (Pessoa, 2009; Vuilleumier, 2005). Even though, in general, emotional stimuli attract attention and are preferentially encoded (Kensinger & Corkin, 2004), complex emotional stimuli as in the traumatic film of Study 1 may have more complex effects on encoding. Due to the aversiveness of the traumatic film, participants may have been motivated to distract their attention from the events depicted in the film. To minimize such effects, participants were instructed to watch the film with their full attention and to keep their gaze focused on the screen for the entire presentation time (which was controlled for by video surveillance), some participants may nevertheless have removed their attention from the film's scenes, which could have impaired memory encoding of the traumatic film. Additionally, participants may also have engaged memory control processes which disrupted memory encoding of the traumatic film, as investigated by means of directed forgetting paradigms (see section I-4.1; for a review see Anderson & Hanslmayr, 2014). A disruption to memory encoding of the traumatic film could also have contributed to the observed reduction in the impact of intrusive trauma memories in Study 1. In line with this account, PTSD patients have been found to show reduced directed forgetting effects as compared to other trauma survivors, indicating that they are less able to inhibit encoding of unwanted memories

(Cottencin et al., 2006; Zwissler et al., 2012). It is not clear, however, whether the same control process is involved in suppressing both the encoding and retrieval of unwanted memories. If the same inhibitory control process underlies both phenomena, as proposed in the *flexible control hypothesis* (Anderson, 2005), this process may also be involved in suppressing memory recall of intrusive trauma memories. The suppression of traumatic memories may therefore be achieved by an inhibitory control process affecting both encoding and retrieval of traumatic events.

2.1.3 INTERFERENCE ACCOUNTS OF SUPPRESSION-INDUCED FORGETTING

An alternative explanation for the results of Study 1 is provided by interference accounts of suppression-induced forgetting (Tomlinson et al., 2009). This approach is based on the "Search of Associative Memory" (SAM) model of recall (Raaijmakers & Shiffrin, 1981), assuming that memory recall consists of two stages: a *sampling stage* that locates (or samples) the memory, and a *recovery stage* that actually retrieves the memory. Tomlinson et al. (2009) proposed that interference during the recovery stage may account for retrieval suppression without the necessity for an inhibitory control mechanism actively suppressing the memory trace. According to this view, when a no-think cue is presented, in some trials the target will automatically be sampled and this incomplete representation will then be associated with the new response "sitting quietly". This newly learned association between the incomplete memory representation and "sitting quietly" will interfere with the previously learned association between the incomplete representation and the recovery of the complete memory. This two stage model can explain why suppression-induced forgetting also occurs when the target is cued with an independent cue (i.e. a cue that has not been learned

previously), which is usually taken as strong evidence for an inhibitory control process actively suppressing the memory trace of the target (Anderson & Green, 2001; Anderson & Hanslmayr, 2014; Anderson et al., 2004). If transferred to retrieval suppression of intrusive trauma memories, the interference account would indicate that the memory trace of the traumatic event itself is not suppressed, but rather that there is interference from newly learned associations to potential trauma-reminders.

Contrary to the interference account, recent neuroimaging findings indicate that, activity in prefrontal control areas (e.g. dlPFC) leads to a downregulation of hippocampal activity during suppression (Benoit & Anderson, 2012; Gagnepain et al., 2014) and that this reduced hippocampal activity predicts subsequent suppression-induced forgetting effects (Depue et al., 2007; Levy & Anderson, 2012). These findings can hardly be explained by the interference account, as the interfering memory trace would also require hippocampal activity, thus making the observed below baseline down-regulation of the hippocampus during no-think trials very unlikely.

Furthermore, ERP findings also contradict the interference account: as previous studies have indicated, the enhanced N2 elicited by no-think trials is very likely to reflect an inhibitory control process that actively suppresses the memory trace (Bergström et al., 2009a; Mecklinger et al., 2009). Bergström et al. (2009a) observed significant ERP differences in the time window of the N2 only when no-think items were directly suppressed, as compared to using thought substitution as a strategy to avoid remembering the target word. This indicates that the N2 reflects a control process which is relatively independent of interference, as it was not enhanced during thought substitution which should have promoted

interference. Furthermore, in another study, the no-think N2 was associated with the N2 elicited when a prepotent motor response is inhibited (Mecklinger et al., 2009), underlining the interpretation that the N2 reflects an inhibitory control process.

