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Emotional Reactivity in Posttraumatic Stress Disorder: Behavioral and Neurobiological Correlates of Underlying Mechanisms and the Role of Emotional Memory Modification

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Memory ...

is the diary that we all carry about with us

- Oscar Wilde -

TABLE OF CONTENT

ABBREVATIONS

ANOVA	Analysis of Variance
ACC	Anterior Cingulate Cortex
ANS	Autonomic Nervous System
BA	Brodmann Area
BP	Blood Pressure
CAN	Central Autonomic System
CNS	Central Nervous System
CS	Conditioned Stimulus
CR	Conditioned Reaction
DBT-PTSD	Dialectical Behaviour Therapy for Posttraumatic Stress Disorder
DSM	Diagnostic and Statistical Manual of Mental Disorders
e.g.	example gratia, for example
fMRI	Functional Magnetic Resonance Imaging
FDR	False Discovery Rate
FPS	Fear Potentiated Startle
FWE	Family Wise Error
HC	Healthy Control
HF	High Frequency
GS	Generalization Stimulus
HR	Heart Rate
HRV	Heart Rate Variability
i.e.	id est, that is
LF	Low Frequency
MMSS	Mutlimodal Sensory Stimulation
MNI	Montreal Neurological Institute
NS	Neutral Stimulus
ORR	Online Risk Rating
OE-R	Online Expectancy Rating
SCR	Skin Conductance Response
TC	Trauma Control
PAG	Periaqueductal Gray
PNS	Parasympathetic Nervous System
PTSD	Posttraumatic Stress Disorder
RA	Reappraisal
RMSSD	Root Mean Squared Successive Differences

SNS	Sympathetic Nervous System
SPM	Statistical Parametric Mapping
US	Unconditioned Stimulus
vmPFC	Ventromedial Prefrontal Cortex

A. THEORETICAL BACKGROUND

The risk of experiencing traumatic events has always been a part of human life. However, the acceptance of a symptom pattern evoked by an external stressor (i.e. traumatic event) compared to internal processes (i.e. inability of the individual to cope with stressful life events) has only been fully accepted in 1980 in the third edition of the Diagnostic and Statistical Manual (DSM III, American Psychological Association, 1980), and here firstly labeled as posttraumatic stress disorder (PTSD). A long time before PTSD was introduced, Pierre-Marie-Félix Janet (*30.05.1859) had already stated that overwhelming experiences result in a change of the normally integrated consciousness: “The subject is unable to recite the events as they occurred and yet, he remains confronted with a painful situation (…) The struggle to continually repeat this situation leads to fatigue and exhaustion which have a considerable impact on his emotion” (Janet, 1925, p.663). This emphasizes the complex interplay between disturbed memory processes and difficulties in emotion regulation, which provide a profound impact on emotional reactivity in PTSD.

Overall, emotional reactivity is defined as a shift in the quality and intensity of affect in response to an emotion-provoking event. More detailed, negative emotions arise, whenever something important to us is threatened and in order to initiate a coordinated set of behavioral and physiological action tendencies ensuring the ability to deal with those demands. However, emotional responses can also be maladaptive, especially when situations differ extremely from those, which shaped our emotions (Gross, 1998, 2002). With respect to PTSD, altered emotional reactivity patterns are increasingly acknowledged, providing a complex picture of contrasting emotional states covering enhanced emotional reactivity (re-experiencing, hyperarousal), and reduced emotional reactivity (derealization, depersonalization) (Etkin & Wager, 2007; Lanius, Vermetten, et al., 2010; Nicholson et al., 2015; Reinders et al., 2014; Wolf et al., 2014). Herein, and in line with Janet’s observations, it is increasing consent, that both memory alterations and emotion regulation difficulties are important factors in contributing to altered emotional reactivity in PTSD (Brewin, 2001; Ehlers & Clark, 2000; Lanius, Vermetten, et al., 2010; Lissek & van Meurs, 2015; van der Kolk, 1994). Importantly, although 69.7% of the general population cross-national experience traumatic events during lifetime, only a small proportion actually develop PTSD (5.6%) (Koenen et al., 2017; see also Hapke, Schumann, Rumpf, John, & Meyer, 2006; Hauffa et al., 2011; Jacobi et al., 2014; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; Perkonigg, Yonkers, Pfister, Lieb, & Wittchen, 2004). This emphasizes the need to understand predisposing, as well as protective factors contributing to the development and maintenance of PTSD.

In the present doctoral thesis, I will address different aspects that may contribute to altered emotional reactivity in PTSD: Section A will provide a theoretical background on memory

functioning and emotion regulation in PTSD, with respect to its contribution to altered emotional reactivity. Herein, the importance of alterations in specific memory processes and alterations in neurobiological markers of emotion regulation in PTSD that contribute to altered emotional reactivity are introduced. In the last part of section A, current understanding of an experimental approach that combines a basic learning mechanism (=reconsolidation) with behavioral and pharmacological interventions is presented, as it aims at attenuating emotional memory and its associated emotional response. Research questions and aims of the present work will be derived in section B with respect to the presented investigations in section C. Finally, I will present findings of the empirical investigations in section D, and integrate the results in a general discussion, examining their implications with respect to further PTSD research.

A1. EMOTIONAL REACTIVITY AND MEMORY IN PTSD

The symptom pattern of posttraumatic stress disorder (PTSD) comprises the symptom cluster “involuntary distressing memories” pointing towards a relationship between memories and change in the affective state, i.e. emotional reactivity (American Psychological Association, 2013, p.271). Specifically, “intense psychological distress at exposure to internal or external cues that symbolize or resemble the traumatic event” (American Psychological Association, 2013, p.271) constitute an important factor in PTSD symptomatology. From a process-oriented perspective, enhanced emotional reactivity has been linked to aberrant memory functioning (Lissek & van Meurs, 2015). Therefore, a short introduction in relevant memory concepts are presented and subsequently linked to PTSD.

A1.1 Implicit and explicit memory

Overall, memory has been subdivided into long- and short-term memory (Cowan, 2008) (see Figure 1). The systems differ with respect to the duration and the amount of information that can be maintained. Specifically, short-term memory is conceptualized as a type of memory that can hold a limited amount of information in an accessible state for a restricted amount of time. On the contrary, long-term memory refers to a permanent store, which is assumed to be rather limitless in duration and capacity. Long-term memory is further divided into explicit and implicit memory (Squire, 1992; Squire & Dede, 2015). In more detail, explicit memory contains two components: Episodic memory, which ensures the memory of time and space specific events, and semantic memory, enabling the retrieval of more general facts about the world (Tulving, 1985a, 2001). In contrast, implicit memory contains a variety of abilities (Squire & Dede, 2015): Herein, non-associative learning (habituation and sensitization), associative learning (classical conditioning), procedural (skills and habits), and the perceptual representation system (perceptual priming) are summarized. With respect to the present work, subcategories of the described long-term memory are of importance such that these will be focussed on (Figure 1). In particular, the emphasis will be laid on semantic memory (explicit memory), non-associative learning and classical conditioning (implicit memory).

With respect to explicit memory, semantic memory was firstly conceptualized by Endel Tulving (1972). He defined semantic memory as containing general knowledge and as allowing ”an organism to be aware of, and to cognitively operate on, objects and events, and relations among objects and events, in the absence of these objects and events” (Tulving, 1985b, p.3). Thus, this form of memory enables us to remember important aspects, with no need to retrieve when, where, or how the learning occurred, but to use this information in order to deal with upcoming events.

With respect to implicit memory, non-associative learning firstly comprises habituation, which refers to a progressive decline in responding due to repeated stimulation (Rankin et al.,

2009; Thompson & Spencer, 1966). Thus, habituation has often been described as a simple form of learning, but it seems to provide the opportunity to filter out irrelevant information and ensures the focus on salient stimuli (Rankin et al., 2009). Moreover, sensitization, representing the other component of non-associative learning and serves to intensify responding due to repeated stimulation (Groves & Thompson, 1970). This is especially important in a fear context, as sensitization with respect to the activation of the fear system promotes enhanced responses to novel, but also to fear-relevant unconditioned stimuli (Marks & Tobena, 1990). Thus, the latter is also a simple form of learning, providing the basis for other forms, as it ensures stronger responding during stimulation of the fear system for example. Associative learning is an additional component of implicit memory. It refers to a process in which a contingent relationship between events, stimuli, or a behavior is formed (Shanks, 1995). Specifically, on one side, it comprises operant conditioning, which describes the formation of an association between a particular behavior and a consequence. Based on the form of the consequence, i.e. positive or negative, the occurrence of the behavior will be shaped, with positive consequences increasing and negative ones decreasing the occurrence (Skinner, 1974). On the other side, associative learning comprises classical conditioning, which is relevant with respect to the present thesis. More detailed, classical conditioning is a process in which a link between a neutral stimulus (NS) and an emotional event (US) is formed. Based on the latter process, the prior neutral stimulus serves as a conditioned stimulus (CS, danger cue), bearing the capacity to elicit the conditioned response (CR), i.e. emotional reaction, which was previously only related to the aversive event (Pavlov, 1927).

In the following section, alterations in PTSD with respect to the latter mentioned concepts are described.

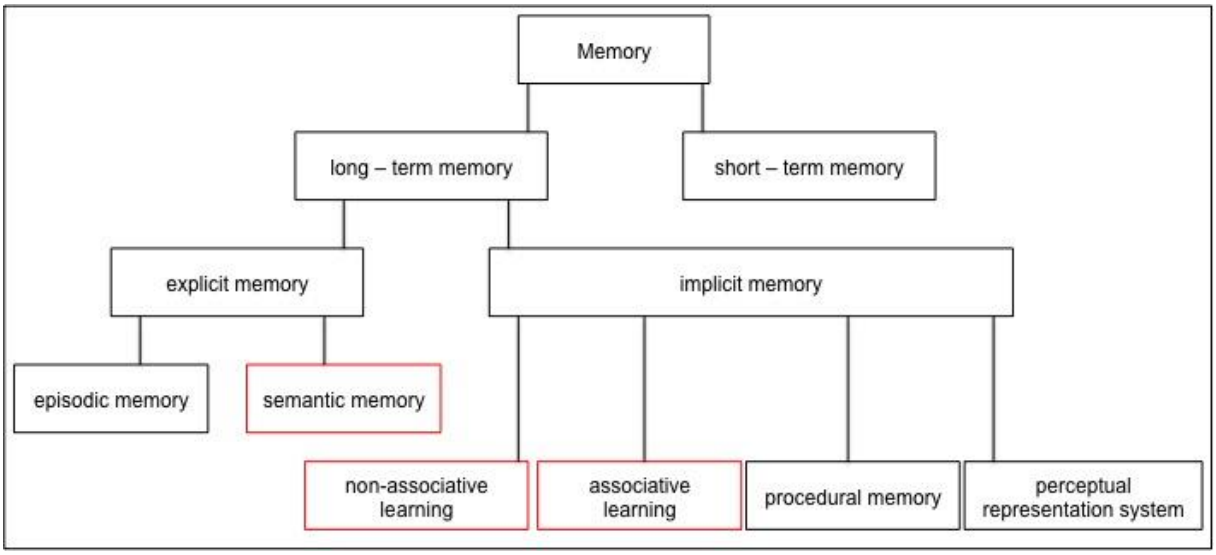

Figure 1. Memory model (adopted from Squire 2004)
Discussed memory components with respect to PTSD are depicted in red squares.

A1.2 Implicit and explicit memory in PTSD

Over the past two decades, an increasing amount of research has tried to elucidate learning alterations in PTSD (Lissek & van Meurs, 2015). Herein, PTSD literature suggests alterations in both implicit and explicit memory (for review see Lissek & van Meurs, 2015).

Alterations within these memory systems have primarily been studied in fear conditioning paradigms. Often, these paradigms comprise a baseline period, in which neutral stimuli are presented without aversive events. In a subsequent learning phase, a neutral stimulus is paired with an aversive event (US). As mentioned before, the learned contingency results in the fact, that the prior neutral stimulus becomes a conditioned stimulus (CS+, danger cue) and thus bears the opportunity to elicit the fear response formerly only associated with the US. Moreover, another neutral stimulus is not paired with an aversive event, representing the safety cue (CS-). This phase is mostly followed by a fear extinction phase, in which the CS+ is never followed by a US anymore, resulting in a diminished fear response to the CS+ over the course of the phase. Correlates of implicit memory systems comprise physiological responding (e.g. fear potentiated startle response, electrodermal activity), while explicit learning is reflected by the subjectively indicated learned contingency of the association, i.e. risk expectancy ratings of whether the presented stimulus is followed by an aversive event.

With respect to **implicit memory**, it has been hypothesized that both non-associative, as well as associative forms of learning might be affected.

Non-associative forms of learning are hypothesized to promote the observed PTSD characteristic of broad anxious reactivity to novel cues, which is also characterized by the hyperarousal criterion of the DSM 5, describing hypervigilant bodily reactions and exaggerated startle response in PTSD in general (American Psychological Association, 2013). With respect to the underlying non-associative learning processes, this is thought to result from a resistance of habituation learning, and/or enhanced sensitization processes (Lissek & van Meurs, 2015). Theoretically, on one side, increased reactivity during baseline phases in conditioning experiments could be indicative for alterations in the respective learning process. Moreover, heightened response to both stimuli (danger and safety cues), compared to control groups could hint towards alterations in broad anxious reactivity. Evidence towards enhanced baseline reactivity has been observed in some studies (Blechert, Michael, Vriends, Margraf, & Wilhelm, 2007; Grillon & Morgan, 1999; Jovanovic, Blanding, et al., 2009; Morgan, Grillon, Southwick, Davis, & Charney, 1995; but see also Diener et al., 2016; Jovanovic, Ely, et al., 2013; Jovanovic et al., 2010; Steiger, Nees, Wicking, Lang, & Flor, 2015b; Wessa & Flor, 2007). Nevertheless, it is important to note that baseline responding is often not reported or not even included per se, restricting the interpretability of PTSD related alterations during baseline testing, when no aversive event is presented (Davis, 2006; Fani et al., 2012; Jovanovic et al., 2011; Norrholm et al., 2011;

Rabinak, Mori, Lyons, Milad, & Phan, 2017). Moreover, with respect to the overall responding during fear conditioning several studies did observe overall increased responding in PTSD compared to the control group (Blechert et al., 2007; Davis et al., 2013; Grillon & Morgan, 1999; Grillon, Morgan, Davis, & Southwick, 1998; Jovanovic, Blanding, et al., 2009; Jovanovic et al., 2010; Jovanovic et al., 2011; Norrholm et al., 2011; but see also Fani et al., 2012; Jovanovic, Norrholm, et al., 2009; Jovanovic, Sakoman, et al., 2013; Wessa & Flor, 2007).

Alterations in associative learning processes are also postulated in contributing to enhanced emotional reactivity in PTSD. Specifically, the confrontation with stimuli or events associated to the trauma, resulting from the inability to distinguish between danger and safety (Lissek & van Meurs, 2015). In fear conditioning experiments, this is recognizable by reduced differential responding to the conditioned danger and safety cue. Moreover, aberrant fear extinction is proposed, i.e. prolonged differential responses to the CS+ and CS-, in contributing to enhanced emotional reactivity. Although a variety of PTSD related changes have been found, a clear picture is still missing. With respect to the acquisition of fear, results are heterogeneous. Some studies revealed reduced discrimination abilities in physiological responding between the CS+ and CS- (Davis et al., 2013; Gamwell et al., 2015; Grillon & Morgan, 1999; Jovanovic, Ely, et al., 2013; Jovanovic et al., 2010; McLaughlin et al., 2015), while others found no differences (Blechert et al., 2007; Fani et al., 2012; Garfinkel et al., 2014; Jovanovic, Blanding, et al., 2009; Jovanovic, Norrholm, et al., 2009; Jovanovic et al., 2011; Jovanovic, Sakoman, et al., 2013; Milad et al., 2008; Norrholm et al., 2011; Wessa & Flor, 2007). In terms of alterations regarding the extinction of a learned fear contingency, rather homogeneous findings have been observed. Studies have mostly revealed delayed or deficient extinction learning in PTSD on a physiological level (Blechert et al., 2007; Fani et al., 2012; Jovanovic, Ely, et al., 2013; Norrholm et al., 2011; Wessa & Flor, 2007). Nevertheless, few studies contrarily did not report differences in extinction learning (Garfinkel et al., 2014; Milad et al., 2008).

Regarding **explicit memory**, alterations in the subjective expectation of the contingency between the conditioned stimuli and the aversive event could also add to alterations in emotional responding. With respect to the overall risk expectation of whether a cue is followed by an aversive event, irrespective of the presented stimulus (danger or safety cue), most investigations have not observed increased responding in PTSD (Blechert et al., 2007; Diener et al., 2016; Jovanovic et al., 2011; Norrholm et al., 2011; Steiger, Nees, Wicking, Lang, & Flor, 2015a; Wessa & Flor, 2007; but see Rabinak et al., 2017). Results on fear acquisition seem to be rather clear in providing mostly evidence for successful learning in PTSD, i.e. higher expectation of risk in response to the danger cue compared to the safety cue (Blechert et al., 2007; Diener et al., 2016; Jovanovic et al., 2011; Norrholm et al., 2011;

Wessa & Flor, 2007). Nevertheless, two studies found that explicit learning of the CS-US contingency was altered in PTSD: Rabinak et al. (2017) revealed that PTSD individuals started to differentiate between the conditioned CS+ and CS- only during the end of the acquisition phase, pointing towards slower learning. Furthermore, another investigation reported less discrimination between contexts that have been associated with an aversive or no aversive outcome (Steiger et al., 2015a). Regarding the explicit learning of fear extinction, a reduced of extinction learning was observed in PTSD (Blechert et al., 2007; Diener et al., 2016; Norrholm et al., 2011; Rabinak et al., 2017; Steiger et al., 2015a).

Thus, the picture regarding alterations in implicit and explicit fear learning abilities in PTSD is yet unclear: Difficulties in the extinction of fear have been found consistently regarding both, implicit and explicit memory. In contrast, disturbances in the acquisition of fear have been observed in several studies regarding implicit memory, however not consistently. Yet, fear learning was negatively affected only in a few studies regarding explicit memory. With respect to overall increased responding irrespective of the stimulus type, this again has been observed regarding implicit memory, but only in a few investigations concerning explicit memory.

It is important to note, that it is clinical consensus and also emphasized in criterion B of the DSM 5, that PTSD individuals experience “intense psychological distress and physiological reactivity (…)” to stimuli that “(…) may symbolize or resemble the traumatic event” (American Psychological Association, 2013, p.271). Thus, it is not solely an intense implicit or explicit fear reaction to a specific cue, which is causing an extreme burden in PTSD, but also that these responses are generalized to a broad set of stimuli. Thus, the latter is hypothesized to challenge PTSD individuals’ belief that they are safe (Hermans, Baeyens, & Vervliet, 2013). However, as mentioned above, classical fear conditioning paradigms are mostly restricted to two conditioned stimuli and cannot address the question of whether fear is transferred to a broad range of stimuli. Yet, investigations focusing directly on implicit and explicit fear memory in response to a range of stimuli resembling the danger cue in PTSD are sparse.

A1.3 Emotional reactivity and memory generalization in PTSD

Generalization is based on classical conditioning processes (section A1.1): Associations are formed between a neutral cue and an e.g. aversive event, leading to the capacity of the prior neutral cue to elicit a fear response. With respect to generalization, this link is extended to stimuli not present during the initial learning situation. The association can be formed based on prior associations between the cues or perceptual similarity between the cues. Thus, additional stimuli also bear the opportunity to elicit a fear response (Dunsmoor & Murphy, 2015).

In general, generalization is a crucial human ability, as it is thus helpful in transferring an acquired response to other similar stimuli and/ or events that are not the same (Dunsmoor &

Paz, 2015). In terms of stimulus information predicting particularly an aversive outcome, it seems even more necessary to generalize responses to a wider range of even rather dissimilar stimuli: To incorrectly classify a situation as safe, might cause negative consequences, thus the decision is rather costly, while a false alarm is preventing negative consequences. Especially in the context of repeated, stressful life events, generalization might be extremely helpful in dealing with an unsafe environment full of complex stimuli. However, if this mechanism is still used, although adverse life events are no longer happening anymore, generalization can lead to maladaptive responses (Hermans et al., 2013).

A paradigm that has been recently adopted from animal research and applied to test human fear memory generalization is the fear conditioning and generalization paradigm (Armony, Servan-Schreiber, Romanski, Cohen, & LeDoux, 1997; Lissek et al., 2008; for a review on generalization paradigms see Dunsmoor & Paz, 2015). The paradigm is based on classical conditioning and consists of three phases: pre-acquisition, acquisition, and generalization test (Lissek et al., 2008). First, subjects are exposed to two neutral stimuli, which perceptually differ (e.g. in size). Within a second phase, one of the stimuli is followed by an electric shock, thus representing the CS+ (danger cue), while the other one is the conditioned CS- (safety cue). In the last part both the CS+ and CS-, as well as additional stimuli are presented. The latter decrease in similarity to the danger cue and increase in similarity to the safety cue (generalization stimuli, GS) and thus creating a continuum of perceptual similarity between both conditioned stimuli. Fear responses to each stimulus can be summarized within a generalization gradient: Herein, the highest fear responses are expected to the CS+, while fear responses are hypothesized to decline along the continuum of similarity regarding the GS, concluded by lowest responses to the CS-. In healthy humans and animals quadratic slopes have been observed, while linear, thus less steep slopes, have been found to predict levels of anxiety (Lenaert et al., 2014), and have been associated with anxiety disorders, which is referred to as overgeneralization (Ahrens et al., 2016; Lissek et al., 2014; Lissek et al., 2010; but also see Tinoco-Gonzalez et al., 2015).