Taken together, the interference account does offer a plausible alternative explanation for the behavioral suppression-induced forgetting effect observed in Study 1, however, the ERP findings support the assumption that the underlying mechanism of this effect is an inhibitory control process that is reflected by the N2.

2.1.4 RESEARCH ON THOUGHT SUPPRESSION

Another approach to investigating whether we can keep unwanted thoughts out of our minds has tested the effects of thought suppression. Studies investigating thought suppression usually examine whether participants can suppress a single target thought over an extended period of time (Wegner, 1994; Wegner et al., 1987; Wenzlaff & Wegner, 2000). In a typical thought suppression paradigm, participants are instructed to spend 5 min excluding all thoughts about a particular target (e.g. white bears) from awareness, while thinking about what they wish (i.e. suppression period). Additionally, participants are told to ring a bell every time they happen to think of the target anyway. After this 5 min period, participants are told that for the next 5 minutes they are allowed to think of anything, including the target, and again ring a bell every time they think about the target (i.e. expression period). Researchers have generally observed that thought suppression leads to a reduced frequency of thoughts about the target as compared to the expression period, but does not eliminate the thought completely. Furthermore, in the expression period following the suppression period,

the frequency of thoughts about the target is typically increased, even when compared to an expression period that was not preceded by a suppression period (Wegner, 1994; Wegner et al., 1987; Wenzlaff & Wegner, 2000). A common interpretation of these effects is that attempts to suppress the unwanted thought cause a rebound in its occurrence, thus indicating that thought suppression is counterproductive.

At first glance, these results seem to contradict findings from retrieval suppression, however, a central difference between the two phenomena is that the thought suppression paradigm explicitly refers to a specific forbidden thought that must be suppressed. This task is therefore somewhat paradoxical as, in order to accomplish it, participants need to keep in mind the target they are not supposed to think about. On the other hand, in retrieval suppression paradigms, participants are instructed not to think about a target associated with a certain cue word, so that there is no need to keep in mind what the target was in order to accomplish this task, thus making retrieval suppression possible. In line with this, there is growing evidence for successful retrieval suppression (see Anderson & Hanslmayr, 2014).

2.1.5 EFFECTS OF EMOTION REGULATION

In Study 1, behavioral and ERP estimates of retrieval-suppression predicted the distress experienced during ambulatory trauma intrusions, however, no significant correlation with the frequency of intrusive trauma memories was observed. Several plausible explanations for this pattern of results, including motivational issues, have already been discussed above (see section II-5).

Nevertheless, previous findings from research on emotion regulation could also account for these findings. To investigate emotion regulation, for example, Ochsner, Bunge, Gross, and Gabrieli (2002) presented participants with negatively valenced pictures and either instructed them to focus on their natural feelings (i.e. attend condition) or to reinterpret the picture in a less negative way (i.e. reappraisal condition). They found that reappraising the pictures led to a decrease in negative affect as compared to the attend condition. Furthermore, during reappraisal trials, activity in the dlPFC was enhanced while activity in the amygdala was decreased as compared to the attend condition. Similarly, several neuro imaging findings indicate that during the regulation of emotion, activity in the prefrontal cortex (e.g. dlPFC, ACC) is typically enhanced, whereas activity in the amygdala is reduced (for reviews see Frank et al., 2014; Ochsner & Gross, 2005). Delgado, Nearing, LeDoux, and Phelps (2008), using a fear conditioning paradigm, found that emotion regulation led to reduced fear responses, as indicated by reduced SCRs. Furthermore, the brain imaging findings indicate that the dlPFC down-regulates amygdala activity through connections to vmPFC regions. As several studies show engagement of the dlPFC during retrieval suppression (Anderson et al., 2004; Benoit & Anderson, 2012; Depue et al., 2007), emotion regulation and suppression-induced forgetting may be achieved by the same cognitive control process. Banich and Depue (2015) have recently discussed this issue and concluded that several areas in the right hemisphere play a critical role in inhibitory control. Whether the specific process varies with the domain that is inhibited — motoric, memory, or emotional — remains an open question (Banich & Depue, 2015). Hence in Study 1, the same control process that is involved in retrieval suppression may also have led to the reduction of distress during intrusive memories by down-regulating the associated emotions, thus causing the observed

correlations between behavioral and ERP estimates of retrieval-suppression and distress during intrusive trauma memories. Further research is needed to examine whether the same control process is relevant for both domains.

2.1.6 RETRIEVAL SUPPRESSION AND MEMORY ELABORATION

Recent brain imaging findings indicate that a certain degree of reactivation of an unwanted memory is necessary for successfully suppressing it: in a study using the TNT task, participants rated to what extend an unwanted memory entered awareness for every suppression trial. Stronger reduction of hippocampal activity was observed in those no-think trials when the cue triggered retrieval of its associated target as compared to those trials when no memory intruded (Levy & Anderson, 2012). Furthermore, the hippocampal down-regulation predicted later forgetting only in those trials when an unwanted memory entered awareness, suggesting that a memory trace needs to be reactivated in order to suppress it. Similarly, Depue et al. (2007) have reported that during the first attempts to suppress an unwanted memory, enhanced activity in the hippocampus was observed for no-think items that were subsequently successfully forgotten as compared to no-think items that were subsequently remembered (for similar results see Detre, Natarajan, Gershman, & Norman, 2013), supporting the idea that memories, when reactivated, are in a labile state that allows modifications (Lee, 2009; Tronson & Taylor, 2007). Memories that are more activated initially may become better elaborated and thus susceptible to cognitive control mechanisms (Depue et al., 2007). This corresponds to the frequent clinical observation that reactivating traumatic memories leads to a reduction of intrusive reexperiencing (Brewin, 2014; Ehlers, 2015). Indeed, treatment approaches involving voluntary memory retrieval of the traumatic

event show the best therapeutic outcomes (see section I-6; Bisson et al., 2007; Bradley et al., 2005; Cloitre, 2009; Ehlers et al., 2010; Seidler & Wagner, 2006; Van Etten & Taylor, 1998; for contradictory resuts see Benish et al., 2008). Examining how such a reactivation of the trauma memory affects intrusive memories is one of the aims of Study 2 (see chapter III).

2.2 STUDY 2: CONDITIONED RESPONSES TO TRAUMA REMINDERS

Study 2 aimed to investigate whether conditioned responses to trauma-associated stimuli are stable over time and whether they are affected by imaginal exposure. Intrusive memories and subjective fear, as a reaction to trauma-associated stimuli, were, indeed, observed and largely remained stable over the entire assessment period of one week, providing further evidence for the assumption that associative learning plays a crucial role in the development and maintenance of intrusive memories after traumatic events. Furthermore, subjective indexes of conditionability predicted subsequent ambulatory intrusive memories, however, physiological parameters assessing emotional arousal as a reaction to the trauma reminders did not show these effects. Moreover, imaginal exposure had no impact on conditioned responses to trauma-associated stimuli or intrusive trauma memories.

2.2.1 CONDITIONED RESPONSES TO TRAUMA REMINDERS

Conditioning models of PTSD assume that neutral stimuli which happen to be present during a traumatic event, acquire the potential to trigger conditioned responses, such as fear, physiological arousal, and intrusive memories, through temporal contiguity (Brewin, 2001, 2014; Ehlers & Clark, 2000; Foa et al., 1989; Keane et al., 1985; Rothbaum & Davis, 2003).

In line with these models, presenting acoustic conditioned trauma reminders against a neutral background soundscape triggered intrusive memories and anxiety. Furthermore, these findings indicate that conditioned stimuli retain their potential to trigger intrusive memories and anxiety for a timespan of at least one week. This observed temporal stability of conditioning effects is a crucial requirement for conditioning models of PTSD, as temporal stability of intrusive memories is typical for this disorder. Indeed, intrusive memories of the traumatic event can occur even after several months or years. Additional support for conditioning models of PTSD comes from the finding in this study that conditionability was correlated with subsequent ambulatory trauma intrusions.