Recently, this paradigm has also been applied to study overgeneralization in PTSD related to combat exposure for the first time (Kaczkurkin et al., 2016). In this study PTSD patients were characterized by a wider generalization of the conditioned fear response in their explicit memory, as well as on an implicit memory (neuronal) level compared to trauma control individuals. In detail, individuals with PTSD and subthreshold PTSD reported higher risk to stimuli differing to a greater extent from the danger cue. On the contrary, generalization in trauma control subjects can be described as extending only to those generalization stimuli most similar to the danger cue. The behavioral gradients of both, subthreshold and PTSD patients were described by a linear, while those in trauma control individuals were best

described by a quadratic function, thus pointing to behavioral overgeneralization in PTSD and subthreshold PTSD. This pattern of gradients was mirrored also on a neuronal level: Alterations were observed in brain regions recently implicated in fear generalization (e.g. anterior insula, dorsolateral prefrontal cortex, ventral hippocampus). Specifically, generalization gradients reflecting brain activation to the presented cues were characterized by a stronger quadratic decline in trauma controls compared to PTSD individuals. In line with the latter findings, Morey and colleagues (2015) conditioned fear in military veterans by coupling an aversive event to fearful facial stimuli. Although the paradigm differed from the aforementioned one, they also found stronger neural engagement of various cerebral areas and altered connectivity during processing stimuli of a higher emotional intensity than the prior fear conditioned stimulus in PTSD compared to trauma control subjects. Additionally, the observed effects were more pronounced in those participants reporting childhood maltreatment. Thus, these findings highlight that in PTSD more danger cue dissimilarity is needed before safety processes take effect, meaning that PTSD individuals were characterized by an overgeneralized fear response. Specifically, emotional reactivity seems to be enhanced to a wider range of stimuli and therefore hamper the opportunity for PTSD patients to feel save. Nevertheless, both studies so far did not include healthy control subjects without a history of traumatization. This restricts the interpretability of the findings, as it cannot be disentangled whether traumatization per se might already have an impact on generalization processes, or whether the development of PTSD contributes to the observed effect. Moreover, both investigations focused solely on military veterans. An important consideration is that interpersonal violence during childhood and adolescence has been increasingly associated with the development of PTSD (Kessler et al., 1995; for review see also Nemeroff, 2016), while it further seems to be of particular importance for promoting fear generalization (Morey et al., 2015). Therefore, it is important to study these processes in this vulnerable population, to identify factors predisposing or protecting individuals later in life.

As studies investigating fear generalization in PTSD are sparse, it is still unclear, how overgeneralization can be linked to the fear conditioning literature in PTSD. Importantly, the concept of overgeneralization has also been linked to the prior mentioned alterations in implicit and explicit learning during fear conditioning: Herein, mainly the reduced implicit and explicit discrimination between the danger and the safety cue was referred to as overgeneralized responding (e.g. Gamwell et al., 2015; Jovanovic, Ely, et al., 2013; McLaughlin et al., 2015; Steiger et al., 2015a). Thus, it is important to test whether those alterations might promote overgeneralization.

It is also important to note, that there is an ongoing debate about the interaction and distinguishability of generalization processes and perceptual discrimination (Struyf, Zaman, Vervliet, & Van Diest, 2015). The described generalization studies are based on the concept

that generalization is a process beyond discrimination. Herein, the strength of the fear response is hypothesized to change in relation to the physical similarity, but based on the CS-US relationship (Lissek et al., 2008). An alternative theory is that the responding is solely based on the inability to perceptually discriminate between stimuli. Both views are not necessarily exclusive, but both need to be considered while investigating generalization. The issues while investigating these mechanisms are that one's emotional state during these tasks influences stimulus processing, memory accuracy and perception (Pourtois et al., 2013). Thus, testing perceptual discrimination within a neutral context prior to generalization testing might cause non-relatable results, as the emotional state between these tasks differs. In addition, fear conditioning is also found to change the perception of a stimulus, resulting in reduced discrimination and therefore promotes wider generalization (Laufer, Israeli, & Paz, 2016; Resnik, Sobel, & Paz, 2011; Schechtman, Laufer, & Paz, 2010). Thus, applying a perceptual discrimination task after fear conditioning allows to test whether fear conditioning might impact perceptual discrimination differently across groups and whether this might be related to the prior tested generalization paradigm.

Altogether, studying implicit and explicit memory processing in terms of fear memory, with an additional emphasis on generalization processes, could help in gaining a deeper understanding of alterations in enhanced emotional reactivity.

A2. EMOTIONAL REACTIVITY AND EMOTION REGULATION IN PTSD

Besides altered learning mechanisms that may contribute to enhanced emotional reactivity, there is an increasing interest in investigating the physiological and neuronal correlates of emotion regulation disturbances in PTSD patients. Specifically, contrasting states of emotion regulation in those with PTSD are described, ranging from under- to overmodulation of one's emotional responses. This opposing pattern is thought to underlie the complex pattern of enhanced emotional reactivity (re-experiencing, hyperarousal) and detachment from emotional reactivity (depersonalization, derealization) (Lanius, Frewen, Vermetten, & Yehuda, 2010; Lanius, Vermetten, et al., 2010; Nicholson et al., 2015; Wolf et al., 2014). In the following section, emotion regulation in general is introduced and then related to neurobiological correlates of emotion regulation in PTSD.

A2.1 Emotion regulation and its neurobiological correlates

Emotion regulation is broadly defined as the engagement of conscious or non-conscious strategies to start, stop or modulate emotions (enhance or reduce) (Gross, 2015). Strategies are initiated as soon as an emotion is evaluated as being either "good for me", or "bad for me". Based on this evaluation, strategies are applied to aim at maintaining momentary, as well as longer-term goals in any given situation (Etkin, Buchel, & Gross, 2015). Specifically, explicit and implicit emotion regulation strategies have been distinguished. Herein, explicit strategies engage conscious processing, as they need insight and awareness of the current emotional state, which is permanently monitored. The most prominent explicit strategy is reappraisal. Reappraisal is defined as an active strategy, in which the self-relevant appraisal of an emotion-inducing cue is modified. On a neuronal level, brain regions of the frontoparietal executive network have been associated with reappraisal (Etkin et al., 2015). The latter network covers the dorsolateral prefrontal cortex (dlPFC), the ventrolateral PFC (vlPFC) and the parietal cortex, as well as the supplemental motor area (SMA) and the pre-SMA (Buhle et al., 2014) (see Figure 2). Moreover, implicit strategies are stated to be automatically elicited by a stimulus itself and do not need awareness or constant monitoring (Gyurak, Gross, & Etkin, 2011). An example is the regulation of emotional conflict, which is accompanied e.g. in the classic Stroop paradigm (control over reading a depicted word in favor of labeling the color of the word) (Gyurak et al., 2011). On a neuronal level, increased activation of the ventral anterior cingulate cortex (vACC) and the ventromedial PFC (vmPFC) has been consistently reported (Egner, Etkin, Gale, & Hirsch, 2008; Etkin, Egner, Peraza, Kandel, & Hirsch, 2006; Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010; Kerns et al., 2004). Vice versa, disturbances in emotion regulation are thought to explain emotional problems, as emotional reactivity is not sufficiently modulated, which challenges goal directed behavior (Gross, 2015). Alterations in the neuronal response pattern of the above mentioned structures are hypothesized to be indicative of these disturbances.

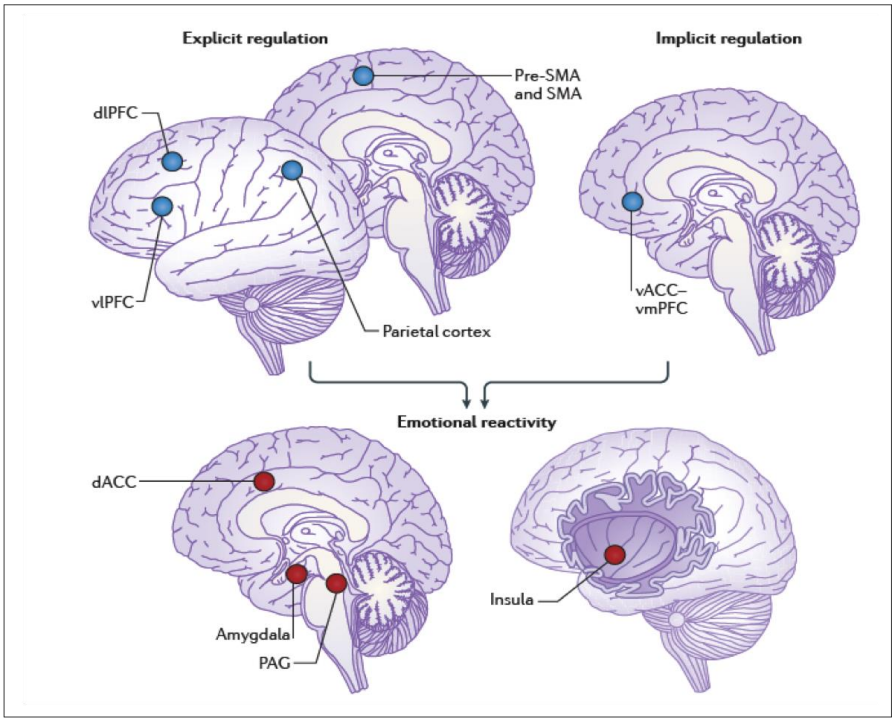

Figure 2. Brain regions implicated in emotional reactivity and emotion regulation (adopted from Etkin et al. 2015)
Brain regions depicted in blue are associated with emotion regulation. Herein, the dlPFC, vlPFC, parietal cortex and the pre -, and SMA have been linked to explicit emotion regulation, while the vACC and vmPFC have been implicated in implicit emotion regulation. Brain regions displayed in red refer to emotional reactivity.

Another important marker of an individual's regulatory capacity is heart rate variability (HRV), as HRV reflects the flexibility of an organism to adjust physiological arousal in response to environmental demands (Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012; Thayer & Brosschot, 2005). Specifically, HRV is proposed to reflect the state of the autonomic nervous system (ANS) (Thayer et al., 2012): Herein, the latter covers two branches, that is, the sympathetic (SNS) and the parasympathetic nervous system (PNS). Importantly, both branches act complementarily, meaning that the SNS is associated with energy mobilization, whereas the PNS is associated with restorative and vegetative functioning. In a resting state, the PNS dominates the SNS, while challenges in the environment engage the SNS, leading to a change in heart rate (HR). Thus, a flexible adaptation of the HR results in a high HRV (Thayer et al., 2012). In contrast, an imbalanced ANS is reflected by reduced HRV, which has also been associated with hypervigilant and maladaptive cognitive responses to emotional stimuli (Park & Thayer, 2014; Ruiz-Padial & Thayer, 2014), reduced suppression of unwanted memories (Gillie & Thayer, 2014) and thoughts (Gillie, Vasey, & Thayer, 2015), and reduced fear inhibition and extinction (Wendt, Neubert, Koenig, Thayer, & Hamm, 2015). HRV scores are mainly derived from two different classes of analyses (i.e. time domain and frequency domain indices). In the view of this, the most commonly used time domain index representing vagal cardiac influence (PNS) is the root mean square of successive beat

differences (RMSSD), which is highly correlated to the high-frequency (HF-) HRV, the most prominent frequency domain score (at 0.15 – 0.40 Hz) (Berntson, Lozano, & Chen, 2005). Vice versa, low-frequency (LF-) HRV (at 0.04 -0.15 Hz) reflects mainly sympathetic activation (Beissner, Meissner, Bar, & Napadow, 2013).

In the following section, alterations in PTSD with respect to the latter mentioned correlates are described.

A2.2 Emotion regulation and its neurobiological correlates in PTSD

Studies investigating emotional reactivity and regulation in PTSD have mainly applied paradigms in which neurobiological reactions were measured in response to threat – related, and/or trauma-related stimuli: PTSD has been associated with elevated tonic cardiovascular activity and with a marked increase in HR (Adenauer, Catani, Keil, Aichinger, & Neuner, 2010; Adenauer, Pinosch, et al., 2010; Ehlers et al., 2010; Lanius et al., 2005; Orr, Metzger, & Pitman, 2002; for meta-analysis/review see e.g. Orr, McNally, Rosen, & Shalev, 2004; Orr & Roth, 2000; Pole, 2007). Furthermore, it has been shown that PTSD patients with a predominant pattern of hyperarousal symptoms exhibited decreased neuronal activity in prefrontal regions (e.g. medial prefrontal cortex), while simultaneously activity of the dorsal anterior cingulate, anterior insula, amygdala, and hippocampus has been found to be increased (for meta-analyses see Etkin & Wager, 2007; Hayes, Hayes, & Mikedis, 2012; Patel, Spreng, Shin, & Girard, 2012; Rauch, Shin, & Phelps, 2006; Sartory et al., 2013; Stark et al., 2015). This activation pattern is often referred to as a reduced top-down inhibition of limbic regions, and is related to enhanced activation in brain structures related to emotional reactivity and reduced in those related to emotion regulation (Figure 2). Thus, studies reflect a hypersensitivity towards threat related stimuli in PTSD on a neuronal and autonomic level, contributing to a permanent state of alertness and highlight difficulties in regulating their emotional state (Andrews, Brewin, Rose, & Kirk, 2000; Badour & Feldner, 2013; Badour, Resnick, & Kilpatrick, 2015; Coyle, Karatzias, Summers, & Power, 2014; Santangelo et al., 2014).

Thereby, chronically accelerated arousal and reactivity in particular, found in PTSD patients, is assumed to result from an imbalance of the ANS, with a hyperactivated sympathetic branch and a hypoactive parasympathetic (Buckley, Holohan, Greif, Bedard, & Suvak, 2004; Thayer et al., 2012). HRV investigations in PTSD mostly revealed reduced parasympathetic activity at rest (time domain measurements, HF-HRV score) (Blechert et al., 2007; Chang et al., 2013; Cohen, Benjamin, et al., 2000; Cohen et al., 1998; Dennis, Dedert, et al., 2016; Dennis et al., 2014; Hauschildt, Peters, Moritz, & Jelinek, 2011; Kamkwalala et al., 2012; Lee et al., 2013; Lee & Theus, 2012; Meyer et al., 2016; Minassian et al., 2014; Moon, Lee, Kim, & Hwang, 2013; Norte et al., 2013; Rissling et al., 2016; Shah et al., 2013; Shaikh al arab et al., 2012; Tan, Dao, Farmer, Sutherland, & Gevirtz, 2011; Wahbeh & Oken, 2013; but also

see Agorastos et al., 2013; Keary, Hughes, & Palmieri, 2009). Yet, findings regarding sympathetic activity (LF-HRV score) are heterogeneous, with most studies finding lower scores (Chang et al., 2013; Dennis, Dedert, et al., 2016; Dennis et al., 2014; Rissling et al., 2016; Shah et al., 2013; Wahbeh & Oken, 2013), while some investigations found higher scores in PTSD subjects (Cohen, Benjamin, et al., 2000; Cohen et al., 1998; Lakusic et al., 2007; but also see regarding no differences Hauschildt et al., 2011; Keary et al., 2009; Moon et al., 2013). Moreover, the few studies that investigated cardiac response to stressful tasks did not reveal changes in response to affective cues (Cohen, Kotler, Matar, & Kaplan, 2000; Cohen et al., 1998; Hauschildt et al., 2011; Kamkwalala et al., 2012), whereas two studies reported a higher decrease in HRV in PTSD (Keary et al., 2009; Norte et al., 2013).
Overall, studies point to a reduced HRV in PTSD, while further alterations in neuronal top-down regulation have been observed, combining both parameters is hypothesized to contribute to gain a better understanding of the observed difficulties in regulating states of altered emotional reactivity.

A2.3 Emotional reactivity and emotion regulation in PTSD

On a neuronal level, integrative control centers for the ANS functions are located in the brainstem, which have been mainly derived from animal studies (Benarroch, 1993; Cechetto & Chen, 1990; Saper, 2002; Verberne & Owens, 1998). Yet, less is known about cerebral processing in humans. Nevertheless, the central autonomic network (CAN) is proposed to be a crucial link between the central nervous system (CNS) and the ANS (for meta-analyses see Beissner et al., 2013; Thayer et al., 2012). The CAN covers the ventromedial prefrontal cortex (vmPFC), anterior cingulate cortex (ACC), insular cortex, amygdala, hypothalamus, periaqueductal gray (PAG), parabrachial complex, nucleus of the tractus solitaris, and the ventrolateral medulla (Benarroch, 1993; Cersosimo & Benarroch, 2013; Palkovits, 1999; Thayer & Brosschot, 2005). The primary output of the CAN is mediated through preganglionic sympathetic (stellate ganglion) and parasympathetic neurons (vagus nerve), which further innervate the heart. Thus, it is hypothesized that both components, the ANS and CAN, are reciprocally interconnected. Specifically, efferent signaling to the CNS affects the heart and afferent signaling to the heart affects the CNS. Here, the crucial function of the cardiovascular system is to regulate the arterial blood pressure and to ensure an optimal blood flow to the brain and organs. If environmental demands are reduced (safety perception), the blood pressure and flow are regulated due to the arterial bararoreflex. The bararoreceptors herein send afferent signals to the brain. Consequently, efferent signaling from the brain ensures adjustment of the blood pressure, in this example an increase, leading to a decrease in HR, and thus to an activation of the PNS and inhibition of the SNS. This interactions leads to the complex variability underlying a healthy HRV time series

(Thayer & Brosschot, 2005). To date, there is no study investigating both processes simultaneously in PTSD.

Conclusively, HRV is stated to constitute an important factor in dealing with environmental demands and provides an index of the organisms' flexibility (Thayer et al., 2012; Thayer, Hansen, Saus-Rose, & Johnsen, 2009). Since, as mentioned before, alterations in the neuronal regulation of emotional states are reported, studying the latter in combination with autonomic functioning is hypothesized to help gain a better understanding of PTSD patients' neurobiological underpinnings in regulating emotional states. Deficient processing of those biomarkers would thus point towards emotional reactivity alterations in PTSD.

A3. EMOTIONAL REACTIVITY AND TRANSLATING EXPTERIMENTAL FINDINGS INTO THERAPY

As summarized above, altered emotional reactivity is a key characteristic in PTSD. Impairments in memory functioning and difficulties in regulating emotional states are hypothesized to contribute to emotional reactivity. To date, a number of evidence based treatments are available effectively targeting PTSD symptomatology, inclusively the latter highlighted aspects. Herein, large effect sizes (Cohen, 1988) have been revealed for eye movement desensitization processing therapy (EMDR; Shapiro & Solomon, 1995; g = 1.01) and cognitive behavioral therapies (g = 1.63), comprising e.g. cognitive therapy (CT; Ehlers & Clark, 2000), prolonged exposure (PE; Foa, Hembree, & Rothbaum, 2007), cognitive processing therapy (CPT; Resick & Schnicke, 1992), or other exposure based treatments like narrative exposure therapy (NET; (chauer, Schauer, Neuner, & Elbert, 2011) (see also Watts et al., 2013). Importantly, when it specifically comes to psychological interventions for PTSD in adult survivors of childhood abuse, a recent meta-analysis found moderate to large effect sizes for the reduction of PTSD symptomatology pointing towards a higher heterogeneity of effective therapies for the respective population (Ehring et al., 2014). Therefore, although effective treatments are available, the varying effect sizes call for the need to gain a better understanding, how and which strategies are effective. Upcoming evidence points towards a memory mechanism (= reconsolidation) that might specifically facilitate symptom improvement (Smith, Doran, Sippel, & Harpaz-Rotem, 2017). This mechanism is introduced in the following section. Experimental studies investigating behavioral and pharmacological protocols in combination with reconsolidation are subsequently presented. The section is concluded with implications for therapeutical strategies.

A3.1 Reconsolidation

Attempts to attenuate fear memory, especially in the therapeutic context (exposure techniques) are primarily based on extinction learning (Hofmann & Smits, 2008; Norton & Price, 2007; Olatunji, Cisler, & Tolin, 2010). Extinction learning can be described as a process in which a ‘new’ inhibitory memory is formed in order to reduce the behavioral expression of fear, as this new memory is dominating the original one (Bouton, 2002; Finnie & Nader, 2012; Milad & Quirk, 2002; Rescorla, 2001). Thereby, the emotional memory remains intact, while solely the behavioral expression is silenced. Vice versa, the fear expression can spontaneously recover over time or be reactivated when exposed to a prior associated cue in general, or when the subject is exposed to the relevant cue in a new context (Bouton, 2004; Harris, Jones, Bailey, & Westbrook, 2000; Myers, Ressler, & Davis, 2006; Rescorla, 2004). However, new insights in the field of neuroscience provide a different promising technique, which might modify well-consolidated fear memory permanently, instead of inhibiting the original memory trace. Groundbreaking work by Nader and

colleagues in 2000 triggered research within this field. They revealed that well consolidated memory enters a labile state again, in which it is sensitive to disruption. Upon retrieval of consolidated memories, they must stabilize again in order to persist – a process known as reconsolidation. After this publication, there has been an enormously growing body of work supporting the existence of reconsolidation within a variety of species (Choi, Kim, & Kaang, 2010; Debiec, Bush, & LeDoux, 2011; Debiec, LeDoux, & Nader, 2002; Lee, 2008; Lewis, 1979; Schiller, Kanen, LeDoux, Monfils, & Phelps, 2013; Soeter & Kindt, 2015b; Tian et al., 2011).

A3.2 Behavioral and pharmacological interventions during reconsolidation

A typical paradigm to study human reconsolidation is based on classical Pavlovian (fear) conditioning. The crucial component within this procedure is that 24 hours after (fear) memory encoding, reconsolidation processes are disrupted upon retrieval of the memory trace, resulting in diminished fear responses to the conditioned stimuli later on. In detail, this effect has been replicated several times for the administration of the ß-adrenergic receptor antagonist propranolol before (Kindt, Soeter, & Vervliet, 2009) and after memory retrieval (Sevenster, Beckers, & Kindt, 2013, 2014a, 2014b; Soeter & Kindt, 2010, 2011, 2012b, 2015b), as well as for behavioral interference protocols which mainly applied an extinction training upon retrieval of the memory trace (Agren, Bjorkstrand, & Fredrikson, 2017; Agren, Engman, et al., 2012; Agren, Furmark, Eriksson, & Fredrikson, 2012; Bjorkstrand et al., 2015; Oyarzun et al., 2012; Schiller et al., 2013; Schiller et al., 2010; Steinfurth et al., 2014; for meta-analysis see Kredlow, Unger, & Otto, 2016).

Interestingly, effects on disrupted reconsolidation processes of fear memories differ regarding the dependent variable: Herein, the administration of the ß-adrenergic receptor antagonist propranolol has been shown to attenuate fear potentiated startle (FPS) response, which involves amygdala engagement. Contrarily, declarative memory, which is referred to the explicit awareness of the CS-US contingency, was not altered by a propranolol administration (Kindt et al., 2009; Sevenster et al., 2013, 2014b; Soeter & Kindt, 2010, 2011, 2012a, 2012b, 2015b). However, investigations studying extinction protocols in interfering with reconsolidation particularly attenuated skin conductance response (SCR), which is known to be strongly related to the explicit learning about contingencies (Agren et al., 2017; Agren, Engman, et al., 2012; Agren, Furmark, et al., 2012; Bjorkstrand et al., 2015; Oyarzun et al., 2012; Schiller et al., 2013; Schiller et al., 2010; Steinfurth et al., 2014). However, in contrast to propranolol administration, the few behavioral interventions that also measured FPS response did not observe attenuation of the emotional response (Golkar & Ohman, 2012; Kindt & Soeter, 2013; Soeter & Kindt, 2011).

Nevertheless, an increasing number of studies did not replicate these findings (Bos, Beckers, & Kindt, 2012, 2014; Fricchione et al., 2016; Golkar & Ohman, 2012; Kindt & Soeter, 2013;

Klucken et al., 2016; Meir Drexler et al., 2014; Sevenster, Beckers, & Kindt, 2012; Soeter & Kindt, 2011; Warren et al., 2014). This suggests an urgent need to investigate reconsolidation interference in healthy individuals before these approaches can be translated into clinical practice.

A3.3 Emotional reactivity and therapeutical techniques during reconsolidation

A recent concept paper proposes that change within psychotherapy occurs by incorporating new (emotional) experiences and information into reactivated distressing memories and this repeated reconsolidation is thought to maintain positive therapy effects (Lane, Ryan, Nadel, & Greenberg, 2015; for a critical discussion see also Spanagel & Bohus, 2015). Unfortunately, explicit experimental studies testing therapeutical techniques within the reconsolidation time window are lacking. Herein, it is important to provide evidence, whether (and how) certain strategies can be effectively combined with reconsolidation.

In line with the latter, it is important to consider which strategies in PTSD treatment in general are effective and whether those can be combined with reconsolidation. Interestingly, Schnyder and colleagues recently proposed key components of the available empirically supported PTSD treatments introduced in the beginning of section A3. (Schnyder et al., 2015): Specifically, Schnyder et al. firstly listed psychoeducation, in order to provide relevant information on important aspects of posttraumatic stress reactions. The authors emphasize the importance of this strategy especially in terms of optimizing commitment. A second commonality is the training of emotion regulation skills. This refers to an active teaching of skills to regulate intense emotional states and thus, to tolerate high distress. The authors emphasize further imaginal exposure as another central element. Although this might differ between treatments, exposure to the trauma memory holds a crucial part in every evidence based trauma treatment. Exposure can range from in vivo exposure to threatening stimuli, to concentrating on the reappraisal of the event without a direct or detailed in sensu confrontation. The authors conclude the list by stating that cognitive processing and restructuring is another important element. This is stated to target erroneous beliefs about the trauma. Thus, the latter treatment strategies aim at reducing emotional reactivity. This is achieved on one hand by enhancing emotion regulation skills and on the other hand, by restructuring trauma related memory, thus simultaneously targeting associated emotions.

Interestingly, a first hint in testing imaginal exposure in combination with reconsolidation comes from a recent study by Agren and colleagues (Agren et al., 2017): In order to reactivate the prior conditioned fear memory, participants were either exposed to the conditioned stimulus or subjects had to imagine the conditioned stimulus, prompted by a voice (= imaginal exposure). The authors derived the experimental paradigm from Foas' "emotional processing theory" (Foa et al., 2007), suggesting that fear reduction can be achieved via 1) the activation of fear memory, and 2) the presence of new information,

incongruent to the original memory. As mentioned before, trauma therapy is mostly based on imaginal exposure. Herein, memory is verbally activated and restructured. According to this theoretical framework, the authors applied the respective technique and compared it to the standard visual reactivation protocol in reconsolidation paradigms. They found that both imaginal exposure successfully reduced the expression of fear measured via skin conductance response in healthy participants.

Besides therapeutic techniques, preliminary studies tested the effects of propranolol after trauma memory reactivation in a clinical setting (script-driven imagery) and provided first hints towards a reduction of trauma-related physiological responding (Brunet et al., 2008; Poundja, Sanche, Tremblay, & Brunet, 2012; see also for a case study Kindt & van Emmerik, 2016). However, findings could not be replicated (3 studies: Wood et al., 2015). Thus, this emphasizes again, that further testing in an experimental set up is needed, before this approach can be translated into clinical practice to enhance current treatments in their effectiveness in reducing emotional reactivity in PTSD (for positive effects on spider fear reduction in an experimental set up see Bjorkstrand et al., 2016; Soeter & Kindt, 2015a).

B. SCIENTIFIC AIMS AND HYPOTHESES

The overall aim of this doctoral thesis was to gain a better understanding of alterations in emotional reactivity in PTSD. Moreover, the current effort aimed at testing an experimental approach tailored to reduce emotional reactivity, i.e. to gain further insights into potential processes promoting a change in emotional reactivity in general. As introduced in chapter A., associated aspects of proposed underlying mechanisms of emotional reactivity in PTSD, that is disturbed memory processing, as well as emotion regulation were targeted. Specifically, considering the evidence on alterations in fear memory processing in PTSD, one focus was directed towards clarifying the role of fear memory generalization and its implication on emotional reactivity in PTSD (section A1.). With respect to emotion regulation in PTSD, studies have emphasized alterations in both the central and the autonomic nervous system. Here, I aimed at extending those findings by combining both parameters for the first time (section A2.). Promising evidence points towards potential beneficial effects in making use of basic learning approaches (reconsolidation) in the attenuation of emotional reactivity linked to a memory trace. Therefore, another focus of the present thesis was to accompany this strategy and test its effectiveness with respect to therapeutical techniques (section A3.). Three studies were conducted, each dealing with one of these objectives (Figure 3). In the following section, the specific hypotheses of these studies are presented.

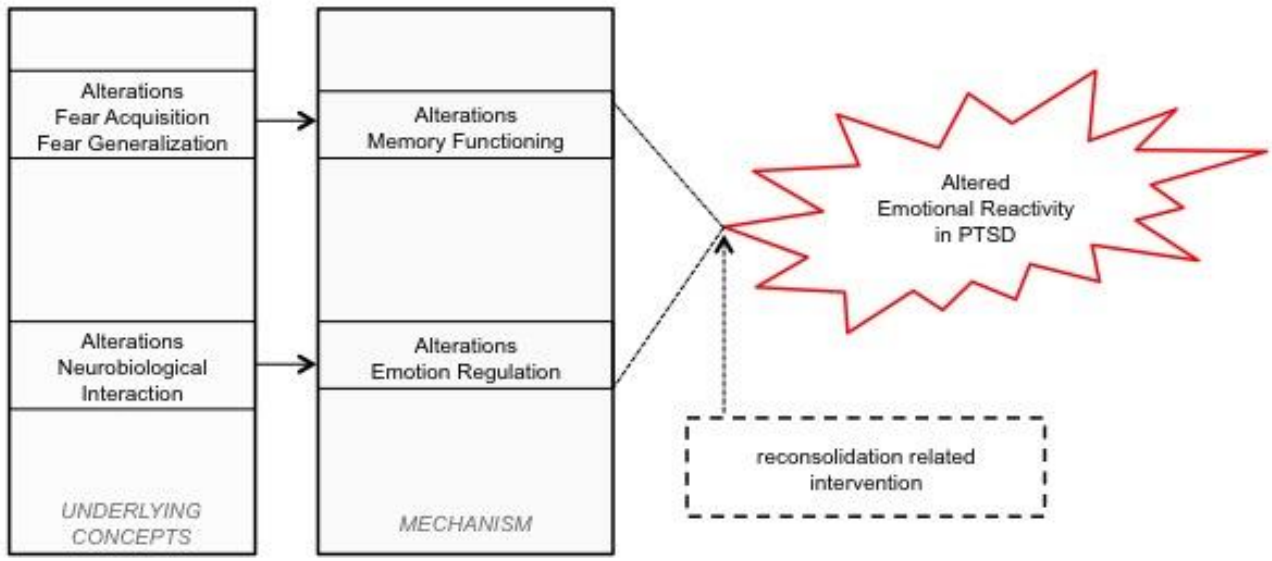

Figure 3. Conceptual framework of the doctoral thesis

B1. AIMS OF STUDY I

A vast amount of research based on learning theories has focused on maladaptive (fear) conditioning processes in explicit and implicit memory systems contributing to altered emotional reactivity in PTSD (section A1.). Yet, a clear picture is missing, as studies so far focused on a response pattern restricted to stimuli that have been presented during the initial learning phase. However, it is proposed that emotional responses actually tend to spread to a variety of stimuli in PTSD. The latter process is referred to as overgeneralization. Extending the classic paradigm should provide insights into the respective pathomechanism. Generalization was induced by a fear conditioning and generalization paradigm introduced by Lissek et al. (Lissek et al., 2008). This paradigm offers the opportunity to study baseline reactivity as well as alterations in fear learning, while moreover the amount of generalization can be tested with respect to both, implicit and explicit memory. Within a first phase, individuals were exposed to two neutral stimuli to assess baseline reactivity. In a subsequent learning phase, one of the neutral stimuli was followed by an aversive event (danger cue), while the other was never followed (safety cue). In a concluding phase, a range of additional stimuli was displayed, which were parametrically varying in their similarity and thus, forming a continuum between the danger and safety cue. This allowed the testing of fear transfer to stimuli that resemble the danger cue, but were not present during the initial learning phase. Implicit memory, as indicated by fear potentiated startle response and reaction times, and explicit memory, indicated by the explicit evaluation of risk whether a displayed cue was followed by an aversive event were measured.

Based on the literature in A1., it was hypothesized, that PTSD individuals are characterized by enhanced responding during baseline testing, especially regarding implicit memory processes (**Hypothesis 1**). In addition, PTSD patients were thought to show alterations in fear learning with respect to implicit memory (**Hypothesis 2**). Moreover, fear transfer to stimuli resembling the danger cue was proposed to be wider in PTSD subjects with respect to both implicit and explicit memory (**Hypothesis 3**). Additionally, it was hypothesized that the strength of fear overgeneralization is related to alterations in baseline testing and fear learning (**Hypothesis 4)**. To disentangle effects of a trauma history from PTSD psychopathology, the PTSD group was contrasted to both a group of healthy control subjects with and without a trauma history. Thus, the proposed effects are hypothesized to be specifically PTSD related. Since early adverse experiences have been found to increase the risk in developing a PTSD and seem to be especially related to generalization (Kessler et al., 1995; Morey et al., 2015), only subjects with a history of childhood maltreatment were included in both trauma groups.

B2. AIMS OF STUDY II

A constant finding in PTSD literature comprises alterations in the physiological correlate of emotion regulation, i.e. HRV (section A2.). As HRV reflects the flexibility of an organism to adjust physiological arousal on a momentary basis (Thayer et al., 2012; Thayer & Brosschot, 2005), a reduced HRV could thus promote alterations in emotional reactivity. Additional evidence for emotion dysregulation comes from neuroimaging studies: Here, a pattern of decreased activation in prefrontal brain regions, with increased activation in limbic regions has been revealed in PTSD. This is referred to as reduced lack top-down control (Etkin & Wager, 2007; Hayes et al., 2012; Patel et al., 2012; Rauch et al., 2006; Sartory et al., 2013; Stark et al., 2015). Importantly, a growing number of studies investigated the relationship between HRV and neuronal activation in healthy controls. With respect to the latter, the neuronal representation of autonomic control is thought to comprise the vmPFC, ACC, insula, amygdala, hypothalamus, thalamus, as well as brainstem structures that is the PAG and labeled as central autonomic network (CAN). To date, there is no study in PTSD research studying the association between both, the CAN and HRV. Altogether, combining HRV and neuronal responses could help to further explore the neurobiological underpinnings of the emotion regulation, in which disturbances are thought to add to the alterations in emotional reactivity.

To address this question, PTSD and healthy control subjects underwent resting state fMRI, while simultaneously cardiac activity was measured. Seed based functional connectivity of key regions of the CAN (vmPFC, amygdala, PAG) was examined. Observed connectivity patterns were related to resting HRV. Based on prior findings pointing to reduced emotion regulation ability in PTSD, it was hypothesized that HRV is reduced in PTSD (**Hypothesis 5**). Moreover, the connectivity pattern between key CAN regions and subcortical and cortical brain regions was proposed to be altered in PTSD (**Hypothesis 6**). Additionally, a reduced relationship between CAN connectivity and HRV in PTSD was hypothesized (**Hypothesis 7**).

B3. AIMS OF STUDY III

Reconsolidation processes have been increasingly recognized as a crucial component in modifying existing emotional memory tracing, bearing the opportunity to alter memory and its associated emotional reaction (section A3.). Although therapeutic implications are increasingly discussed, there is a lack of studies investigating whether therapeutic approaches actually have the potential to interfere with reconsolidation processes. Thereby, to date it is not clear, whether this combination provides a reasonable possibility to improve therapeutical effectiveness. With respect to PTSD and enhanced emotional reactivity, Dialectical Behaviour Therapy for Posttraumatic Stress Disorder (DBT-PTSD) has been proven to be an effective therapy for PTSD patients with a history of childhood sexual abuse (Bohus et al., 2013). The therapy is specifically tailored for patients suffering from strong emotional engagement. Herein, exposure-based techniques are combined with multimodal sensory stimulation to maintain the balance between emotional reactivity during exposure and the awareness of being present in the moment, since emotional over-engagement is proposed to disturb learning (see skills-assisted exposure Görg et al., 2016). Moreover, these strategies have been combined with reappraisal. The latter is conceptualized in DBT-PTSD by “questioning non-justified secondary emotions” and “radically accept trauma related biographic facts” (Bohus et al., 2013). Thus, and as described earlier, a focus is direct on the emotion-eliciting event, while simultaneously the appraisal is achieved to be changed, leading to a reduced its emotional impact (Ochsner, Bunge, Gross, & Gabrieli, 2002; Ray et al., 2005; Ray, Wilhelm, & Gross, 2008). With respect to enhanced emotional reactivity in PTSD, it would be of interest whether strategies like reappraisal and multimodal sensory stimulation might be effectively combined with reconsolidation, leading to a modification of the original memory trace and thus to reduced emotional responding. Since this has not been tested, the effectiveness of a combination of both on prior-conditioned fear memory was tested in healthy control subjects and compared to the established propranolol interference protocol.

To study reconsolidation, a differential fear conditioning paradigm was applied: On day 1, two stimuli (CS+) were associated with an aversive event, while one (CS-) was never followed by an aversive event. A day later, pharmacological (propranolol) and behavioural (reappraisal, multimodal sensory stimulation) intervention protocols were applied upon memory reactivation of one of the two CS+ (reconsolidation disruption) and contrasted to a placebo control condition. On a third day, effects of the applied protocols on fear memory were tested during extinction and reinstatement testing. One aim was to replicate fear memory attenuation by propranolol (**Hypothesis 8**) and testing whether established psychotherapeutical approaches may also interfere with reconsolidation processes, and thus, also attenuate fear memory (**Hypothesis 9**).

C. EMPIRICAL STUDIES

C1. STUDY I: GENERALIZATION OF FEAR IN PTSD RELATED TO PROLONGED CHILDHOOD MALTREATMENT: AN EXPERIMENTAL STUDY

Submitted as: ‘Thome, J., Hauschild, S., Liebke, L., Rausch, S., Herzog, J.I., Müller-Engelmann, M., Steil, R., Priebe, K., Hermans, D., Schmahl, C., Bohus, M., Lis, S. (under review). Generalization of fear in PTSD related to prolonged childhood maltreatment: An experimental study. *Psychological Medicine*

C1.1 Abstract

Background: Fear responses are particularly intense and persistent in posttraumatic stress disorder (PTSD), and may be evoked by unspecific cues resembling the original traumatic event. Overgeneralization of fear might be one of the underlying mechanisms. We investigated the generalization and discrimination of fear in individuals with and without PTSD who experienced interpersonal violence during childhood and adolescence.

Methods: Sixty trauma-exposed women with (n=30) and without PTSD (n=30) as well as 30 healthy control participants (HC) underwent a fear conditioning and generalization paradigm. In a contingency learning procedure, one of two circles with different sizes was associated with an electrical shock (danger cue), while the other circle represented the safety cue. During generalization testing, online risk ratings, reaction times, and fear potentiated startle were measured in response to the safety and danger cues as well as to eight generalization stimuli, i.e. circles of parametrically varying size creating a continuum of similarity between danger and safety cue.

Results: PTSD patients were slower when judging the risk of an aversive event related to stimuli of moderate similarity to the danger cue than HC. Moreover, they expected a higher risk of an aversive event independent of stimulus type and task.

Conclusions: Alterations in generalization constitute one part of fear memory alterations in PTSD after childhood maltreatment. Thereby, neither the accuracy of a risk judgment nor the strength of the induced fear was affected. Instead, alterations of the certainty with which these judgments are made may contribute to an individual's inability to feel safe.

C1.2 Introduction

Trauma exposure is experienced by 69.7% of the population cross-national during life-time and 5.6% of those affected develop posttraumatic stress disorder (PTSD) (Koenen et al., 2017). In PTSD, fear responses are intense and persist over time (Blechert et al., 2007; Jovanovic, Blanding, et al., 2009; Wessa & Flor, 2007). In addition, patients suffering from PTSD respond with strong physiological reactions to cues that symbolize or resemble the traumatic event (Hayes et al., 2012; Parsons & Ressler, 2013; Pole, 2007). This suggests an overgeneralization of fear responses, i.e. an induction of fear by a variety of stimuli that are not directly linked to the original traumatic event. Since the pioneering work of Watson and Rayner (1920) describing the generalization of fear responses of 'small Albert', it is well known that particularly the induction of fear by a wide range of diverse stimuli may cause an extreme burden and leads to an absence of the feeling of safety in every-day life (Hermans et al., 2013). However, in contrast to many studies revealing alterations of acquisition and extinction of fear responses in PTSD (e.g. Bremner et al., 2005; Gamwell et al., 2015; Jovanovic, Ely, et al., 2013; McLaughlin et al., 2015), experimental data on fear generalization alterations in PTSD are sparse.

From a process oriented perspective, overgeneralization is based on classical fear conditioning and is conceptually best related to the "fear network" (Lang, 1985): Herein, a neutral stimulus (NS) is associated with an aversive unconditioned stimulus (US). The NS then elicits as a conditioned stimulus (CS+) the conditioned fear response (CR). Additional stimuli that have not been present during the initial learning phase may be integrated in the fear network only depending on perceptual similarities or a former association with the CS+ and as a consequence equally trigger fear responses (see also Ehlers & Clark, 2000; Keane & Barlow, 2002). From an evolutionary perspective, generalization is a highly advantageous process, which facilitates learning by transferring prior learning experiences to similar situations (Armony et al., 1997; Lissek et al., 2008). However, it may also hamper functioning, if fear overgeneralizes to harmless stimuli resulting in a too widespread fear network (Hermans et al., 2013).

The few experimental studies, which explicitly investigated fear generalization in PTSD, point towards an overgeneralization of fear in this disorder (Kaczkurkin et al., 2016; Morey et al., 2015). In PTSD related to combat exposure, Kaczkurkin et al. (2016) investigated fear responses to a danger and safety cue, as well as to stimuli with a varying degree of perceptual similarity with the danger and safety cues (generalization stimuli). Their findings revealed stronger fear responses to generalization stimuli in PTSD compared to trauma exposed controls (Kaczkurkin et al., 2016). Similar preliminary findings have been reported in PTSD related to mixed traumatic events (Lissek & van Meurs, 2015).

Childhood maltreatment seems to be particularly important for fear overgeneralization later in life: Morey at al. (2015) identified childhood trauma as an aggravating factor in overgeneralization of fear in military veterans with PTSD. In general, the risk of developing PTSD in the aftermath of prolonged childhood maltreatment is not only extremely increased (e.g. US: 39.1%; Molnar, Buka, & Kessler, 2001), but has also been associated with a distinct psychopathological profile: A specific diagnostic entity has been proposed and will be included in the revision of the ICD 11, i.e. complex PTSD (Maercker et al., 2013; Shevlin et al., 2017). In addition to the core PTSD symptoms such as re-experiencing, avoidance and hyperarousal, the symptom pattern comprises “disturbances in self-organization”, i.e. affect dysregulation, negative self-concept, and interpersonal disturbances. Disturbances in self-organization are generalized to a variety of contexts, with the potentiality of a detachment from the traumatic event (Hyland et al., 2017). To date, there are no experimental studies investigating fear generalization processes after prolonged interpersonal childhood abuse (CA) in individuals with and without PTSD.

The aim of the present study was to experimentally investigate fear generalization in PTSD related to CA, since these individuals may be especially prone in developing a generalized symptom pattern. To investigate whether alterations in generalization processes are indeed indicative for CA – related PTSD or constitute a unspecific alteration in fear processing linked to trauma exposure, we contrasted PTSD patients not only to non-trauma exposed healthy controls, but also to participants with a history of CA, but who were free of any mental disorder throughout their life (trauma controls). We hypothesized (1) that an overgeneralization of fear characterizes PTSD as compared to controls, i.e. that they show stronger subjective and physiological fear responses to stimuli that are perceptually similar to a stimulus that has been previously linked to an aversive event. Moreover, we aimed at elucidating potential underlying mechanisms of overgeneralization: We investigated whether the groups differ in basal cognitive processes such as the perception and discrimination of stimulus features or in the acquisition of fear responses. We hypothesized (2) that PTSD patients differ from both healthy and trauma controls already during fear acquisition, but not in basal perception processes, and (3) that alterations during acquisition are linked to the extent of fear overgeneralization.