Another explanation for the effects observed comes from cognitive neuroscience research on episodic memory, especially on pattern separation (Kheirbek, Klemenhagen, Sahay, & Hen, 2012): When we encounter stimuli that bear a similarity to previously encoded memories, two opposing processes are believed to determine whether the two episodes are kept separate or the previous memory is retrieved: pattern separation and pattern completion. Pattern separation is defined as a process creating separate memory representations for similar experiences to prevent interference, whereas pattern completion is the reconstruction of previously stored memory representations from similar inputs (Colgin, Moser, & Moser, 2008; Moser, Kropff, & Moser, 2008; Treves & Rolls, 1994). Several studies have indicated that neurogenesis in the dentate gyrus, a section of the hippocampus, involved in memory formation and retrieval, mediates pattern separation (Bakker, Kirwan, Miller, & Stark, 2008; Lacy, Yassa, Stark, Muftuler, & Stark, 2011; Rolls, 2013; Sahay, Wilson, & Hen, 2011). If pattern separation is impaired (e.g. through stress during a traumatic event), this would lead to enhanced generalization so that sensory inputs bearing a resemblance to representations of

the trauma memory could trigger these traumatic memories (Kheirbek et al., 2012; Sahay et al., 2011). Thus, in Study 2, stress experienced during the traumatic film may have led to impaired pattern separation, so that the trauma-associated sounds, encountered during the memory triggering task, may not have been separated from representations in memory of the traumatic film, leading to pattern completion (i.e. episodic retrieval) of these memories (Kheirbek et al., 2012; Sahay et al., 2011). Furthermore, deficient pattern separation could also account for the observed positive correlation between conditionability (i.e. the difference between traumatic memories triggered by the CS+ and CS- sounds) and ambulatory intrusive trauma memories, as participants who show deficient pattern separation for CS+ items in the memory triggering task should also be more likely to experience intrusive memories when encountering trauma reminders in everyday life. Pattern separation therefore offers an alternative account for explaining the findings observed.

The two explanations, however, are not mutually exclusive, as pattern separation has recently also been taken into account when explaining stimulus generalization in fear conditioning paradigms (Lissek et al., 2014). According to the neural framework of fear conditioning from Lissek et al. (2014), representations of potential triggers in the sensory cortex undergo a schematic matching assessment by the hippocampus, in which they are compared to the CS+ (see also Otto & Eichenbaum, 1992; Sander, Grandjean, & Scherer, 2005). If this overlap is relatively small, the patterns of the two representations will be separated by the hippocampus, leading to activation of fear inhibiting areas (e.g. vmPFC). If the degree of overlap is relatively high, the hippocampus will complete the pattern of brain activity representing the CS+, leading to enhanced activation of fear excitation areas (e.g. amygdala, anterior insula, dACC, and dmPFC). In line with findings from Study 2, pattern

separation in the hippocampus seems to be a relevant process for both episodic memory retrieval and fear conditioning. To conclude, the memory processes described above may act in concert in the development and maintenance of intrusive trauma memories.

2.2.2 IMAGINAL EXPOSURE

In contradiction to our hypotheses, imaginal exposure led neither to reductions in conditioned responses to trauma reminders nor to reductions in ambulatory intrusive trauma memories, indicating that imaginal exposure in Study 2 had no significant influence on conditioned reactions to trauma-associated stimuli. As conditioned intrusive trauma memories and anxiety were still observable one week after film presentation, the acquired associations may have been too robust to be impacted by a single imaginal exposure session.

According to Conway's model of the autobiographical memory system, incorporating traumatic episodic memories into the autobiographical knowledge base should have facilitated the inhibition of automatic retrieval triggered by associated memory cues (Conway, 2005; Conway & Pleydell-Pearce, 2000). In PTSD patients, however, this elaboration seems to fail, preventing appropriate control of the automatic retrieval of trauma memories (Brewin, 2001; Ehlers & Clark, 2000). From this perspective, imaginal exposure to traumatic memories should have led to an integration of these episodic memories and, in turn, should allow the central control process — the working self — to control their retrieval. This was not, however, the case in Study 2, as imaginal trauma exposure did not lead to a reduction in trauma memories, which indicates that the traumatic memories may have failed

to be incorporated into the autobiographical knowledge base, which suggests that imaginal exposure may not have activated the relevant episodic memories.