C1.3 Methods

C1.3.1 Sample Description

Thirty female individuals meeting criteria for PTSD related to repeated CA were matched for age and years of education to two female healthy control samples. The trauma control group (TC) consisted of 30 mentally healthy participants with a history of repeated CA. The healthy control group (HC) consisted of 30 healthy, non-trauma exposed controls. All individuals within both healthy control groups were free of any mental disorder throughout their life (see also Rausch et al., 2016). Enrolment was restricted to women aged between 18 and 65 years. Diagnostic and consenting procedures, as well as in- and exclusion criteria are included in section C1.7.1.

PTSD symptom severity was assessed with the Davidson Trauma Scale (DTS; Davidson et al., 1997), depressive symptom severity with the Beck Depression Inventory (BDI-II; Hautzinger, Kuehner, Buerger, & Keller, 2003). The severity of childhood traumatic experiences was measured with the Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998). Sample characteristics are summarized in Table 1.

Table 1. Sample characteristics

	PTSD N=30		TC N=30		HC N=30		test-statistics	*p*	post hoc tests
Demographics									
age *(SD)*	31.87	(9.27)	31.17	(12.02)	31.77	(8.41)	0.2[a]	.977	
years of education *(SD)*	10.93	(1.34)	11.33	(0.96)	11.37	(0.99)	1.31a	.275	
Clinical Characteristics									
CTQ - total *(SD)*	76.93	(21.35)	52.92	(13.12)	30.60	(5.98)	66.25[a]	<.001	PTSD>TC>HC
CTQ emotional abuse *(SD)*	18.95	(5.72)	12.60	(5.02)	6.60	(1.92)	50.40[a]	<.001	PTSD>TC>HC
CTQ physical abuse *(SD)*	11.27	(6.24)	9.12	(3.78)	5.30	(0.75)	13.79[a]	<.001	PTSD=TC>HC
CTQ sexual abuse *(SD)*	16.39	(6.51)	11.24	(5.99)	5.07	(0.25)	33.52 [a]	<.001	PTSD>TC>HC
CTQ emotional neglect *(SD)*	19.27	(5.77)	12.27	(4.59)	7.63	(3.44)	41.30 [a]	<.001	PTSD>TC>HC
CTQ physical neglect *(SD)*	11.78	(4.55)	6.90	(2.02)	6.00	(1.88)	25.63 [a]	<.001	PTSD>TC=HC
BDI II *(SD)*	33.73	(10.95)	4.69	(6.29)	4.63	(4.64)	119.52 [a]	<.001	PTSD>TC=HC
DTS-total *(SD)*	75.64	(17.96)	12.14	(12.85)	--	--	15.21[b]	<.001	PTSD>TC
DTS-intensity *(SD)*	38.61	(10.08)	6.66	(6.45)	--	--	12.91 [b]	<.001	PTSD>TC
DTS-frequency *(SD)*	37.04	(9.24)	6.69	(8.57)	--	--	14.39 [b]	<.001	PTSD>TC
Current Comorbidities (n)									
Affective Disorder	16		--		--				
Substance Dependency	0		--		--				
Substance Abuse	1		--		--				
Anxiety Disorder	18		--		--				
OCD	3		--		--				
Somatization Disorder	2		--		--				
Eating Disorder	6		--		--				
BPD	16		--		--				
Psychotropic Medication (n)									
SSRI	9		--		--				
SNRI	4		--		--				
Neuroleptics	0		--		--				
Anticonvulsants	0		--		--				
State Characteristics									
anxiety *(SD)*	53.37	(10.58)	32.66	(5.75)	30.7	(4.95)	79.84[a]	<.001	PTSD>TC=HC
vigilance *(SD)*	3.10	(1.32)	2.07	(0.99)	1.87	(0.86)	10.39[a]	<.001	PTSD>TC=HC
arousal *(SD)*	3.29	(0.66)	2.12	(0.74)	2.08	(0.51)	33.42[a]	<.001	PTSD<TC=HC
shock intensity *(SD)*	19.17	(9.93)	16.80	(8.73)	18.73	(8.52)	0.49[a]	.616	

Significance threshold p <.05
[a] = F-Value, [b] = T-value
Abbreviations: PTSD = posttraumatic stress disorder group, TC = trauma control group, HC = healthy control group, OCD = obsessive-compulsive disorder, BPD = borderline personality disorder, CTQ = Childhood Trauma Questionnaire, DTS = Davidson Trauma Scale; BDI-II = Beck Depression Inventory, anxiety = State-Trait-Anxiety Inventory – State (STAI-S, (Laux, Glanzmann, Schaffner, & Spielberger, 1981), vigilance = Stanford Sleepiness Scale (SSS, (Hoddes, Zarcone, Smythe, Phillips, & Dement, 1973), arousal = Self-Assessment Manikin (SAM, (Bradley & Lang, 1994), SSRI = Selective Serotonin Reuptake Inhibitor, SNRI = Selective Noradrenalin Reuptake Inhibitor, SD = standard deviation

C1.3.2 Experimental procedure

Experimental tasks:

Fear conditioning and generalization were tested with the fear conditioning and generalization paradigm introduced by Lissek and colleagues (Lissek et al., 2008). It assesses fear responses to both conditioned danger (CS+) and safety cues (CS-), as well as to generalization stimuli (GS) parametrically varying in similarity to the CS+ and CS-. The paradigm comprises three test phases, i.e. pre-acquisition, acquisition, and generalization.

Stimuli were 10 circles of gradually increasing size (Figure 4c). Herein, the smallest and the largest circle served as the conditioned danger cue (CS+) and conditioned safety cue (CS-), respectively (counterbalanced across participants, Figure 4a). The remaining eight stimuli represented the generalization stimuli (GS) (Figure 4c, C1.7.2). During testing, stimuli were presented on a computer screen (17'' screen, stimulus duration 8 seconds, Figure 4b).

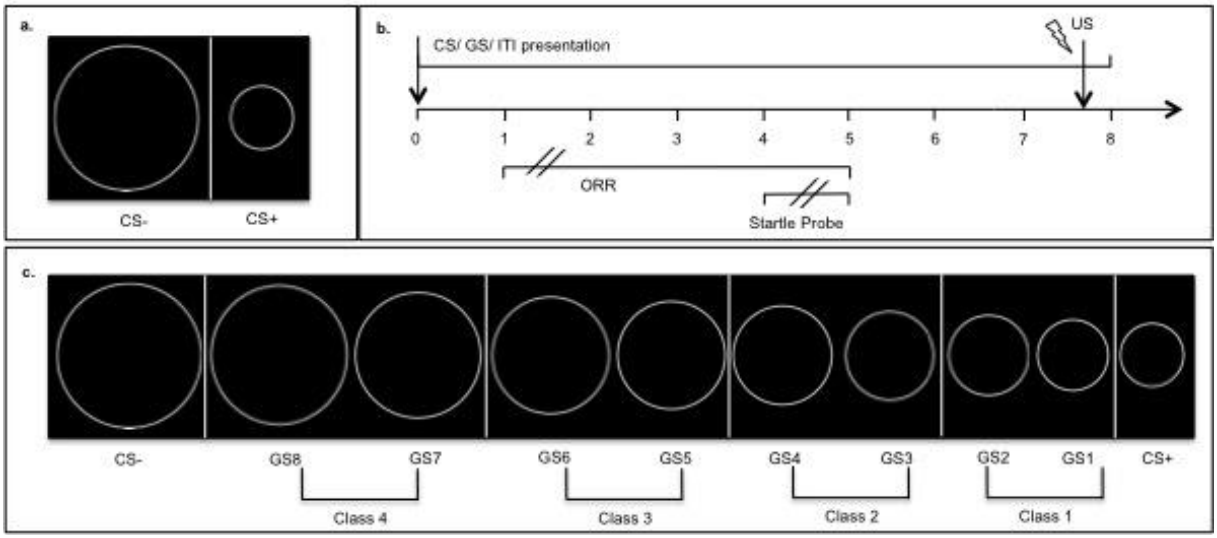

Figure 4. Stimuli presented during the different phases of the experimental paradigm together with the timing of an individual trial
a) Stimuli presented as danger (CS+) and safety (CS-) cues during fear acquisition
b) Timing of an individual trial exemplary for a reinforced stimulus presentation (ORR: online risk rating for the risk of the occurrence of an aversive event (US) during a time interval between 1 or 2 s following stimulus onset and until 5s following stimulus onset; startle probe 4 or 5s after stimulus onset; : 2 ms electric shock 80 ms before stimulus offset during reinforced trials)
c) Stimuli presented during generalization testing, i.e. as danger (CS+), safety (CS-) and generalization cue (GS). Please note, that the 8 GS are combined for analyses into 4 generalization classes
Please note: The assignment of the large and small circle as conditioned danger and safety cue and accordingly the generalization was balanced across participants.

Participants were instructed that they were going to see several circles; some of them were sometimes followed by an electrical shock. Participants were asked to learn to predict, whether a displayed picture will be followed by an electrical shock.

During pre-acquisition, the two CSs were presented 6 times together with 6 inter-trial-intervals (ITI, fixation-cross). None of the stimuli were paired with an electrical shock. The pre-acquisition phase was preceded by 9 startle probes to reduce initial startle reactivity (habituation).

During acquisition, the CS+ was paired with an aversive unconditioned stimulus (US, 2 ms, electrical shock intensity was individually set to a level "highly uncomfortable, but not painful", see Table 1 for shock intensities) (Lissek et al., 2008). Overall, 12 CS+ and 12 CS- trials, as well as 12 ITIs were presented with a reinforcement rate of 75% for the CS+.

Generalization testing started after a 5 minute resting period. Participants were instructed to remember what they had learned before and were informed that they were going to see the circles again. During testing, the CS+ (8 trials), CS- (8 trials), ITI (8 trials) and each of the 8 GS (4 trials) were presented in a pseudorandomized order. To prevent extinction of the conditioned fear response, two of the CS+ trials were combined with an electrical shock (25 % reinforcement). Generalization testing was preceded by two startle probes to reduce initial startle reactivity (habituation).

A perceptual discrimination task was additionally conducted to assess accuracy of basal perceptional processes, i.e. the basal ability to discriminate stimuli of varying sensory similarity. During this task, each trial started with the presentation of either the CS+ or CS- (stimulus duration 2s). Subsequently, a comparison cue was presented in the center of the screen. Participants had to assess the similarity between stimuli on a 10-point Likert Scale (1 = no to 10 = high similarity). After the response, stimulus presentation was terminated and the next trial started after a variable ITI (range 1500-3000 ms, mean duration 2170 ms). Each conditioned stimulus (CS+/CS-) was presented 10 times and combined with the stimulus itself, the other conditioned stimulus and each GS, resulting in 20 trials.

Measurement variables:

Online risk ratings (ORR), reaction time of ORR (RT), as well as fear-potentiated startle (FPS) served as dependent measurements during all phases of the fear conditioning and generalization paradigm (Figure 4b).

ORR were the evaluations of the risk of the occurrence of an electric shock associated to the presented stimulus (10-point Likert ranging from 1 = no risk, to 10 = high risk). Additionally, RT of the ORR was measured. RTs indicate the certainty during the evaluating with slower RTs related to a higher uncertainty about the association of a stimulus with an aversive event (Lissek et al., 2014; Lissek et al., 2010).

FPS was measured as the potentiated eye-blink startle reflex to a loud noise (40 ms, 95 dB[A]) by electromyography of the orbicularis oculi muscle. To measure FPS, CS and GS stimuli were followed after 4 or 5 s by acoustic startle probes. In addition, a similar number of startle probes was presented during ITIs. For further details see C1.7.2.

According to previous studies, ORR and FPS were assessed in separate trials (50%), since startle response may be influenced by simultaneous ratings due to attentional demands or movement preparation (Lissek et al., 2008).

C1.3.3 Statistical analyses

For the fear conditioning and generalization paradigm, dependent variables were averaged separately for each experimental phase and stimulus type. Measurement variables of GS stimuli were further combined for two consecutive levels of similarity each, resulting in four generalization classes (Figure 4c, C1.7.2, Lissek et al., 2008). Mean FPS, ORR and RT were

analyzed separately for each task with repeated measure variance-analytical designs (rmANOVA). All designs comprise the between-participants factor 'group' (PTSD, TC, HC) and the experimental factor 'stimulus type'. For pre-acquisition and acquisition, this resulted in a 3 x 2 rmANOVA with CS+ and CS- as the factor 'stimulus type'. For generalization testing, the design was extended by the GS classes as additional steps of the factor 'stimulus type' resulting in a 3 x 6 rmANOVA.

Similarity ratings during the perceptual discrimination task were analyzed with a 3 x 2 x 6 rmANOVA with the between-subject factor 'group', and the within subject factors 'reference' (CS+,CS-) and 'comparison stimulus' (CS+, CS-, class 1 – 4).

For further description of statistical effects in the ANOVA designs, post-hoc comparisons were calculated - if appropriate - by sub-analyses of the main design, or pairwise comparisons (Bonferroni-adjusted for multiple testing).

To test covariation of alterations in fear generalization with alterations of perceptual discrimination, fear responses during baseline, fear acquisition and the severity of childhood maltreatment and PTSD symptomatology, Pearson's correlation coefficients were calculated.

For criteria regarding the exclusion of single participants in the statistical analyses, please see C1.7.2. Statistical significance was set to $p < .05$. Effect sizes were calculated as Cohen's d. All analyses were performed using SPSS (version 22; SPSS Inc., USA).

C1.4 Results

C1.4.1 Fear conditioning and generalization paradigm

Pre-Acquisition:

ORR differed between groups ($F_{2,83} = 8.96$, $p < .001$; Table 2A): PTSD participants rated the risks higher as compared to both HC and TC participants (PTSD: 4.43, SD = 2.01; HC: 2.50, SD = 1.47; TC: 3.14, SD = 1.82; PTSD vs. HC: $p < .001$; PTSD vs. TC: $p = .024$). No difference was found between TC and HC ($p = .536$). ORR did not differ between stimulus type ($F_{1,83} = 0.75$, $p = .388$; group x stimulus type: $F_{2,83} = 1.14$, $p = .326$).

Neither *RT* nor *FPS* differed between groups or stimulus types (Table 2A).

Acquisition:

ORR differed between groups independent of the stimulus type ($F_{2,85} = 5.33$, $p = .007$; group x stimulus type: $F_{2,85} = .42$, $p = .661$; Table 2B, Figure 5): PTSD participants rated the risk higher compared with HCs ($p = .005$), but not with TC individuals ($p = .462$). There were no differences between the TC and HC group ($p = .224$). In general, participants reported higher risk expectation for the CS+ compared to the CS-, suggesting successful fear conditioning ($F_{1,85} = 492.96$, $p < .001$).

RTs differed between groups depending on the stimulus type ($F_{2,86} = 11.92$, $p < .001$; Table 2B, Figure 5). RT of both PTSD and TC participants differed from HC, but not between PTSD

and TC (2x2-ANOVA sub-design: group x stimulus type: PTSD vs. HC: $F_{1,58} = 20.69$, $p < .001$; TC vs. HC: $F_{1,57} = 12.37$, $p = .001$; PTSD vs. TC: $F_{1,57} = 0.99$, $p = .325$): Responses to the CS- were slower in PTSD ($p = .003$) and on a trend level in TC compared with HC ($p = .064$). In contrast, no group differences in RT to the CS+ were found (all *p's* > .205). Comparing RTs between stimulus types revealed, that PTSD and TC participants responded slower to the CS- as compared to the CS+ (PTSD: $p < .001$; TC: $p = .018$). In contrast, HC responded faster to the CS- as compared with the CS+ ($p = .007$).

FPS differed between groups depending on the stimulus type ($F_{2,75} = 4.39$, $p = .016$; Table 2B, Figure 5). Post-hoc analyses revealed that FPS to the CS+ was reduced in PTSD compared with HC (2x2-ANOVA sub-design: group x stimulus type: PTSD vs. HC: $F_{1,49} = 7.86$, $p = .007$; CS+: $p = .018$; CS-: $p = .585$). In contrast, no differences were observed between PTSD and TC, or TC and HC (2x2-ANOVA sub-design: group x stimulus type: PTSD vs. TC: $F_{1,52} = 2.29$, $p = .136$; HC vs. TC: $F_{1,49} = 2.49$, $p = .121$). In general, FPS to the CS+ was higher compared to the CS- ($F_{1,75} = 50.65$; $p < .001$), suggesting successful fear conditioning.

Generalization Test:

ORR differed between groups ($F_{2,84} = 4.19$, $p = .018$; Table 2C, Figure 5): PTSD individuals demonstrated heightened risk irrespective of the stimulus type compared with HC ($p = .029$), and as a trend with TC ($p = .064$). In general, participants differentiated between stimulus types, however stimulus types did not differentially affect ORR between groups (stimulus type: $F_{5,420} = 253.05$, $p < .001$; stimulus type x group: $F_{10,420} = 1.44$, $p = .162$). For further description of the generalization gradient see C1.7.3.

RT differed between groups depending on stimulus type ($F_{10,430} = 1.85$, $p = .050$; Table 2C, Figure 5). PTSD did not differ from TC (2x6-ANOVA sub-design: group $F_{1,57} = .01$, $p = .946$; stimulus type x group $F_{5,285} = .58$, $p = .715$). In contrast, PTSD, and as a trend TC differed from HC depending on the stimulus type (2x6-ANOVA sub-design: group x stimulus type: HC vs. PTSD: $F_{5,290} = 3.04$, $p = .011$; HC vs. TC: $F_{5,285} = 1.91$, $p = .093$). To further describe this effect, RTs for each GS and CS+ respectively were compared with the CS- to determine to which level of perceptual similarity RT indicated heightened uncertainty during risk evaluation. In HCs increased RTs were found towards the two generalization classes (class 1 and 2) least similar to the safety cue (p's < .031). In contrast, trauma-exposed participants, i.e. PTSD patients as well as TCs, responded slowest only to generalization class 2 compared to the safety cue (p's < .031). Thus, they experienced a higher uncertainty during risk rating towards generalization stimuli only when GS were less similar to both the danger and the safety cue. An additional explorative analysis revealed that a higher percentage of HC responded slowest to GS most similar to the CS+ when compared with both traumatized groups, suggesting that both, PTSD and TC group were slower during risk evaluation of GS

less similar to the CS+ (HC vs. PTSD: $\chi 2 = 10.34$, $p = .003$; HC vs. TC: $\chi 2 = 8.02$, $p = .007$; TC vs. PTSD: $\chi 2 = .16$, $p = .748$).

FPS did not differ between groups, neither in general ($F_{2,74} = .05$, $p = .955$; Table 2C, Figure 5), nor depending on the stimulus type ($F_{10,370} = .564$, $p = .844$). FPS differed depending on the stimulus types ($F_{5,370} = 18.86$, $p < .001$). For further description of the generalization gradient see C1.7.3.

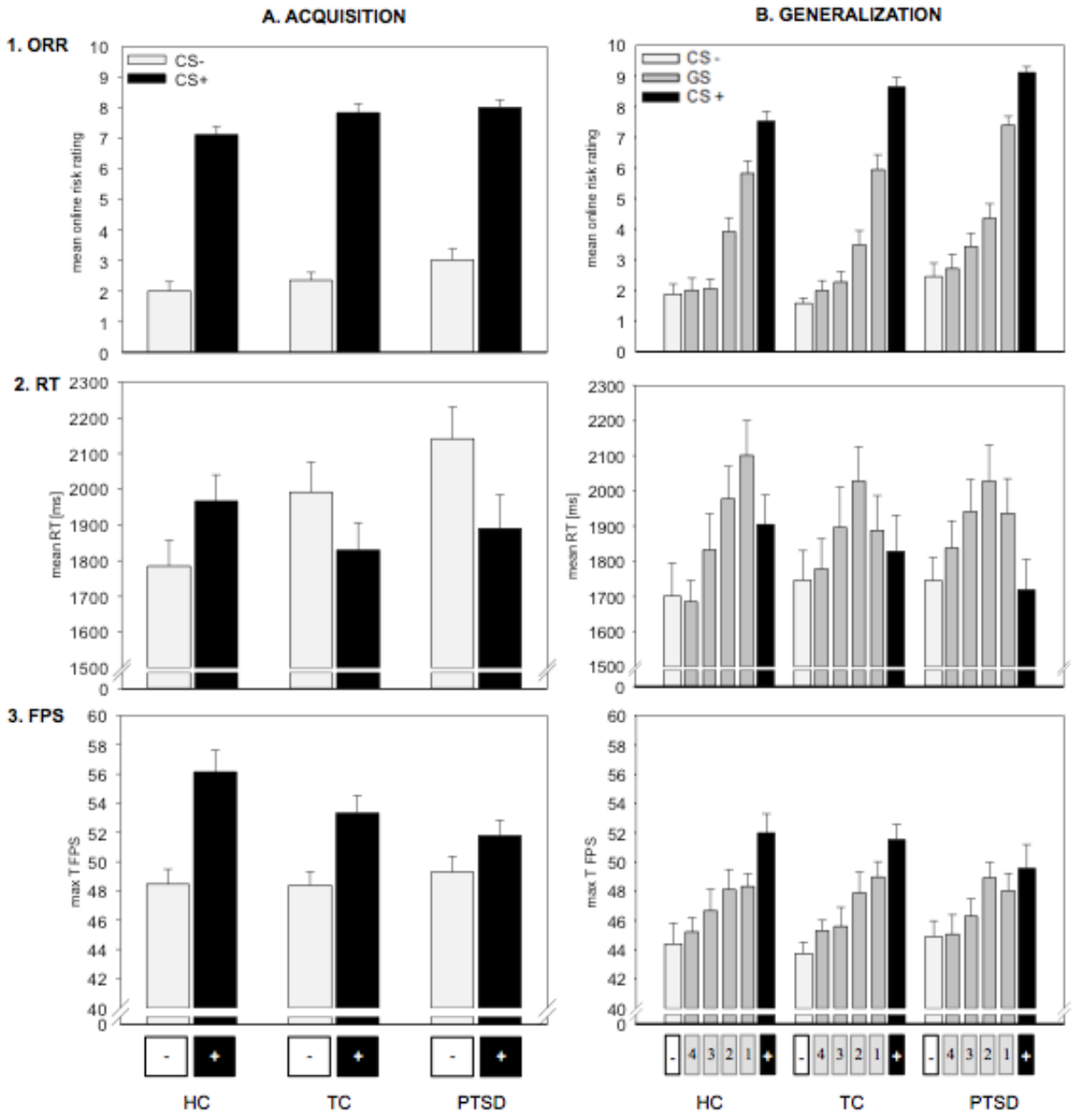

Figure 5. Online risk ratings (1.), reaction times (2.), fear potential startle magnitudes (3.) for each group regarding fear acquisition (A.) and fear generalization (B) for healthy controls (HC), trauma controls (TC) and PTSD patients (PTSD)
+: CS+; -: CS-; 1-4: generalization class 1 - 4

Table 2. Results of the analyses of variance for mean online risk ratings (ORR), reaction times (RT), and fear potential startle magnitudes (FPS) in the different phases of the experimental task.
A. pre-acquisition, B. fear acquisition, and C. fear generalization for mean online risk ratings (ORR), reaction times (RT), and fear potential startle magnitudes (FPS).

	ORR					RT					FPS				
	F	df	*p*	d		F	df	*p*	d		F	df	*p*	d	
A. Pre-Acquisition															
Group	8.96	2/83	<.001	.797	*	1.37	2/83	.260	.333		0.38	2/77	.684	.168	
Stimulus Type	0.75	1/83	.388	.089		0.02	1/83	.892	<.001		0.72	1/77	.400	.089	
Group x Stimulus Type	1.14	2/83	.326	.155		0.08	2/83	.921	<.001		1.03	2/77	.363	.168	
B. Acquisition															
Group	5.33	2/85	.007	.255	*	0.96	2/86	.387	.263		.94	2/75	.394	.238	
Stimulus Type	492.96	1/85	<.001	3.256	*	4.07	1/86	.047	.168	*	50.65	1/75	<.001	.869	*
Group x Stimulus Type	0.42	2/85	.661	.063		11.92	2/86	<.001	.424	*	4.39	2/75	.016	.333	*
C. Generalization															
Group	4.19	2/84	.018	.300	*	0.003	2/86	.997	<.001		0.05	2/74	.955	<.001	
Stimulus Type	253.05	5/420	<.001	2.293	*	11.19	5/430	<.001	.414	*	18.86	5/370	<.001	.753	*
Group x Stimulus Type	1.44	10/420	.162	.155		1.85	10/430	.050	.238	*	.564	10/370	.844	.168	

Significance threshold p <.05
Abbreviations: df = degrees of freedom, d = Cohen's d

C1.4.2. Perceptual discrimination task

Perceptual discrimination did not differ between groups (group: $F_{2,86} = 1.83$, $p = .166$; group x stimulus type: $F_{10,430} = 1.28$, $p = .238$; group x reference stimuli: $F_{2,86} = .30$, $p = .739$; group x stimulus type x reference stimuli: $F_{10,430} = .47$, $p = .912$). For further details see C1.7.3.

C1.4.3. Correlation of alterations in generalization with baseline responses, and responses during fear acquisition

To explore whether alterations during generalization testing in trauma-exposed groups (i.e. increased stimulus-independent ORR and RT increase from CS- to GS-class2) were related to alterations during other cognitive processes (i.e. fear responses during pre-acquisition and acquisition) correlations were calculated separately for each group (for correlation coefficients and groups statistics see Table 3). Higher ORR during generalization testing was linked to higher ORR during acquisition in all groups and during pre-acquisition in HC, but only as a trend in TC and PTSD (Table 3). Moreover, higher ORR during generalization was linked to a lower differentiation between CS+ and CS- during fear acquisition in FPS response in PTSD (Table 3), and regarding RT response in HC (Table 3). With respect to RT Class 2, longer reaction times were linked to higher ORR during acquisition in TC participants, and as a trend in PTSD (Table 3).

C1.4.4 Correlation of alterations in generalization with trauma severity

Alterations in ORR and RTs during generalization testing were not significantly related to the severity of childhood traumatization or PTSD symptomatology (Table 3).

Table 3. Correlation of alterations in generalization with baseline responses, as well as responses during fear acquisition, and clinical measurements

	correlation within group									comparison between groups								
	PTSD			TC			HC			PTSD vs. TC			PTSD vs. HC			TC vs. HC		
	r	*p*		r	*p*		r	*p*		Z	*p*		Z	*p*		Z	*p*	
ORR generalization testing																		
pre-acquisition																		
overall risk	.355	.064	(*)	.374	.060	(*)	.492	.007	*	.08	.470		.31	.377		.23	.409	
acquisition																		
overall risk	.646	<.001	*	.579	.001	*	.629	<.001	*	.38	.351		.10	.459		.28	.389	
differential RT	.058	.764		-.114	.563		-.470	.010	*	--	--		2.05	.020	*	1.41	.079	(*)
differential FPS	-.396	.045	*	.062	.764		-.319	.138		1.63	.051	(*)	.28	.386		--	--	
clinical measurements																		
CTQ total	.091	.659		.078	.694		-.209	.276		--	--		--	--		--	--	
DTS total	.141	.483		.052	.796		--	--		--	--		--	--		--	--	
differential RT class 2 - safety cue																		
pre-acquisition																		
overall risk	-.128	.509		-.124	.539		.022	.908		--	--		--	--		--	--	
acquisition																		
overall risk	-.343	.063	(*)	-.417	.027	*	-.190	.325		.31	.378		.60	.274		.89	.184	
differential RT	.174	.357		-.106	.591		.084	.665		--	--		--	--		--	--	
differential FPS	.242	.223		-.232	.255		-.148	.490		--	--		--	--		--	--	
clinical measurements																		
CTQ total	.188	.348		.125	.528		.244	.194		--	--		--	--		--	--	
DTS total	.029	.882		.253	.203		--	--		--	--		--	--		--	--	

Significance threshold p <.05
Abbreviations: PTSD = posttraumatic stress disorder group, TC = trauma control group, HC = healthy control group, CTQ = childhood trauma questionnaire, DTS = Davidson Trauma Scale, RT = reaction time, FPS = fear potentiated startle

C1.5 Discussion

The present study investigated whether patients with PTSD after exposure to repeated CA are characterized by an overgeneralization of fear. Indeed, our findings support alterations in generalization processes in CA-related PTSD revealed by an increased uncertainty during risk assessments. However, generalization of the fear itself as indicated by explicit risk assessments as well as startle responses was not affected by PTSD. Importantly, trauma exposure per se seems to contribute to the observed effects, since trauma control participants partly mirrored effects observed in PTSD.

Overgeneralization is the spreading of fear to stimuli that bear a similarity to the danger cue, i.e. generalization stimuli. We applied a fear conditioning and generalization paradigm (Lissek et al., 2008) and our findings confirm alterations in processes linked to the generalization of fear in PTSD related to CA. These alterations are less revealed by how strongly an aversive event is expected within a specific stimulus context, but rather by the uncertainty with which people achieve this judgment: PTSD patients differed from healthy controls in the processing times during risk evaluations, but not in the evaluation of the level of risk itself or the evoked startle response. In general, increased reaction times have been associated with higher uncertainty about threat information linked to a specific stimulus (Kaczkurkin & Lissek, 2013; Lissek et al., 2014; Lissek et al., 2010). Our data revealed a shift in uncertainty in PTSD towards stimuli of lower similarity with the danger cue. In this group, reaction times were highest for generalization stimuli of moderate similarity to the danger cue. In contrast, healthy controls were most uncertain in response to stimuli most similar to the danger cue. This suggests that PTSD patients feel less certain about a risk related to safer stimuli. Beyond, they were equally certain of the risk for an aversive event whether the danger cue itself or its closest approximation was presented. In sum, our data suggest that the explicitly assessed level of risk is not affected, but the certainty with which these judgments are made. One may hypothesize that this altered pattern might contribute to PTSD patients' difficulties to perceive an environment as safe (Steiger et al., 2015a; Wicking et al., 2016).

Beyond these findings, risk expectation was increased in PTSD. However, this effect was independent of the type of stimuli presented suggesting an alteration unrelated to generalization processes. A stimulus-independent higher risk expectation during generalization testing is in line with findings by Lissek and colleagues (Lissek & van Meurs, 2015). These authors discussed their finding as a reflection of sensitization processes. Sensitization represents a non-associative learning mechanism, in which fear is elicited when confronted with novel cues by an activation of the fear system in response to an aversive event (Marks & Tobena, 1990). In contrast to generalization, these novel cues are not necessarily related to the aversive event (Maier & Watkins, 2005). This interpretation is in

line with the heightened risk expectation in PTSD patients already during baseline testing and fear learning in the present study. However, the differentiation between generalization and sensitization requires an experimental paradigm extended by additional stimuli that clearly diverge from the danger cue. By applying this approach in veterans with and without PTSD, Kaczkurkin et al. (2016) demonstrated that the conditioned fear response did not generalize from the danger cue to a novel control stimulus, suggesting that the observed effects of overgeneralization are not due to sensitization processes.

It seems worth to mention that the concept of fear overgeneralization in PTSD literature was driven by the idea that a reduced discrimination between danger and safety cue during fear learning represents a form of overgeneralization (e.g. Gamwell et al., 2015; Jovanovic, Ely, et al., 2013; McLaughlin et al., 2015; Steiger et al., 2015a). Following this line of reasoning, we observed a reduced startle potentiation to the danger cue in PTSD indicating an attenuated differentiation between danger and safety. Moreover, the certainty in evaluating the risk of the presented cues was altered during fear acquisition: PTSD patients were slower in response to the safety cue, but faster to the danger cue. In healthy controls, this pattern was reversed. This suggests that PTSD patients were more uncertain regarding the threat information of the safety cue. Altogether, these findings on the differentiation between the danger and safety cue may additionally support alterations in processes linked to generalization of fear in PTSD, although similar to the generalization testing explicit assessments of risk were not altered.

Based on the theoretical framework of generalization, it is important how alterations during fear acquisition might impact fear transfer to a wider range of stimuli. Indeed, the present investigation confirms relatedness: Uncertainty during generalization testing was less pronounced in those PTSD patients who reported a higher expectation of risk already during fear acquisition. Moreover, we found that higher expectation of risk during generalization testing was related to higher expectation of risk during fear acquisition and a reduced differentiation in FPS between the safety and danger cue in PTSD. However, the latter alteration affected risk expectations independently of the similarity of stimuli with danger and safety cues, revealing that they are less relevant for the strength of generalization.

It is important to note, that traumatization per se seems to influence the observed effects: Differences in reaction times were mirrored by traumatized control participants compared to healthy controls, although they were less pronounced, i.e. were revealed by statistical analyses only on a trend level. This shift of uncertainty across the range of generalization stimuli was less pronounced in those trauma controls who reported a higher risk during fear acquisition, which is comparable to the relation observed in PTSD. In sum, alterations in explicit fear responses were indicative for PTSD, while hints towards differences in an implicit measurement, e.g. reaction time, were also found in trauma controls. In contrast to a study

by Morey and colleagues (2015), we found no relation between the severity of childhood traumatization and alterations during generalization neither within groups, nor across traumatized participants. However, Morey et al. (2015) focused on the neural correlates of generalization in a different type of trauma, i.e. PTSD in war veterans. This could have probably resulted in a higher variability of this feature within the studied sample.

Finally, some limitations of the present study have to be addressed. The observed effects during generalization testing are restricted to behavioral measurements and were not observable in FPS as a measure closely related to the activation of the amygdala (Davis, 2006). One possible explanation might be psychotropic medication in the PTSD group (Table 1, section C1.7.1), since e.g. antidepressants are known to dampen FPS response, potentially resulting in a floor effect (Arnone, Horder, Cowen, & Harmer, 2009). In additional exploratory analyses excluding PTSD patients with psychotropic medication, we observed the same pattern of results for all parameters (FPS, ORR, RT). However, this has to be interpreted with caution due to low statistical power. Importantly, studies investigating generalization processes in anxiety disorders did also not consistently find overgeneralization on both, physiological and behavioral levels (Ahrens et al., 2016; Kaczkurkin et al., 2016; Lissek et al., 2014; Lissek et al., 2010; Morey et al., 2015; for null findings see Greenberg, Carlson, Cha, Hajcak, & Mujica-Parodi, 2013; Tinoco-Gonzalez et al., 2015). Nevertheless, overgeneralization may constitute a transdiagnostic alteration in fear processing, but further studies are needed to disentangle the different correlates of fear generalization processes within and between mental disorders. Our data emphasize the importance of taking adverse life events such as traumatization into account when studying generalization processes in other mental disorders. Thereby, a finer-grained measurement of type and timing of maltreatment seems to be promising since these factors are increasingly recognized as modulating the impact of traumatization (Teicher & Samson, 2016).

C1.6 Conclusion

In conclusion, our results demonstrate alterations in generalization processes of conditioned fear for the first time in a sample of PTSD patients with a history of repeated CA. As this population is extremely vulnerable to develop a complex pattern of PTSD, it is important to identify factors predisposing or protecting individuals during later life. The present study extends findings regarding alterations in fear memory in PTSD after CA, as it provides first experimental data on actual fear transfer, which may contribute to the loss of the feeling of safety in every-day life.

C1.7 Supplemental Material

C1.7.1 Supplemental Participants

Diagnostic and consenting procedures:

The diagnostic interviews in order to assess inclusion- and exclusion criteria were conducted by trained clinical psychologists by using the BPD section of the IPDE (Loranger, Janca, & Sartorius), and the Structured Interview for DSM-IV (SCID-I; Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997), as well as the Clinician Administered PTSD Scale for DSM-5 to further assess PTSD (CAPS; Weathers et al., 2013). PTSD patients were recruited from an ongoing study at the Department for Psychosomatic Medicine and Psychotherapy, CIMH Mannheim. Both, TC and HC groups were recruited through the database at the Department for Psychosomatic Medicine and Psychotherapy, CIMH Mannheim, as well as through newspaper advertisements and the distribution of flyers at public places (e.g. cafés, supermarkets). Approval was obtained from the independent Ethics Committee of the Medical Faculty Mannheim at Heidelberg University. All participants provided written informed consent.

Inclusion and exclusion criteria:

The inclusion criterion for trauma exposed individuals (PTSD and TC group) was the exposure to physical and/ or sexual violence prior to the age of 18. Since PTSD individuals took part of a longitudinal treatment study, which evaluated two trauma treatments for individuals with posttraumatic stress disorder related to childhood and adolescent maltreatment (RELEASE-study), they also had to fulfill at least 3 borderline personality disorder criteria, as defined by the International Personality Disorder Examination (Loranger et al.).The exclusion criteria for TC, as well as HC individuals contained a lifetime diagnosis of any axis-I or Borderline Personality Disorder, the intake of psychotropic drugs or experiences of psychotherapeutic interventions. Exclusion criteria for the PTSD sample included a lifetime diagnosis of schizophrenia or bipolar-I disorder, current substance dependence, a body mass index <16, or the intake of the following psychotropic drugs: tricyclic antidepressants, neuroleptics, trazedon, benzodiazepines, anxiolytic drugs, as well as beta adrenergic blocking agents. For safety reasons, PTSD individuals who had attempted suicide within the last two months were excluded as well.

C1.7.2 Supplemental Experimental Procedure

Fear conditioning and generalization paradigm:

Stimuli: Two circles served as conditional stimuli. For half of the participants within each group, the small circle (5.5 cm) was associated with the aversive outcome (CS+) and for the remaining subjects this was reversed, meaning that the big circle (12.5 cm) served as the CS+. Within the generalization test, eight additional circles were presented (GSs). The

generalization stimuli decreased in similarity in regard to the CS+ and increased in their similarity to the CS-. In detail, each GS increased 0.875 cm in diameter starting from the smallest circle (5.5 cm) and thus representing a continuum from the smallest to the biggest circle. Prior to analyses, responses to every two GSs were averaged resulting in four generalization classes. This procedure was based on the concern that including each GS as a separate stimulus would lead to an long experiment, while including only four GS would not allow a gradual enough continuum between CS+ and CS-. Thus, presenting 8 GSs, while analyzing 4 generalization classes seemed to be a good compromise (see Lissek et al., 2008). A fixation-cross (size: 1 cm) appeared on the screen during inter-trial intervals (ITI). Electrical stimulation (20 ms) served as a unconditioned stimulus (US) and was controlled by Digitimer DS7A constant current stimulator (Digitimer, Herfordshire, UK) via a bar stimulating electrode with two durable stainless steel disk electrodes of 8 mm diameter each and with 30 mm spacing between, placed on the upper wrist of the non-preferred hand and fixated with a Velcro strap. Electrodes were filled with conductive gel (Signa Gel, Parker). US intensity calibration was set individually starting with 10 mA, while intensity was increased by steps of 20 mA until it felt 'unpleasant but not painful'. Herein, the following steps have been important: the participant was instructed to provide feedback as soon as the electrical shock felt 'unpleasant' for the first time. Next, intensity was further increased until the participant mentioned, that the electric shock felt 'painful'. The intensity than was decreased by 20 mA. The participant was than instructed to rate, whether this intensity felt 'unpleasant, but not painful', while it should further feel more unpleasant compared to the startle probe, which has been presented one time before starting the US intensity calibration.

Stimulus Sequence: Stimulus sequence for pre-acquisition, acquisition as well as generalization phase were pseudorandomized across groups and participants. Presentation of the stimulus sequence, electrical stimulation and startle probes were controlled by Presentation (Neurobehavioral System). All stimuli were presented on a monitor screen (17'', resolution 1024 x 786 x 32 pixel, picture size 456 x 456 pixel). Regarding the *pre-acquisition* and *acquisition phase*, a random sequence for six blocks (pre-acquisition) and 12 blocks (acquisition), each containing a CS+/CS- and an ITI, was created. Next, three pseudorandomized sequences (swapping position of a) CS+ and CS- stimuli, b) CS+ and ITI; c) CS- and ITI) were developed. The *generalization phase* comprised a random sequence for four blocks, each containing two presentations of the CS+/CS- and the ITI, as well as one presentation of each GS. Next, 17 pseudorandomized sequences (within each block, stimuli were rotated, meaning that each stimuli is placed on each possible position within a particular block) were created.

Behavioral Measures: Online risk ratings (ORR) were the evaluations of the risk of the occurrence of an electric shock associated with the presented stimulus (10 point Likert

ranging from 1 = no risk, to 10 = high risk). Additionally, reaction times of ratings were measured. To indicate their response, subjects had to move a red dot from a starting area to one of 10 target area displayed in an equal distance to the starting area.

Physiological Measures: Fear potentiated startle (FPS) was measured as the potentiated eyeblink startle reflex to a loud noise by electromyography (EMG) of the (left) orbicularis oculi muscle. The acoustic startle reflex is a specific measure for fear (Hamm & Weike, 2005), and is directly connected with and modulated by the amygdala (Davis, 2006). The noise consisted of a burst of white noise (40 ms, 95 dB, bandwith of 20 Hz – 20 kHz) and was presented binaurally via headphones (Sennheiser HD 25-1-II). Two electrodes with a diameter of 13 mm each, filled with electrolyte gel (Synapse, Costumer Kinetics) positioned approximately 1 cm under the pupil and 1 cm below the lateral canthus (Blumenthal et al., 2005). The eye-blink EMG activity was measured with an EMG amplifier (Varioport, Becker Meditec, input resistance of 500 MΩ, bandwidth of 19–500 Hz (-3dB), sampling rate 1024Hz). EMG data were pre-processed using in-house software (MatLab 2011b, MathWorks) following a standard procedure: Raw data were filtered (50Hz notch filter, 28-Hz high-pass filter, 4th order Butterworth filter), rectified and smoothed (low-pass filter 50Hz). Startle amplitude was measured as the maximum peak within a time window of 20-150 ms following the onset of the startle probe referenced to mean baseline level (50 ms before onset of the startle probe). Outliers were defined (z-transformation overall trials, within-subject; $Z > 3$) and replaced by the maximum z-score. Trials were visually inspected and excluded from further analyses, when the baseline period is contaminated with noise and movement artifacts (Blumenthal et al., 2005). Missing startle responses were scored as 0 and entered in the calculation of the FPS magnitude. To normalize the data and to reduce the influence of between-subjects variability, startle amplitudes in response to inter stimulus intervals (NA trials) across all phases of the study were standardized together using within-subject t-score conversion (Lissek et al., 2008).

Statistical Analyses: Exclusion Criteria:

Overall, 2 participants within the TC group, as well as 3 participants within the PTSD and 4 of the HC group had to be excluded of all FPS analyses due to a startle signal contaminated by technical artifacts.

Regarding missing values, subjects were excluded in case of more than one out of three trials during pre-acquisition, more than two out of six trials during acquisition and more than two trials out of four during generalization testing (herein, one trial needed to correspond to each generalization stimuli of each class) were missing for each dependent variable and phase separately. With respect to ORR and RTs, four subjects had to be excluded within the pre-acquisition analyses (PTSD = 1, TC = 3). Regarding FPS, one subject had to be

excluded within the pre-acquisition analyses (TC = 1), and 4 subjects within the acquisition and generalization analyses (TC = 1, HC = 3).

In addition, subjects were excluded, if they were statistical outliers. Boxplot analyses have been conducted for each phase, respectively. Herein, the difference in response between the CS+ and the CS- within each phase represented the variable of interest. Subjects were excluded, if the depended variable exceeded >/<= 3 * interquartile range for each dependent variable and phase separately. Regarding ORR, one subject had to be excluded during generalization testing (PTSD = 1). With respect to RT, one subject had to be excluded of all analyses (TC = 1).