Alternatively, considering the relative mildness of the trauma film when compared to real-life trauma, memory integration of the traumatic film may not have been impaired in the first place, so that the working self may have been able to control the retrieval of intrusive memories after a relatively short time. This is in line with the relatively quick decline of intrusive trauma memories observed in Study 2, so the intervention may have brought no additional benefit. Working against this account, however, is the finding that intrusive memories and anxiety as a reaction to trauma-associated stimuli were still present one week after film presentation. The role of memory integration for conditioned trauma memories therefore remains unclear.

In order to keep the two experimental conditions in Study 2 as similar as possible, the control condition also included an imaginal exposure session, but of the neutral film. This approach allowed the exclusion of potential effects of recalling a particular memory or effects of the social interaction with the experimenter, which means the only difference between the two conditions was the memory content retrieved during imaginal exposure. However, remembering the neutral film presented in close temporal connection to the traumatic film may inadvertently also have promoted memory integration. Even though participants in this condition were instructed to remember only the neutral film, they may have remembered the traumatic film as well, contrary to instructions. Even though none of the participants in the control group reported that they remembered the trauma film during this phase, this possibility cannot be ruled out with certainty. Comparing imaginal exposure

to the traumatic film with a differently designed control group, however, may help to gain further insights into the effects of imaginal exposure.

Although in Study 2 imaginal exposure to the traumatic film had no beneficial effects on conditioned or spontaneous intrusive trauma memories, this should not be interpreted as general ineffectiveness of imaginal exposure as an intervention technique for PTSD. To the contrary, several meta-analyses indicate that trauma-focused treatment approaches as TFCBT or EMDR show the best outcomes for PTSD (Bisson et al., 2007; Bradley et al., 2005; Cloitre, 2009; Ehlers et al., 2010; Seidler & Wagner, 2006; Van Etten & Taylor, 1998), however, the underlying memory mechanism remains unclear.

3 LIMITATIONS AND CAVEATS

Although both studies presented in this thesis provide important insights toward a better understanding of the memory processes underlying intrusive memories of traumatic events, there are some limitations that need to be considered.

3.1 TRAUMA FILM PARADIGM

In recent years, the trauma film paradigm has proven to be one of the most realistic laboratory analogues of traumatic events and in many previous studies has successfully induced analogue PTSD symptoms, such as intrusive memories (Holmes & Bourne, 2008). It remains unclear, however, to what extent findings from studies using the trauma film paradigm can be transferred to real-life traumatic events that meet the diagnostic criteria of the DSM-5 (see Appendix, Table VI-1; American Psychiatric Association, 2013).

Accordingly, the intrusive memories reported by our participants do not resemble the intensity and vividness of intrusive memories in PTSD. Even though we presented film footage that was rated as very aversive and which has been able to induce intrusive memories in previous studies (Nixon et al., 2007; Qin et al., 2009; Verwoerd et al., 2010; Weidmann, Conradi, Gröger, Fehm, & Fydrich, 2009), these stimulus materials still constitute a relatively mild stressor as compared to a real-life trauma. Ethical considerations inevitably set limits on the intensity of laboratory stressors.

3.2 ASSESSMENT OF INTRUSIVE MEMORIES

Assessing ambulatory intrusive memories with an electronic diary also leads to certain disadvantages. Because participants are instructed to document every spontaneous intrusive memory in their everyday life, several factors outside of experimental control will influence this measurement: participants may differ in the frequency of encountering potential trauma reminders, which may cause systematic differences in the occurrence of intrusive memories. Furthermore, as participants must keep in mind that their task is to document every intrusive memory, interindividual differences in motivation and personality traits may influence the reliability of this assessment. Finally, the electronic mobile device itself may have the potential to act as a trauma reminder and thus may have inflated the number of intrusive memories.