Regarding online risk ratings, subjects were excluded if they did not report a CS+/US and CS-/no US contingency. Declarative memory of a CS+/US and CS-/no US contingency was defined as a greater ORR response to the CS+ than CS- during the end of fear acquisition phase (trial 5 and 6). Subjects were thus further excluded from ORR generalization testing (PTSD = 2).

C1.7.3 Supplemental Results

Generalization Testing:

Online Risk Ratings (ORR): ORR differed between stimulus types, irrespective of the group ($F_{5,420}$ = 253.05, p <.001; stimulus type x group: $F_{10,420}$ = 1.44, p = .162; Table 2C, Figure 5). Trend analyses of the generalization gradient indicated significant linear and quadratic slopes for the stimulus type across all groups (linear: stimulus type: $F_{1,84}$ = 563.81, p < .001; stimulus type x group: $F_{2,84}$ = 1.38, p = .258; quadratic: stimulus type: $F_{1,84}$ = 100.76, p < .001; stimulus type x group: $F_{2,84}$ = .72, p = .491). To further describe this effect, ORR ratings for GS und CS+ stimuli were compared with the CS-, according to the procedure of Lissek et al (2010). These comparisons serve to determine at which degree of dissimilarity between a stimulus and the CS- increased risk is reported, i.e. to which degree of perceptual similarity fear generalized. All groups reported higher ORR to the CS+ and the three generalization classes most similar to the CS+, i.e. class 1, 2, and 3 (p < .001), but not for the generalization class most similar to the CS-, i.e. class 4 (p > .1).

Fear Potentiated Startle (FPS): FPS did differ between stimulus types, irrespective of the group ($F_{5,370}$ = 18.86, p < .001; $F_{10,370}$ = .56, p = .844; Table 2C, Figure 5). Trend analyses of the generalization gradient indicated significant linear slopes for the stimulus type across all groups (stimulus type: $F_{1,74}$ = 92.39, p < .001; stimulus type x group $F_{2,74}$ = 1.33, p = .270). To further describe this effect, FPS in response to each GS und CS+ was compared with the CS-, respectively. All groups showed increased FPS to the CS+ and the two generalization classes most similar to the CS+, i.e. class 1 and 2 (p < .001), but not for the remaining generalization classes, i.e. class 3 and 4 (all p > .189).

Perceptual Discrimination Task:

Similarity ratings did not differ between groups ($F_{2,86}$ = 1.83, p = .166). Similarity ratings differed between comparison stimuli depending on the reference stimuli ($F_{5,430}$ = 13.27, p < .001). Similarity ratings were higher, when the CS+ was the reference stimulus (p's < .023), except when comparing the CS+ and CS- to each other (p = .669). There was no further significant interaction effect (all p's > .238).

C2. STUDY II: DESYNCHRONIZATION OF AUTONOMIC RESPONSE AND CENTRAL AUTONOMIC NETWORK CONNECTIVITY IN POSTTRAUMATIC STRESS DISORDER

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C2.1 Abstract

Objectives: Although dysfunctional emotion regulatory capacities are increasingly recognized as contributing to posttraumatic stress disorder (PTSD), little work has sought to identify biological markers of this vulnerability. Heart rate variability (HRV) is a promising biomarker that, together with neuroimaging, may assist in gaining a deeper understanding of emotion dysregulation in PTSD. The objective of the present study was therefore to characterize autonomic response patterns, and their related neuronal patterns in individuals with PTSD at rest.

Methods: PTSD patients (N=57) and healthy controls (N=41) underwent resting-state fMRI. Connectivity patterns of key regions within the central autonomic network (CAN) - including the ventromedial prefrontal cortex (vmPFC), amygdala, and periaqueductal grey (PAG) - were examined using a seed-based approach. Observed connectivity patterns were then correlated to resting HRV.

Results: In contrast to controls, individuals with PTSD exhibited lower HRV. In addition, whereas controls engaged a localized connectivity pattern of CAN-related brain regions, in PTSD, key CAN regions were associated with widespread connectivity patterns in regions related to emotional reactivity (vmPFC and amygdala to insular cortex and lentiform nucleus; PAG to insula) and motor readiness (vmPFC and amygdala to precentral gyrus; PAG to precentral gyrus and cerebellum). Critically, whereas CAN connectivity in controls was strongly related to higher HRV (insula, mPFC, superior frontal cortex, thalamus), HRV covariation was absent in PTSD subjects.

Conclusions: This study provides the first evidence for a specific psychophysiological – neuronal profile in PTSD individuals characterized by lower resting HRV and a lack of HRV covariation with CAN-related brain connectivity.

C2.2 Introduction

As evidenced by the newly added symptoms of “negative alterations in cognition and mood” and the “inability to experience positive emotions” in the DSM-5 (2013), posttraumatic stress disorder (PTSD) is increasingly acknowledged as involving persistent negative emotional states. The integration of heightened negative states and the decreased ability to experience positive emotions into these diagnostic guidelines highlights an emerging focus on emotion regulatory capacities in PTSD (Friedman, Resick, Bryant, & Brewin, 2011; Lanius, Bluhm, & Frewen, 2011; Lanius, Frewen, Tursich, Jetly, & McKinnon, 2015; Nawijn et al., 2015; Powers, Cross, Fani, & Bradley, 2015; Powers, Etkin, Gyurak, Bradley, & Jovanovic, 2015; Resick et al., 2008; Sadeh et al., 2015; Taylor, 2015; van Wingen, Geuze, Vermetten, & Fernandez, 2011). Accordingly, numerous studies have begun to characterize emotional dysregulation associated with contrasting states of emotional under- and over-modulation. These opposing states have been linked to the experience of heightened or depressed emotionality, including re-experiencing symptoms and a detachment from emotional experience that occurs during emotional numbing and states of depersonalization and derealization, respectively (Etkin & Wager, 2007; Lanius, Vermetten, et al., 2010; Nicholson et al., 2015; Reinders et al., 2014; Wolf et al., 2014).

Heart rate variability (HRV) is one promising psychophysiological indicator that may assist in gaining a deeper understanding of emotion regulatory capacity in PTSD. HRV reflects vagal activity that indexes the state of the autonomic nervous system (ANS), enabling the organism to calibrate bodily, emotional, and cognitive reactions to contextual demands. The ANS is separated into two branches, normally behaving in a balanced fashion: the parasympathetic nervous system (PNS), associated with restorative and vegetative functioning, and the sympathetic nervous system (SNS), linked to energy mobilization. Imbalance of these two branches is associated with blunted flexibility to react to environmental changes, increased vulnerability to somatic diseases, and has been associated with mental disorders (Carney & Freedland, 2009; Stein et al., 2000; Thayer & Brosschot, 2005). Thus, HRV is thought to guide the individual`s ability to organize emotional, cognitive, and behavioral responses, and higher levels of HRV to be a physiological index of the ability to respond in a context appropriate manner (Gillie & Thayer, 2014; Melzig, Weike, Hamm, & Thayer, 2009; Thayer & Lane, 2000).

To date, HRV investigations in PTSD have revealed that indices of high-frequency HRV (HF-HRV) and root mean squared successive differences (RMSSD) of the inter-beat interval time series at rest, both indexing activity of the PNS, are reduced as compared to both trauma and non-trauma exposed healthy control subjects (for meta-analyses see Chalmers, Quintana, Abbott, & Kemp, 2014; Sammito, Thielmann, Zimmermann, & Bockelmann, 2015; but see Agorastos et al., 2013; Keary et al., 2009 for null findings). Fewer studies have

addressed cardiac response to stressful tasks, revealing heterogeneous findings (Cohen, Benjamin, et al., 2000; Cohen et al., 1998; Hauschildt et al., 2011; Keary et al., 2009; Norte et al., 2013). Whereas three studies failed to identify differential effects of affective cues or stressful tasks on HRV response in PTSD as compared to control subjects (Cohen, Benjamin, et al., 2000; Cohen et al., 1998; Hauschildt et al., 2011), two studies reported a greater decrease of HRV in response to stressful tasks or trauma script exposure (Keary et al., 2009; Norte et al., 2013).

A growing number of studies have investigated the relation between HRV and neural activation, where the central autonomic network (CAN) is thought to serve as a critical link between the brain and the ANS (for meta-analyses see Beissner et al., 2013; Thayer et al., 2012). The CAN is comprised of the ventromedial prefrontal cortex (vmPFC), anterior cingulate (ACC), insular cortex, amygdala, hypothalamus, periaqueductal grey, parabrachial complex, nucleus of the tractus solitaris, and the ventrolateral medulla (Benarroch, 1993; Cersosimo & Benarroch, 2013; Palkovits, 1999; Thayer & Brosschot, 2005). These components are reciprocally interconnected, with higher-order cortical functions associated with cognitive functioning regulating the response of subcortical structures, which in turn regulate autonomic input to the heart and allows for the complex variability that characterizes the healthy HR time series (Thayer & Brosschot, 2005). Despite this knowledge, to date, no studies to date have examined connectivity in CAN regions in association with HRV in PTSD.

The aim of the present study was therefore to investigate the functional neural correlates of autonomic activity in individuals with PTSD as compared to controls. As studies in PTSD have suggested not only lower HRV in PTSD but also alterations in top-down modulatory processes on a neuronal level (Etkin & Wager, 2007; Lanius, Vermetten, et al., 2010; Nicholson et al., 2015; Reinders et al., 2014; Wolf et al., 2014), combining resting HRV and neural activation will facilitate a greater understanding of altered emotion regulatory processes in this disorder. Specifically, we investigated resting state neural connectivity patterns using fMRI and their HRV-related associations with three seed regions that comprise key nodes of the CAN: 1) ventromedial prefrontal cortex; 2) amygdala; and 3) the periaqueductal grey (Beissner et al., 2013; Thayer et al., 2012; Thayer & Lane, 2000). Consistent with prior findings indicating impaired emotion regulation capacity, we hypothesized that individuals with PTSD would exhibit diminished HRV (Chalmers et al., 2014; Sammito et al., 2015) and show reduced correlations between HRV scores and connectivity between key structures of the CAN as compared to healthy controls (Beissner et al., 2013; Thayer et al., 2012).

C2.3 Methods

C2.3.1 Sample Discription

Ninety-eight participants were included in the current study: 57 individuals with a primary diagnosis of PTSD and 41 healthy control subjects. Subjects were recruited between 2009 and 2015 from the Department of Psychiatry London Health Services Center (LHSC), through family physician, mental health professionals, psychology/ psychiatric clinics, community programs for traumatic-stress survivors, and posters/ advertisements, all within the London, ON community. PTSD diagnosis was confirmed via the Clinician-Administered PTSD scale, with a cut-off score of 50 for moderate PTSD (Blake et al., 1995). Co-morbid Axis I disorders were diagnosed with the Structured Clinical Interview for DSM-IV Axis I Disorders (First, 1997). Childhood trauma history was assessed with the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003), as well as depressive symptoms with the Beck Depression Inventory (BDI; Beck, Guth, Steer, & Ball, 1997). Subjects also completed the Multiscale Dissociation Inventory (MDI; Briere, Weathers, & Runtz, 2005), capturing dissociative experiences. Immediately after the resting state scanning procedure, subjects were instructed to rate their state anxiety (3 items of the State-Trait Anxiety Inventory: STAI-S; Kvaal, Ulstein, Nordhus, & Engedal, 2005) and their level of state dissociation, re-experiencing, avoidance, and hyperarousal symptoms by means of the Response to Script Driven Imagery Scale (RSDI; Hopper, Frewen, Sack, Lanius, & Van der Kolk, 2007). Clinical and socio-demographic variables are presented in Table 4.

Exclusion criteria for all participants comprised implants or metals that do not comply with 3T fMRI safety standards for research, a history of head injury with any loss of consciousness, significant untreated medical illness, a history of neurological disorders, history of any pervasive developmental disorders, pregnancy, and current use of any psychotropic or cardiovascular medications within one month prior to study (except 1 subject). Further exclusion criteria for individuals with PTSD were a history of bipolar disorder or schizophrenia, alcohol or substance abuse/ dependence not in sustained full remission within 6 month prior to participation of the study, while healthy control subjects had to be free of any lifetime Axis-I mental disorder. Scanning took place either at the Robarts Research Institute's Center for Functional and Metabolic Mapping or at the Lawson Health Research Institute for Imaging in London, ON, Canada. The study was approved by the research ethics board at Western University of Canada. All subjects provided written informed consent.

Table 4. Sociodemographic, clinical and physiological sample characteristics study II.

	PTSD N = 57		HC N = 41		F/χ Value	*p*
Demographics						
age mean (SD)	33.98	(11.57)	37.11	(12.80)	.96	.33
gender (N)						
female	18		26		.27	.61
male	39		15			
Clinical Characteristics						
CAPS Re-experiencing mean (SD)	21.96	(6.73)	-		-	-
CAPS Avoidance/ Numbing mean (SD)	26.22	(7.00)	-		-	-
CAPS Hyperarousal mean (SD)	22.41	(5.99)	-		-	-
CAPS Total mean (SD)	69.16	(15.47)	-		-	-
MDI Depersonalization mean (SD)	8.11	(3.59)	5.24	(0.69)	22.45	<.001
MDI Derealization mean (SD)	9.89	(4.12)	5.27	(0.66)	47.18	<.001
MDI Total mean (SD)	61.96	(20.07)	34.15	(4.04)	64.31	<.001
CTQ mean (SD)	62.47	(23.29)	31.28	(8.37)	65.61	<.001
BDI mean (SD)	26.73	(9.79)	1.54	(2.60)	234.37	<.001
State Characteristics						
STAI-S (SD)	1.97	(.76)	1.22	(.42)	32.66	<.001
RSDI Dissociation (SD)	1.51	(.61)	1.14	(.21)	17.60	<.001
RSDI Re-Experiencing (SD)	1.46	(.67)	1.06	(.19)	16.77	<.001
RSDI Avoidance (SD)	2.04	(1.06)	1.35	(.76)	14.33	<.001
RSDI Hyperarousal (SD)	1.67	(.56)	1.18	(.26)	34.95	<.001
Comorbidities (%)						
Alcohol dependence	0		0			
MDD	18		0			
Panic Disorder w/wo Agoraphobia	11		0			
Social Phobia	7		0			
Specific Phobia	3		0			
Generalized Anxiety Disorder	0		0			
Obsessive Compulsive Disorder	2		0			
Somatization Disorder	5		0			
Somatoform Disorder	8		0			
Eating Disorder	1		0			
HRV characteristics						
RMSDD mean^ (SD)	3.76	(0.09)	4.06	(0.11)	4.79	.031
LF power value mean^ (SD)	6.05	(0.20)	6.91	(0.23)	8.34	.005
HF power value mean^ (SD)	6.35	(0.19)	6.93	(0.25)	4.14	.045

Significance threshold p < .05
Abbreviations: PTSD = posttraumatic stress disorder group; HC = healthy control group; CAPS= Clinician-Administered PTSD scale*; MDI* = Multiscale Dissociation Inventory*; CTQ =Childhood Trauma Questionnaire; BDI* = Beck Depression Inventory*; STAI-S* = State-Trait Anxiety Inventar *; RSDI* = Response to Script Driven Imagery Scale *; MDD = major depressive disorder; RMSSD = root-mean square differences of successive R-R intervals; LF-HRV = low frequency heart rate variability, HF – HRV = high frequency heart rate variability, = natural logarithm*

C2.3.2 fMRI Data Acquisition

All images were collected using a 3.0, whole-body MRI scanner (Magnetom Tim Trio, Siemens Medical Solutions, Erlangen, Germany) with a manufacturer's 32-channel phased array head coil. BOLD fMRI images were obtained with the standard gradient-echo EPI pulse sequence. EPI volumes were acquired with 2 mm isotropic resolution with the following parameters: FOV = 192 mm X 192 mm X 128 mm (94 x 94 matrix, 64 slices), TR/ TE = 3000 ms/ 20 ms, flip angle = 90°, 120 volumes. Participants were instructed to close their eyes, relax and let their minds wander during the 6-min resting scan.

C2.3.3 Statistical Analyses

HRV Analysis:

Pulse data were recorded using a finger-tip pulse oximeter (Powerlab 8/35, LabChart 7 Pro) during the 6-min resting functional MRI scanning procedure and sampled at 200 Hz (Robarts Research Institute) or 40 Hz (Lawson Health Science Institute). Pulse data acquired at 40 Hz were re-sampled at 200 Hz by linear interpolation. In-house software provided by Stefanie Lis was applied for peak detection and visual inspection of the pulse signal. The inter-beat time series were saved as text files and imported to the KUBIOS Heart Rate Variability Software Package (Kuopio, Finland; version 2.2, (Tarvainen, Niskanen, Lipponen, Ranta-Aho, & Karjalainen, 2014). Data were then re-sampled at 4 Hz and common time domain measures were computed (RMSSD). Frequency domain estimates of HF-HRV and LF-HRV were calculated following the Task Force Guidelines (1996). Spectral analysis using a Fast Fourier transform (FFT) algorithm, with a window width of 256 s and a window overlap of 50 % was applied to generate heart period power spectrum. Frequency bands were set to 0.04-0.15 for the LF component and 0.15-0.4 for the HF component, respectively (Kuopio, Finland; version 2.2, (Tarvainen et al., 2014). Raw measurements, including RMSSD, HF-HRV, and LF-HRV were natural log transformed before the analysis in order to normalize their distributions. Further analyses were performed using SPSS (version 22; SPSS Inc., USA). Group differences in HRV measurements were assessed with multivariate analyses of variance (MANOVA).

fMRI Analysis:

Image preprocessing and statistical analyses of the BOLD signal were conducted using Statistical Parametric Mapping (SPM 8, Wellcome Trust Center of Neuroimaging, London, UK: http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 8.3 and 11b (MathWorks Inc.).

Preprocessing:

For each subject, all functional images were realigned to the first image in their series, re-sliced and the mean functional image created. ART software (Gabrieli Lab; McGovern Institute for Brain Research, Cambridge, MA) was used to compute motion outlier regressors, which were applied within the 1st level analysis as a covariate of no interest.

Given that an increasing body of literature points to an influence of head movement on functional connectivity measurements (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Power et al., 2014; Pujol et al., 2014; Satterthwaite et al., 2013; Satterthwaite et al., 2012), we wanted to further ensure that groups did not differ with regard to their frequency of defined outliers. We therefore coded whether the ART software detected any outliers within each individual scan and subsequently ran a Fisher's exact test to examine potential group differences. Here, group differences were not observed (p = .520). The images were further spatially normalized and the mean image was co-registered to the SPM EPI template. The resulting deformation matrix was applied to the functional images. All images were then smoothed using a 6 mm full-width-half-maximum isotropic Gaussian filter and band-pass filtered within a 0.012 - 0.1 Hz range with in house software by Jean Théberge.

Connectivity Analysis:

For each subject, the mean signal intensity time course was extracted from seeds defined in WFU PickAtlas (Functional MRI Laboratory, Wake Forest University School of Medicine, USA) using in-house software by co-author Jean Théberge for each seed region, including the vmPFC ([2 22 -8]; Thayer et al., 2012), right and left amygdala (WFU PickAtlas), and PAG ([-2, -27, -3]; Napadow et al., 2008). All seed regions were based on previous publications and defined as 6 mm spheres for each reported coordinate. Extracted time courses were then used as a regressor within a 1st level multiple regression model for each seed region. Connectivity was thus indicative of a correlation between each seed and other brain areas, where both positive correlations and anti-correlations were examined.

To explore connectivity patterns within groups, one sample t-tests were conducted for each group separately. In order to control for the effects of a current major depression, we re-ran the within-group PTSD analyses by applying a multivariate analysis of covariance (MANCOVA) and including the comorbid diagnosis as a covariate of no interest. Two sample t-tests were used to compare PTSD with healthy control subjects for each seed region. Statistical significance was set at a p-value of < .001 corrected for whole brain FDR and an extent threshold of k = 10 voxels.

Correlations between HRV and BOLD Functional Connectivity:

In order to examine associations between HRV and CAN - related connectivity patterns, separate multiple regression analyses for RMSSD, LF-HRV and HF-HRV scores were examined; each of these scores revealed significant differences between groups. PAG seed correlations were masked with a CAN mask. The CAN mask was created in WFU PickAtlas based on 10 mm spheres on prominent coordinates published in previous literature (Beissner et al., 2013; Thayer et al., 2012), that is, bilateral amygdala ([-20 -6 -18] & [20 -6 -18]; Beissner et al., 2013), right medial prefrontal cortex ([10 54 18]; Thayer et al., 2012), right dorsal cingulate ([2 10 40]; Beissner et al., 2013); left thalamus ([-4 -16 8]; Beissner et al.,

2013). Two additional masks were created, comprising the bilateral insula from the WFU PickAtlas applied to the vmPFC seed correlation, as well as a PAG mask (Napadow et al., 2008) applied to the right and left amygdala seed correlations, each with a 10 mm radius. A 2nd level multiple regression model was established for each seed in combination with each HRV score, respectively. Simple multiple regression models examining both positive and negative associations between scores were conducted and the results masked with the CAN and insula mask. Two-samples t-tests were used to compare PTSD with healthy controls for each seed region and each HRV score respectively, with a covariate (HRV score), and a term that computes the interaction between the covariate and factor group. The interaction effect indicates regions for which the functional connectivity with the seed region is greater in people that have greater HRV scores in controls than individuals with PTSD (and vice versa). Significance was set to $p < .05$, ROI FDR corrected and an extent threshold of k = 10 voxels.

C2.4 Results

C2.4.1 Cardiovascular Responding (HRV)

As compared to controls, individuals with PTSD showed lower RMSSD values ($F_{(1,96)} = 4.79$, $p = .031$, $\eta^2 = .048$), lower LF power ($F_{(1,96)} = 8.34$, $p = .005$, $\eta^2 = .080$) and lower HF power ($F_{(1,96)} = 4.14$, $p = .045$, $\eta^2 = .041$) (see also Figure 6, Table 4).

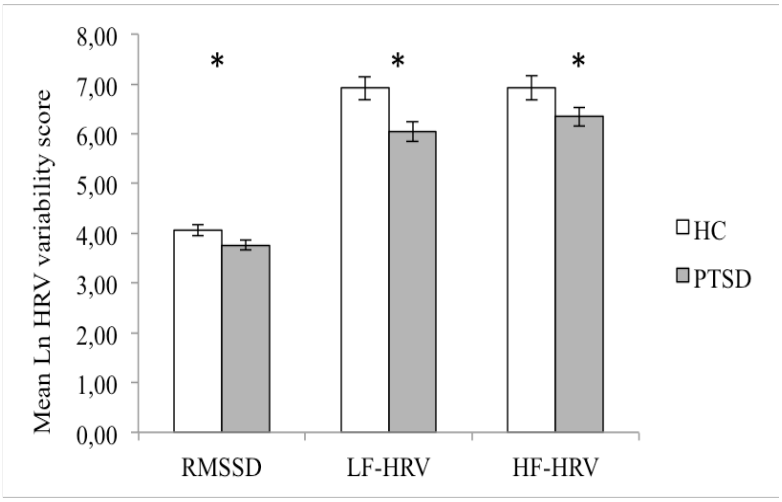

Figure 6. Between group differences in HRV
Figure represents significant lower Mean Natural Log RMSSD, LF-HRV, and HF-HRV in PTSD as compared to the control group (all $F_{(1,96)}$'s > 4.14, all p's < .048).
Statistical threshold p < .05.
Abbreviations: PTSD = posttraumatic stress disorder group; HC = healthy control group; RMSSD = root-mean square differences of successive R-R intervals; LF-HRV = low frequency heart rate variability, HF – HRV = high frequency heart rate variability, ln = natural logarithm

C2.4.2 Seed based functional connectivity

Ventromedial Prefrontal Cortex:

Resting-state activity in the vmPFC predicted a localized connectivity pattern within control subjects. In contrast, vmPFC activity predicted widespread connectivity to multiple cortical and subcortical regions in PTSD. Adding current major depression as a covariate did not change the results (for details on each seed regions see Table 7, Figure 9). Between-group comparisons indicated that HC individuals did not exhibit any significantly greater connectivity to the vmPFC as compared to PTSD individuals. By contrast, PTSD subjects exhibited greater functional connectivity between the vmPFC and cingulate cortex, frontal cortex, bilateral precentral gyrus, left insula, left parahippocampal gyrus, bilateral lentiform nuclei, and left thalamus (see also Figure 7A, Table 11).

Amygdala:

Resting state connectivity with the left and right amygdala predicted a restricted connectivity pattern in controls. In contrast, among individuals with PTSD, left and right amygdala activity predicted widespread connectivity patterns in multiple cortical and subcortical regions. Adding current major depression as a covariate did not change the results (for details on each seed regions see Table 8 & 9, Figure 9). Between-group comparisons indicated that HCs did not exhibit significantly greater connectivity to either the left or the right amygdala as compared to individuals with PTSD. By contrast, PTSD individuals exhibited greater functional connectivity between the left amygdala and the cingulate cortex, frontal cortex, left anterior insular cortex, bilateral parahippocampal gyrus, bilateral thalamus and lentiform nucleus (see also Figure 7B, Table 12). Similarly, individuals with PTSD showed greater functional connectivity between the right amygdala and the cingulate cortex, frontal cortex, bilateral precentral gyrus, right parahippocampal gyrus, bilateral posterior, right anterior insular cortex, and bilateral lentiform nuclei (see also Figure 7B, Table 13).

Periaqueductal grey:

Resting-state activity in the PAG predicted a localized connectivity pattern in control individuals. In contrast, PAG activity predicted widespread connectivity in multiple cortical and subcortical regions in PTSD subjects. Adding current major depression as a covariate did not change the results (for details on each seed regions see Table 10, Figure 9). HC subjects did not show any greater connectivity to the PAG as compared to PTSD subjects. In contrast, individuals with PTSD showed greater functional connectivity between the PAG seed and the bilateral mid cingulate cortex, left dorsal cingulate cortex, bilateral medial frontal gyrus, left superior frontal gyrus, left precentral gyrus, left anterior and posterior insular cortex, bilateral putamen, left thalamus, hippocampus, and right cerebellar vermis (see also Figure 7C, Table 14).

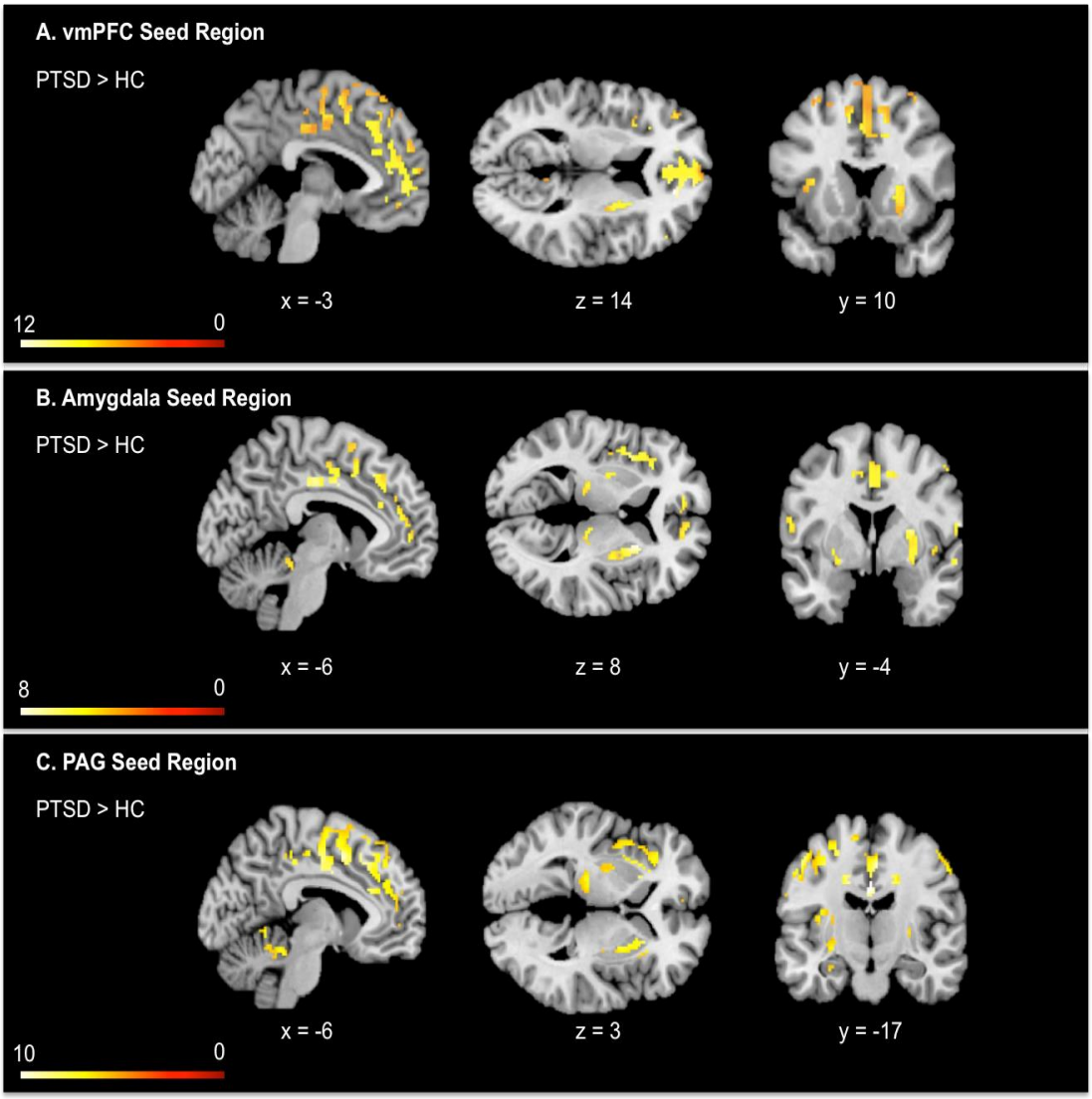

Figure 7. Between group differences in key CAN seed resting state functional connectivity, including vmPFC, amygdala, PAG

Illustration represents greater connectivity between key CAN seed regions, including the vmPFC, amygdala, and PAG with multiple cortical and subcortical regions in PTSD as compared to healthy controls. By contrast, HC individuals did not exhibit any significantly greater connectivity to any of the CAN seed regions as compared to PTSD individuals.

Statistical threshold p < .001 corrected for whole brain FDR, k = 10 for all 2-sample t-tests.

Abbreviations: PTSD = posttraumatic stress disorder group; HC = healthy control group; vmPFC = ventromedial prefrontal cortex; PAG = periaqueductal grey; FDR = false discovery rate

C2.4.3 HRV correlations to CAN related functional connectivity

Ventromedial prefrontal cortex:

In control subjects, higher RMSSD, LF-HRV and HF-HRV values predicted increased functional connectivity between the vmPFC and the right insula (see also Figure 8A, Table 5). In contrast, none of the HRV scores were related to increased or decreased connectivity between the vmPFC and CAN-related brain regions among individuals with PTSD (Table 5). Direct group comparisons revealed that none of the HRV scores predicted increased functional connectivity between the vmPFC and CAN related brain regions in neither controls as compared to PTSD, nor within the reversed contrast (see also Table 6 for additional information regarding FWE corrected results).

Amygdala:

In control subjects, higher RMSSD, as well as higher LF-HRV and HF-HRV values predicted increased connectivity between the left amygdala and the left PAG, while none of the HRV scores were related to the functional connectivity of the right amygdala in controls (see also Figure 8B, Table 5). In individuals with PTSD, none of the HRV scores were related to increased or decreased connectivity between the left or right amygdala and CAN-related brain regions (Table 5). Direct group comparisons revealed that none of the HRV scores predicted increased connectivity between the left amygdala and CAN related brain regions in controls as compared to PTSD, nor within the reversed contrast (see also Table 6 for additional information regarding FWE corrected results). Direct group comparisons revealed that higher RMSSD and HF-HRV values predicted increased connectivity between the right amygdala and the right insula in controls as compared to PTSD. In contrast, none of the HRV scores predicted increased connectivity patterns to the right amygdala in PTSD patients as compared to controls (see also Table 6 for additional information regarding FWE corrected results).

Periaqueductal grey:

In control subjects, higher RMSSD and HF-HRV values also predicted increased functional connectivity between the PAG and the right dorsal cingulate cortex, right medial prefrontal cortex, right superior frontal gyrus and left thalamus. In contrast, LF-HRV did not predict functional connectivity between the PAG and CAN-related brain regions in HC subjects, nor did any of the HRV scores predicted increased functional connectivity patterns to the PAG in PTSD (see also Figure 8C, Table 5). Direct group comparisons revealed that higher HF-HRV values predicted increased functional connectivity between the PAG and the right insula in controls as compared to PTSD. In contrast, none of the HRV scores predicted increased connectivity patterns to the right amygdala in PTSD patients as compared to controls (see also Table 6 for additional information regarding FWE corrected results).

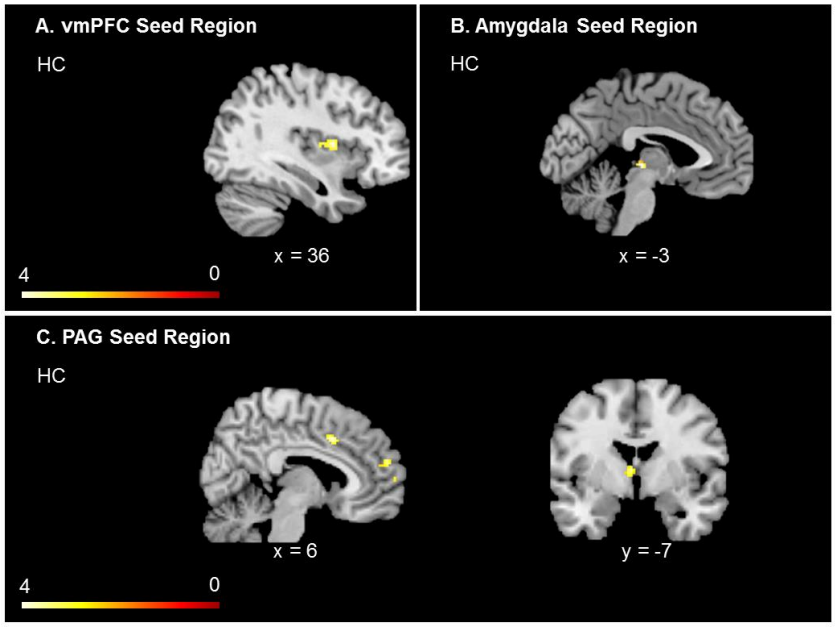

Figure 8. HRV correlations related connectivity to key CAN seed regions within healthy control subjects, including vmPFC, amygdala, PAG

Illustration represents increased functional connectivity patterns to all CAN regions in controls, which is predicted by HRV. In PTSD, analyses did not reveal significant clusters; only healthy control subjects are therefore presented.

Significance threshold p < .05, ROI FDR corrected, k = 10 voxels for all one-sample t-tests.

Abbreviations: PTSD = posttraumatic stress disorder group; HC = healthy control group; vmPFC = ventromedial prefrontal cortex; PAG = periaqueductal grey; ROI = region of interest analysis

Table 5. HRV correlations related connectivity to key CAN seed regions
within healthy control subjects, as well as within PTSD individuals, including the vmPFC, amygdala, PAG.

HRV Score	Brain Regions	BA	r/l^	*x*	*y*	*z*	*k*	*T-value*	*pFDR*	*pFWE*
vmPFC										
HC										
RMSSD	insula	13	R	34	-2	14	55	4.24	.057	.031
HF-HRV	insula	13	R	34	-2	14	116	4.12	.022	.023
LF-HRV	insula	13	R	38	-12	14	49	4.05	.058	.049
PTSD										
n.s.										
left Amygdala										
HC										
RMSSD	PAG, Pulvinar		L	-4	-26	4	15	4.02	.010	.013
HF-HRV	PAG, Pulvinar		L	-4	-28	4	14	4.05	.010	.012
LF-HRV	PAG, Pulvinar		L	-6	-28	4	8	3.15	.055	.092
PTSD										
n.s.										
right Amygdala										
HC										
n.s.										
PTSD										
n.s.										
PAG										
HC										
RMSSD	dorsal cingulate cortex	32	R	6	8	44	87	4.5	.028	.021
	medial frontal cortex	9	R	4	52	24	55	4.33	.028	.033
	medial frontal cortex	10	R	4	56	12	Of55	3.25	.038	.346
	medial frontal cortex	9	R	4	46	18	Of55	2.85	.044	.616
	thalamus	md nucl.	L	-4	-8	10	18	3.97	.028	.080
	superior frontal cortex	10	R	18	58	22	14	3.23	.038	.358
HF-HRV	medial frontal cortex	9	R	4	52	24	63	4.44	.036	.025
	thalamus	md nucl.	L	-4	-8	10	26	4.25	.036	.040
	dorsal cingulate cortex	32	R	6	8	44	32	3.59	.038	.181
	superior frontal cortex	10	R	18	58	22	12	3.26	.049	.341
LF-HRV	n.s.									
PTSD										
n.s.										

Significance threshold p < .05, ROI FDR corrected, k = 10 voxels for all one-sample t-tests
Abbreviations: ^ = right/ left hemisphere; PTSD = posttraumatic stress disorder group; HC = healthy control group; vmPFC = ventromedial prefrontal cortex; PAG = periaqueductal grey; md nucl = mediodorsal nucleus; FDR = false discovery rate; FWE = family wise error, RMSSD = root-mean square differences of successive R-R intervals; LF-HRV = low frequency heart rate variability, HF – HRV = high frequency heart rate variability; BA = Brodmann Areal

Table 6. HRV correlations related connectivity to key CAN seed regions
for healthy control subjects greater than PTSD, as well as for the reversed contrast including the vmPFC, amygdala, PAG.

HRV Score	Brain Regions	BA	r/l^	*x*	*y*	*z*	*k*	*T-value*	*pFDR*	*pFWE*
vmPFC										
HC>PTSD										
RMSSD	insula	13	R	54	2	-6	20	3.16	.147	.050
HF-HRV	insula	13	R	54	2	-6	24	3.19	.094	.049
LF-HRV		n.s.								
PTSD>HC										
n.s.										
left Amygdala										
HC>PTSD										
RMSSD	insula	13	R	54	2	-6	5*	3.08	.208	.055
HF-HRV		n.s.								
LF-HRV		n.s.								
PTSD>HC										
n.s.										
right Amygdala										
HC>PTSD										
RMSSD	insula	13	R	54	2	-8	28	3.95	.015	.007
HF-HRV	insula	13	R	54	2	-8	23	3.6	.034	.020
LF-HRV		n.s.								
PTSD>HC										
n.s.										
PAG										
HC>PTSD										
RMSSD	insula	13	R	48	16	-2	20	2.85	.212	.049
HF-HRV	insula	13	R	48	16	-2	33	3.07	.036	.065
LF-HRV		n.s.								
PTSD>HC										
n.s.										

Significance threshold p < .05, ROI FDR corrected, k = 10 voxels for all 2-sample t-tests
Abbreviations: ^ = right/ left hemisphere; PTSD = posttraumatic stress disorder group; HC = healthy control group; vmPFC = ventromedial prefrontal cortex; PAG = periaqueductal grey; FDR = false discovery rate; FWE = family wise error, RMSSD = root-mean square differences of successive R-R intervals; LF-HRV = low frequency heart rate variability, HF – HRV = high frequency heart rate variability; BA = Brodmann Areal

C2.5 Discussion

To the best of our knowledge, this is the first study to investigate autonomic response and its relation to resting state central autonomic activity in individuals with PTSD. As hypothesized, as compared to controls, individuals with PTSD showed reduced resting HRV. At the neuronal level, resting-state activity in CAN-associated brain regions, including the vmPFC, amygdala, and PAG predicted a localized and restricted connectivity pattern in control subjects. In stark contrast, individuals with PTSD exhibited widespread functional connectivity to brain regions involved in emotional reactivity (Kirby & Robinson, 2015; White, Costanzo, Blair, & Roy, 2015), motor readiness (Herzfeld et al., 2014; Mendoza & Merchant, 2014; Stoodley & Schmahmann, 2010; Stoodley, Valera, & Schmahmann, 2012), self-referential processing (Bluhm et al., 2011; Bluhm et al., 2012; Buckner, Andrews-Hanna, & Schacter, 2008; Spreng, Mar, & Kim, 2009), and stimuli salience detection (Craig, 2009; Sripada et al., 2012; Thome, Frewen, Daniels, Densmore, & Lanius, 2014) (emotional reactivity: all seed regions to the insula, vmPFC and amygdala to the lentiform nucleus; motor readiness: all seed regions to the precentral gyrus, PAG to the cerebellum, self-referential processing: vmPFC and PAG to PCC, dmPFC, amygdala to rostral ACC, salience detection: all seed regions to anterior insula and dorsal ACC). Critically, whereas higher HRV predicted increased functional connectivity within key regions of the CAN, no such correlations were uncovered when examining patients with PTSD, pointing to a relative uncoupling of the ANS from the CAN in this group.

As compared to controls, individuals with PTSD exhibited lower HRV at rest as reflected by all HRV parameters. Indeed, the present findings are consistent with previous cross-sectional studies that reported overall lower resting HRV in PTSD even after controlling for important confounders such as incidence of traumatic brain injury and severity of depression (Minassian et al., 2014; Moon et al., 2013; Norte et al., 2013; Shah et al., 2013; Shaikh al arab et al., 2012; Wahbeh & Oken, 2013), a pattern confirmed by a recent meta-analysis (Chalmers et al., 2014). Blunted HRV in PTSD is also in line with previous theoretical models, such as the neurovisceral integration model (Thayer et al., 2009), which proposes that prefrontal regions moderate parasympathetic activity and vagal nerve inhibition, and that inadequate vagus nerve regulation is associated with a variety of somatic and mental diseases (Danesh et al., 2000; Duncan et al., 2003; Gao & Hong, 2008). In this model, whereas healthy functioning is characterized by a high level of adaptive HRV (Thayer et al., 2012; Thayer et al., 2009; Thayer & Lane, 2000), lower HRV is thought to reflect decreased vagal output leading to behavioral inflexibility.

Consistent with the neurovisceral integration model, the polyvagal theory (Porges, 2011) further posits that a safe environment promotes an increase of vagal outflow, thereby promoting regeneration and homeostatic functions. It is therefore probable that difficulties in

detecting safe environments result in an increase in sympathetic tone and concomitant decreased HRV. Indeed, several studies reported a failure of contextual learning in PTSD resulting in an inability to differentiate between threat and safety contexts (Acheson et al., 2015; Levy-Gigi, Richter-Levin, Okon-Singer, Keri, & Bonanno, 2015; Steiger et al., 2015b; van Wingen et al., 2011). For example, a recent study demonstrated that individuals with PTSD did not differentiate between threat and safety contexts on a behavioral level (contingency ratings) during the acquisition phase of a differential context and cue conditioning paradigm; this was reflected in increased hippocampal activation in response to both contexts (Steiger et al., 2015b). This decreased capacity for safety perception may therefore be associated with sympathetic over reactivity and/or parasympathetic insufficiency, and decreased HRV in PTSD (Tulloch, Greenman, & Tasse, 2014). However, it is important to note that emerging evidence of blunted HRV and reduced flexibility in PTSD is based primarily on cross-sectional studies. Longitudinal studies are therefore urgently needed to determine whether an inflexible ANS represents a vulnerability factor for PTSD or instead emerges as the result of heightened stress states. Interestingly, Minassian and colleagues (2015) recently demonstrated that, in active-duty marines, higher LF/HF ratios at a pre-deployment visit (1 to 2 months before combat exposure) were positively correlated with the risk of developing PTSD as measured at a post-deployment visit (4 to 6 months after return) (Minassian et al., 2015). This study points to the fact that ANS functioning may contribute to an individual's proneness, as well as resiliency, in reacting to stress and may therefore represent a risk factor for the development of trauma-related disorders (see also Shaikh al arab et al., 2012).