3.3 STUDY 1: MEMORY CONTROL AND INTRUSIVE TRAUMA MEMORIES

Study 1 demonstrated that pre-existing retrieval suppression is associated with reduced subjective distress ratings of intrusive trauma memories. It further indicates that the same inhibitory control process involved in retrieval suppression (as reflected by the N2 ERP component) is also involved in suppressing intrusive trauma memories. One major shortcoming, however, is the missing association between suppression-induced forgetting effects and the frequency of intrusive memories, so we found no direct evidence for a reduction in the number of intrusive trauma memories by retrieval suppression. More evidence is therefore needed to support the association between the two phenomena.

Furthermore, Study 1 did not include an independent cue test for suppression-induced forgetting in the think/no-think task. As stated above (see section IV-2.1), significant reductions in no-think items in the independent cue test are usually taken as strong evidence for an inhibitory control process actively suppressing the accessibility of the target (Anderson & Green, 2001; Anderson & Hanslmayr, 2014; Anderson et al., 2004). Based on the results of Study 1, the possibility that interference may have caused the forgetting effects cannot be excluded. Instead of directly suppressing the target word, participants may actually have applied another strategy (e.g. remembering a different word) to avoid retrieval of the target, even though we tried to avoid the usage of such alternative strategies by thoroughly instructing and training participants to directly suppress the target words (as recommended by Anderson & Huddleston, 2012; Hertel & Calcaterra, 2005). Furthermore, the observed N2 as a reaction to no-think items also indicates the employment of an

inhibitory control process, which has previously been linked to inhibiting a prepotent motor response (Mecklinger et al., 2009).

A second shortcoming of the findings from the think/no-think task is that the relatively low number of successfully learned word pairs in Study 1 did not allow us to control for prior learning success. Previous studies have achieved this by including only those items in the analysis that have been recalled correctly after the initial learning phase (e.g. Anderson et al., 2004; Benoit et al., 2014; Mecklinger et al., 2009), thus excluding words that have not been learned in the first place. It is unlikely, however, that there is no learning effect for these words at all, as they have been repeated as often as the successfully learned words, so these words may also have intruded during the think/no-think phase, engaged the same control processes to suppress their automatic retrieval, and led to suppression-induced forgetting. This relatively low initial learning success was also the reason for not including a subsequent forgetting analysis (i.e. examination of the differences in ERP correlates between retrieved and successfully forgotten target words) in the current study as has been done in previous studies (Anderson et al., 2004; Kuhl, Dudukovic, Kahn, & Wagner, 2007; Mecklinger et al., 2009). Thus, in Study 1 the neural correlates of successful retrieval suppression could not be separated from the correlates of attempts to suppress retrieval that did not lead to forgetting.

3.4 STUDY 2: CONDITIONED RESPONSES TO TRAUMA REMINDERS

Study 2 provides evidence for the important role conditioned responses play in the occurrence of intrusive trauma memories, yet there are two major shortcomings limiting the inferences based on these findings: no significant correlations were observed for

physiological measures (SCL, HR) of conditioned responses, and no beneficial effects of imaginal exposure to the traumatic film were observed.

Even though significant conditioning effects were observed for subjective measures (IMQ, STAI-S) in Study 2, no such effects were observed for more objective physiological parameters (SCL, HR). The most plausible reason for this null-effect is the relative mildness of the traumatic film. As discussed above (see section IV-3.1), viewing a film, even if it is very distressing, may not be sufficient to cause conditioned physiological reactions.

Alternatively, this pattern of results may imply that the subjective results reflect effects of demand characteristics (Nichols & Maner, 2008; Orne, 1962). That is, participants may have inferred that the trauma-associated sounds were supposed to trigger intrusive memories of the traumatic film and to elicit fear responses, which may have biased their ratings accordingly. Even though, an attempt was made to minimize these effects by concealing the purpose of the memory triggering task from participants, as in most psychological experiments, effects of demand characteristics cannot be ruled out with absolute certainty.

Furthermore, the missing effects of imaginal exposure need to be mentioned: In Study 2, instructing participants to remember and imagine the traumatic film did not lead to reduced intrusive memories as compared to the neutral film. Potential explanations for this null-effect have already been discussed above (see sections III-5 and IV-2.2.2). As several meta-analyses indicate that trauma-focused treatment approaches provide the best outcomes for PTSD (Bisson et al., 2007; Bradley et al., 2005; Cloitre, 2009; Ehlers et al., 2010; Seidler & Wagner, 2006; Van Etten & Taylor, 1998), these results should not be interpreted as general

ineffectiveness of imaginal exposure. The underlying memory mechanism, however, remains unclear.

4 OUTLOOK AND FURTHER DIRECTIONS

An outlook and further directions for future research, based on the limitations and caveats stated above, will be provided in the following sections.

4.1 STUDY 1: MEMORY CONTROL AND INTRUSIVE TRAUMA MEMORIES

As stated above (section IV-3.3), the results from Study 1 would be even more convincing if a correlation between retrieval suppression and the frequency of intrusive trauma memories had been found. To address this issue, future studies could implement more aversive stimuli or investigate retrieval suppression in participants who are likely to be exposed to a real-life trauma. For example, assessing retrieval suppression ability in soldiers before they are sent to a military operation and correlating their performance with later PTSD symptoms may provide new insights. Another approach would include think/no-think training (i.e. repeatedly performing the think/no-think task over several days) in order to provide evidence for a causal relationship between retrieval suppression and intrusive trauma memories. To the best of my knowledge, however, there is no evidence yet for the trainability of retrieval suppression, so it would be a good first step to test whether this ability can be trained successfully.

Furthermore, future studies should disentangle potential memory suppression effects during encoding of traumatic memories from the effects of suppressing memory retrieval. This

could be accomplished, for example, by examining the way instructing participants to disrupt encoding or suppress automatic retrieval of a traumatic event affects intrusive trauma memories. Alternatively, as a first step, researchers could test whether the different forms of forgetting (i.e. suppression-induced forgetting, directed forgetting) are associated with each other and can be attributed to the same neural mechanisms.

An alternative explanation for the results observed in Study 1 might be that the same control process underlying retrieval suppression may also be involved in regulating emotional reactions (see section IV-2.1.5). There is already some evidence for this connection, as overlapping brain areas seem to be involved in both processes, however, further research is needed to support these findings. Future studies should investigate whether the same control process is involved in retrieval suppression and emotion regulation, for example, by assessing both paradigms for the same participants. Additionally, including an analogue trauma paradigm would also provide insights about potential connections to intrusive trauma memories.

4.2 STUDY 2: CONDITIONED RESPONSES TO TRAUMA REMINDERS

As mentioned above (see section IV-2.2.1), it would be even more convincing if the pattern of results observed for conditioned intrusive memories and anxiety had also been observed for physiological parameters (SCL, HR). The absence of these effects may be due to relatively low contingency of the CS+, as its timing was not as precise as in typical fear conditioning paradigms. Future studies could improve contingency for CS+ stimuli by presenting them immediately preceding the most aversive moments of a traumatic film.

Alternatively, this pattern of results may reflect effects of demand characteristics (see section IV-3.4; Nichols & Maner, 2008; Orne, 1962), so that participants may have inferred the purpose of the memory triggering task in a way that biased their ratings. In future studies, effects of demand characteristics may be controlled for by including a post-experimental assessment of the "perceived awareness of the research hypothesis" (PARH; Rubin, Paolini, & Crisp, 2010).

Several characteristics of Study 2 that may have resulted in the absent effects of imaginal exposure have already been discussed above (see section III-5 and IV-1.2). Future studies could address these potential shortcomings in the current design by separating measurements of initial reactions to the trauma film more carefully from reactions to imaginal exposure (e.g. by separating film presentation and imaginal exposure by a longer time interval), by examining intrusive memories over a longer period of time, and by implementing a different control group (e.g. an inactive control group). Furthermore, implementing more sessions of imaginal exposure may enhance the beneficial effects of imaginal exposure, as in typical clinical practice multiple sessions of imaginal exposure are also held. Finally, potential extinction effects of the memory triggering task, possibly overlaying treatment effects of imaginal exposure, could be ruled out by assessing the MTT only at a follow-up session in future studies.

5 CONCLUDING REMARKS

Two experimental analogue trauma studies addressing separate research questions have successfully demonstrated that (1) retrieval suppression is associated with less distressing

intrusive trauma memories. In addition, the same neural process seems to be involved in both phenomena. Furthermore, (2) our findings support the assumption that intrusive trauma memories are comprised, at least partially, of a conditioned reaction to trauma reminders, as these memories were observed in reaction to trauma reminders and remained stable over a time period of one week.

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APPENDIX

VI APPENDIX

1 ABBREVIATIONS

ANOVA	Analysis of variance
CMS	Common Mode Sense
CR	Conditioned reaction
CS	Conditioned stimulus
CS-	Negative conditioned stimulus
CS+	Positive conditioned stimulus
d	Cohen's measure of effect size
dACC	Dorsal anterior cingulate cortex
dlPFC	Dorsolateral prefrontal cortex
dmPFC	Dorsomedial prefrontal cortex
DSM-5	Diagnostic and statistical manual of mental disorders (5th ed.)
ECG	Electrocardiogram
EEG	Electroencephalogram
EMDR	Eye-movement desensitization and reprocessing
ERP	Event-related Potential
F	F-ratio (used in ANOVA)
fMRI	Functional magnetic resonance imaging
HR	Heart Rate
Hz	Hertz
IAPS	International affective picture system
IES-R	Impact of Event Scale — Revised
IMQ	Intrusive Memory Questionnaire
ISI	Interstimulus interval
M	Mean
MTL	Mediotemporal lobe

MTT	Memory triggering task
N2	Negative peak 350-450 ms after stimulus
OFC	Orbitofrontal cortex
p	p-value
PARH	Perceived awareness of the research hypothesis
PTSD	Posttraumatic Stress Disorder
r	Linear correlation coefficient (Pearson)
rACC	Rostal anterior cingulated cortex
RS	Retrieval suppression
SAM	Search of associative memory
SC	Skin conductance
SCL	Skin conductance level
SCR	Skin conductance response
SD	Standard Deviation
SEM	Standard error of mean
SSRI	Specific serotonin reuptake inhibitors
STAI	State-Trait Anxiety Inventory
t	t-test value
TFCBT	Trauma focused cognitive behavioral therapy
TNT	Think/no-think
UCS	Unconditioned stimulus
vmPFC	Ventromedial prefrontal cortex
η_p^2	Partial eta squared
μS	Micro siemens
ω^2	Omega-squared

2 DIAGNOSTIC CRITERIA OF POSTTRAUMATIC STRESS DISORDER

Table VI-1: Diagnostic criteria of PTSD according to the DSM-5 (American Psychiatric Association, 2013)

Posttraumatic Stress Disorder
A. Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways: 1. Directly experienced the traumatic event(s). 2. Witnessing, in person, the event(s) as it occurred to others. 3. Learning that the traumatic events(s) occurred to a close family member or close friend. In cases of actual threatened death of a family member or friend, the event(s) must have been violent or accidental. 4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s)
B. Presence of one (or more) of the following intrusion symptoms associated with the traumatic events(s), beginning after the traumatic events(s) occurred: 1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s). 2. Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s). 3. Dissociative reactions (e.g. flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. 4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s). 5. Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
C. Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following: 1. Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s). 2. Avoidance of or efforts to avoid external reminders that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
D. Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following: 1. Inability to remember an important aspect of the traumatic event(s). 2. Persistent and exaggerated negative beliefs or expectations about oneself, others or the world. 3. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others. 4. Persistent negative emotional state. 5. Markedly diminished interest or participation in significant activities. 6. Feelings of detachment or estrangement from others. 7. Persistent inability to experience positive emotions
E. Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following: 1. Irritable behavior and angry outbursts typically expressed as verbal or physical aggression towards people or objects. 2. Reckless or self-destructive behavior. 3. Hypervigilance. 4. Exaggerated startle response. 5. Problems with concentration. 6. Sleep disturbances.
F. Duration of the disturbance is more than 1 month.
G. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
H. The disturbance is not attributable to physiological effects of a substance or another medical condition.

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