Although numerous studies have investigated HRV in PTSD, here we describe the first study directly linking HRV to brain regions that modulate the variability of HR time series (CAN). While higher HRV scores in healthy controls predicted increased functional connectivity within regions of the CAN (vmPFC to bilateral insula; left amygdala to the left PAG; PAG to right medial PFC, dorsal cingulate cortex, and left thalamus; for meta-analyses see also Beissner et al., 2013; Thayer et al., 2012), measures of HRV within the PTSD group were unrelated with functional connectivity within CAN-related brain regions. The absence of a correlation between HRV and functional connectivity of the CAN within PTSD subjects may reflect an uncoupling of the ANS from the CAN in PTSD where top-down modulation of cardiac function by higher-order brain regions fails to occur. Such a pattern has indeed been reported across a number of different paradigms including emotion-provoking pictures and film scenes, facial processing, gambling tasks and traumatic script-driven imagery (Cohen et al., 2013; Etkin & Wager, 2007; Felmingham et al., 2008; Hopper, Frewen, van der Kolk, & Lanius, 2007; Lanius, Brand, Vermetten, Frewen, & Spiegel, 2012; Lanius et al., 2015; Mickleborough et al., 2011; Reiser et al., 2014; van Wingen et al., 2011). Interestingly, a

recent positron emission tomography (PET) study in PTSD found an increased correlation between HR and activation in orbitofrontal, precentral and occipital regions in response to traumatic scripts solely among individuals with PTSD (Barkay et al., 2012), suggesting that sensorimotor regions might regulate the stress response induced by traumatic scripts in PTSD. In comparison, the absence of HRV-CAN covariation at rest within the present sample demonstrates a lack of top-down CAN regulation of autonomic responses.

It is important to note that the present sample of individuals with PTSD displayed widespread resting state functional connectivity between CAN-related regions and other brain regions associated with emotional reactivity, motor readiness, self-referential processing, and stimuli salience detection. However, the examined regions appear neither associated with HRV nor associated with anatomical connections to the brain stem, which have been directly related to the vagus nerve. Future studies examining brain stem structures directly are therefore warranted.

There is a growing literature suggesting that low resting HRV and related psychopathological states are associated with undifferentiated threat responses to a wide range of conditions and situations (Melzig et al., 2009; Ruiz-Padial & Thayer, 2014; Wendt et al., 2015). Thus, the present findings of widespread connectivity in PTSD may reflect the neural concomitants of a response pattern, reflecting difficulties in differentiating between threat and safety contexts, which has been observed in other studies (e.g., see Steiger et al., 2015b). However, in contrast, context appropriate activation of localized brain networks has been identified with context appropriate psychophysiological and behavioral responses in persons with high resting HRV, which is associated with a flexibly recruited network of loosely coupled bio-oscillators that has been linked to healthy dynamical systems (Thayer, 2006; Thayer & Lane, 2000). The widespread connectivity exhibited by PTSD patients in the present study might point to a response pattern that is suboptimal in generating context appropriate responses.

The observed pattern of resting state brain activation in PTSD is also consistent with Panksepp' (2012) proposal of a basic affective system. Here, the PAG is thought to gate various affective responses or emotional systems through its connections with higher brain structures whose activity contributes to the functioning of all basic emotional systems. Given the increased widespread PAG resting functional connectivity observed in PTSD subjects, it is further probable that this pattern is reflective of a hypersensitive affective system observed during rest. However, future research is needed to more fully investigate this notion.

Several limitations of the current study are worth noting. Due to the cross-sectional design of the present study, these findings provide no indication of whether decreased HRV is caused by traumatic stress or represents a pre-existing vulnerability factor. We did not include trauma-exposed individuals without PTSD in our analyses, as screened individuals matched

for trauma severity met exclusion criteria for current or past psychiatric disorders. In addition, given that only one related study links HR to cerebral blood flow during traumatic script exposure (Barkay et al., 2012), future studies employing symptom provocation are expected to be useful in identifying potential differential functional connectivity patterns in relation to HRV in PTSD. Here, comparing peripheral physiological and neuronal responses during resting state to those induced during symptom provocation will be necessary to gain insights into emotion regulatory capacity in response to stressors.

C2.6 Conclusion

In conclusion, the present study represents an important first step in linking peripheral (HRV) and central (CAN) measures of autonomic response in PTSD. HRV was reduced in PTSD, while the CAN evidenced increased functional connectivity across myriad of brain regions, including those associated with emotional processing and motor readiness. Moreover, whereas CAN-related functional connectivity was strongly correlated with HRV in controls, a striking lack of covariation between HRV and CAN - functional connectivity was observed in PTSD. The present investigation therefore represents a first step in demonstrating the relative absence of the regulatory capacity of the CAN on the ANS functioning at rest in PTSD, which may partially mediate the negative alterations in cognition and mood observed in this disorder.

C2.7 Supplemental Material

C2.7.1 Within-group seed based functional connectivity

vmPFC:

Control individuals engaged solely clusters within the right anterior cingulate (BA25, BA32) and bilateral medial frontal gyrus (BA11), meaning that functional engagements within controls demonstrate a localized activation pattern. By contrast, in PTSD, vmPFC resting state functional connectivity predicted widespread activation to multiple regions. Here, PTSD individuals showed functional connectivity between the vmPFC seed and the cingulate cortex [bilateral anterior (BA32, BA24), dorsal (BA24), right posterior (BA23, BA30) cingulate cortex], frontal cortex [bilateral medial (BA10), middle (BA6, BA46), inferior (BA9, BA10, BA47)], as well as the temporal gyrus [right superior (BA8) frontal gyrus, the bilateral middle temporal gyrus (BA21)], precentral gyrus (BA4, BA6, BA9), the right precuneus (BA31) and fusiform gyrus (BA20), bilateral lentiform nuclei and insula (BA13, BA47), and the right posterior insula (BA13), the right thalamus and parahippocampal gyrus and the left PAG (see also Table 7, Figure 9).

Amygdala:

Control subjects showed a localized and restricted activation pattern, meaning that functional connectivity of the left amygdala as well as right amygdala predicted activation solely within

the seed region itself. By contrast, in PTSD, within-group analyses of left amygdala functional connectivity predicted widespread activation in multiple cortical and subcortical regions. Specifically, PTSD individuals exhibited functional connectivity between the left amygdala seed and the cingulate cortex [left anterior (BA 24), bilateral midcingulate (BA 24, 32) and posterior cingulate cortex (BA 23, 24, 30, 31)], frontal cortex [bilateral inferior (BA13, 45, 46, 47), middle (BA6, 9, 10, 44, 46), medial (BA6, 9, 32) and superior frontal gyrus (BA6, 8)], temporal gyrus (left middle (BA21), bilateral superior temporal gyrus (BA22, 41)], bilateral parahippocampal gyrus (BA30, 36, 37), bilateral fusiform gyrus (BA37), precentral gyrus (BA6, 44), as well as bilateral anterior and left posterior insular cortex (BA13), bilateral thalamus, left lentiform nucleus, and left superior colliculus (PAG) (see also Table 8, Figure 8). In addition, PTSD individuals exhibited functional connectivity between the right amygdala and the cingulate cortex [bilateral anterior (BA24, 32), midcingulate (BA24, 32), and posterior cingulate cortex (BA23, 24)], frontal cortex [right inferior (BA44, 47), bilateral medial (BA8, 9, 11, 32), and middle frontal gyrus (BA6, 8, 9, 44, 46)], temporal gyrus [right middle (BA21), bilateral superior temporal gyrus (BA 22, 38)], bilateral precentral (BA4, 6), bilateral posterior insula (BA13), bilateral parahippocampal gyrus (BA30, 35), left fusiform gyrus (BA36), right amygdala, and lentiform nucleus, left superior colliculus (PAG) and lentiform nucleus, and right thalamus.

Periagueductal grey:

Control subjects showed a localized and restricted activation pattern, meaning that functional connectivity was found solely between the PAG itself and the bilateral thalamus. By contrast, in PTSD, within-group analyses of PAG resting state functional connectivity revealed widespread activation in multiple cortical and subcortical regions. Specifically, the PTSD group exhibited functional connectivity between the PAG seed and the cingulate cortex [right midcingulate (BA24), left anterior (BA25) and bilateral dorsal posterior cingulate cortex (BA31)], the right superior frontal gyrus (BA9), the right posterior insula (BA13), right amygdala, the right thalamus, putamen, and cerebellum, as well as within the PAG itself (culmen, vermis) (see also Table 10, Figure 9).

C2.7.2 Correlations between HRV, state measurements and CAN related Functional Connectivity in PTSD

In order to examine associations between HRV, state measurements and CAN - related connectivity patterns, separate multiple regression analyses for RMSSD, LF-HRV and HF-HRV scores, as well as state dissociation (RSDI, REF) and anxiety (STAI-S, REF) were conducted. A 2nd level multiple regression model was established for each seed in combination with each HRV score, as well as state dissociation (RSDI) and anxiety (STAI-S), respectively. Simple multiple regression models examining both positive and negative associations between scores were conducted and the results masked with the CAN and

insula mask. To explore connectivity patterns within PTSD individuals, one sample t-tests were conducted, with two covariates (HRV score, state score) and two terms that compute the interaction between the covariates and factor group. Statistical threshold was set to a $p < .001$, based on the respective mask including all listed ROIs, respectively (false discovery rate [FDR]: $p < .05$, cluser size > 10). Overall, no significant results were demonstrated for any of the three seed regions when controlling for state measurements.

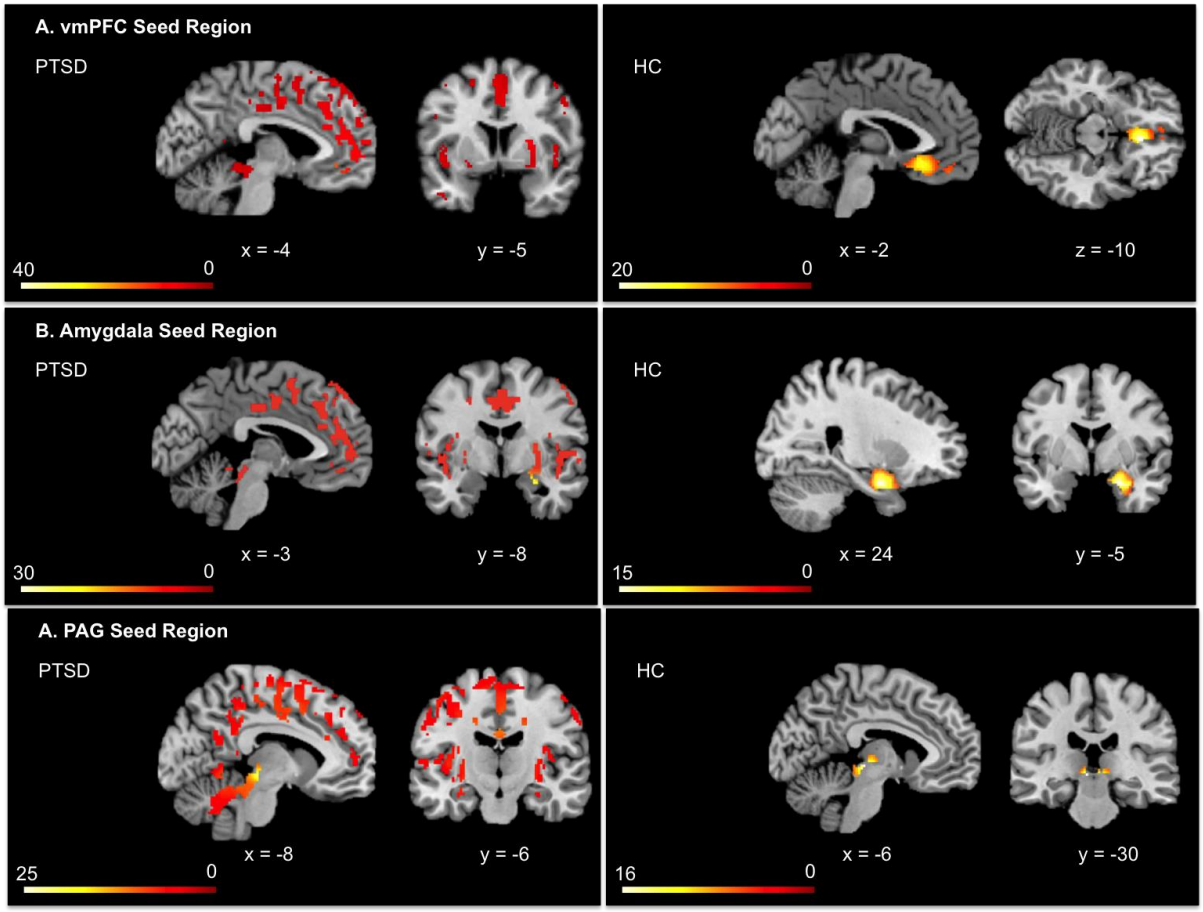

Figure 9. Within-group functional connectivity of A. vmPFC, B. amygdala, C. PAG seed region

Illustration represents functional connectivity between key CAN seed regions, that is, vmPFC, amygdala, and PAG with multiple cortical and subcortical regions in PTSD and a restricted, localized connectivity pattern in controls.

Statistical threshold p < .001 corrected for whole brain FDR, k = 10 for all one-sample t-tests.

Abbreviations: PTSD = posttraumatic stress disorder group; HC = healthy control group; vmPFC = ventromedial prefrontal cortex; PAG = periaqueductal grey

Table 7. Within-group vmPFC resting state functional connectivity

Brain Regions	BA	r/l^	*x*	*y*	*z*	*k*	*T-value*	*pFDR*
Healthy Controls								
anterior cingulate cortex	BA 25,32	R	4	22	-10	451	20.33	<.001
medial frontal gyrus	BA 11	L	-4	42	-12	k451	8.89	<.001
medial frontal gyrus	BA 11	R	4	42	-12	k451	8.12	<.001
PTSD								
anterior cingulate cortex	BA 32	R/L	4	24	-8	5949	47.61	<.001
anterior cingulate cortex	BA 24	R/L	-2	32	12	Of5949	13.82	<.001
medial frontal gyrus	BA 10	R/L	6	52	8	Of5949	12.8	<.001
dorsal cingulate gyrus	BA 24	R/L	-6	-8	50	Of5949	9.73	<.001
inferior frontal gyrus	BA 10	R	40	50	4	36	12.43	<.001
lentiform nucleus	Putamen	R	22	14	6	463	10.94	<.001
anterior cingulate cortex	BA 13, 47	L	-32	24	2	565	11.03	<.001
lentiform nucleus	Putamen	L	-18	14	-4	11	11.03	<.001
anterior cingulate cortex	BA 13, 47	R	32	16	-16	557	10.69	<.001
middle frontal gyrus	BA 46	R	46	38	20	20	9.44	<.001
parahippocampal gyrus	Hippocampus	R	30	-16	-18	15	9.12	<.001
inferior frontal gyrus	BA 10	L	-40	48	2	40	9.09	<.001
inferior frontal gyrus	BA 47	L	-50	36	-4	12	8.91	<.001
lentiform nucleus	Putamen	L	-22	6	-6	32	8.71	<.001
middle frontal gyrus	BA 10	L	-34	46	28	80	8.54	<.001
middle frontal gyrus	BA 9	L	-30	36	40	12	8.31	<.001
precentral gyrus	BA 6, 4	R	44	-8	64	76	8.17	<.001
posterior insular cortex	BA 13	R	34	-26	14	14	8.14	<.001
fusiform gyrus	BA 20	R	32	-38	-26	42	7.97	<.001
parahippocampal gyrus	BA 36	R	24	-34	-22	24	6.56	<.001
PAG, superior colliculus	Vermis	L	-12	-38	-8	584	7.88	<.001
PAG	Pulvinar	L	-8	-28	2	Of584	7.55	<.001
middle temporal gyrus	BA 21	L	-44	0	-28	12	7.81	<.001
middle temporal gyrus	BA 21	R	62	-14	-12	22	7.7	<.001
middle frontal gyrus	BA 9	L	-38	24	36	78	7.59	<.001
posterior cingulate cortex	BA 23, 30	R	2	-56	14	92	7.54	<.001
inferior frontal gyrus	BA 9	R	54	4	32	58	7.51	<.001
thalamus	Pulvinar	R	10	-28	6	55	7.51	<.001
parahippocampal gyrus	BA 27	R	24	-32	-4	Of55	6.42	<.001
middle frontal gyrus	BA 6	R	34	10	62	55	7.15	<.001
parahippocampal gyrus	BA 36	R	28	-42	-14	34	7.12	<.001
sub-gyral	BA 6	L	-20	0	58	12	6.75	<.001
superior frontal gyrus	BA 8	R	34	22	54	14	6.64	<.001
middle temporal gyrus	BA 21	R	54	6	-14	Of14	6.59	<.001
parahippocampal gyrus	BA 36	L	-24	-34	-22	24	6.47	<.001
precuneus	BA 31	R	4	-54	32	Of16	6.05	<.001
middle frontal gyrus	BA 6	L	-24	-8	50	29	6.32	<.001
middle frontal gyrus	BA 6	R	36	-6	60	10	6.3	<.001
precentral gyrus	BA 6, 9	L	-50	-2	36	10	6.15	<.001

Significance threshold p < .001. corrected for whole brain FDR. k = 10 voxels for all one-sample t-tests
Abbreviations: ^ = right/ left hemisphere; PTSD = posttraumatic stress disorder group; HC = healthy control group; vmPFC = ventromedial prefrontal cortex; PAG = periaqueductal grey. FDR = false discovery rate; BA = Brodmann Areal

Table 8. Within-group left amygdala resting state functional connectivity

Brain Regions	BA	r/l^	*x*	*y*	*z*	*k*	*T-value*	*pFDR*
Healthy Controls								
amygdala	p.h.g	L	-26	-6	-16	460	25.04	<.001
amygdala	p.h.g	L	-24	-2	-18	Of460	23.87	<.001
PTSD								
inferior frontal gyrus	BA47	L	-30	8	-18	1097	14.93	<.001
inferior frontal gyrus	BA13	L	-34	8	-14	Of1097	11.86	<.001
anterior insular cortex	BA13	L	-28	20	-2	Of1097	11.78	<.001
precentral gyrus	BA44	L	-42	12	8	Of1097	9.33	<.001
inferior frontal gyrus	BA45	L	-50	26	10	Of1097	9.21	<.001
middle frontal gyrus	BA9, 44	L	-50	16	32	Of1097	7.85	<.001
posterior insular cortex	BA13	L	-38	-8	16	Of1097	6.76	<.001
lentiform nucleus	Putamen	L	-24	4	-6	92	13.73	<.001
posterior insular cortex	BA23	R	4	-32	26	4625	13.51	<.001
posterior insular cortex	BA23	R	6	-20	34	Of4625	12.59	<.001
posterior insular cortex	BA24	L	-4	-24	40	Of4625	11.26	<.001
posterior insular cortex	BA31	R	6	-32	40	Of4625	10.66	<.001
midcingulate cortex	BA32	R	12	6	44	Of4625	10.19	<.001
midcingulate cortex	BA24	L	-2	-4	42	Of4625	10.1	<.001
anterior cingulate cortex cortex	BA24	L	-2	28	20	Of4625	9.55	<.001
posterior insular cortex	BA30	R	6	-54	14	Of4625	9.09	<.001
midcingulate cortex	BA32	R	12	10	40	Of4625	8.98	<.001
midcingulate cortex	BA32	L	-2	16	34	Of4625	8.92	<.001
medial frontal gyrus	BA6	R	6	0	52	Of4625	8.79	<.001
midcingulate cortex	BA32	L	-2	22	32	Of4625	8.75	<.001
posterior insular cortex	BA31	R	14	-44	32	Of4625	8.72	<.001
midcingulate cortex	BA32	R	0	20	36	Of4625	8.72	<.001
medial frontal gyrus	BA9	R	12	40	18	Of4625	8.62	<.001
medial frontal gyrus	BA32	L	-10	10	48	Of4625	8.48	<.001
lentiform nucleus	Putamen	L	-20	12	-6	11	13.01	<.001
parahippocampal gyrus	BA30	R	16	-50	2	2507	11.07	<.001
superior colliculus. PAG		L	-8	-30	-6	Of2507	10.58	<.001
parahippocampal gyrus	BA27	L	-14	-38	-2	Of2507	9.48	<.001
thalamus	Pulvinar	L	-20	-28	2	Of2507	9.17	<.001
parahippocampal gyrus	BA30	L	-10	-42	0	Of2507	9.15	<.001
parahippocampal gyrus	BA37	R	22	-50	-20	Of2507	9.1	<.001
parahippocampal gyrus	BA30	L	-14	-38	-12	Of2507	9.04	<.001
thalamus	Pulvinar	L	-10	-30	6	Of2507	8.8	<.001
lingual gyrus	BA30	L	-14	-42	-4	Of2507	8.45	<.001
culmen		R	2	-58	-18	Of2507	8.02	<.001
fusiform gyrus	BA37	R	32	-54	-20	Of2507	7.96	<.001
posterior insular cortex	BA29	L	-8	-44	6	Of2507	7.78	<.001
fusiform gyrus	BA37	R	28	-40	-18	Of2507	7.71	<.001
fusiform gyrus	BA37	L	-30	-46	-20	Of2507	7.68	<.001
parahippocampal gyrus	BA30	L	-16	-52	0	Of2507	7.49	<.001
thalamus	Pulvinar	L	-10	-26	12	Of2507	7.46	<.001
culmen	BA30	R	4	-46	-8	Of2507	7.31	<.001
fusiform gyrus	BA37	L	-38	-46	-24	Of2507	7.22	<.001
parahippocampal gyrus	BA36	L	-28	-34	-16	Of2507	7.21	<.001
culmen	*	L	-24	-52	-20	Of2507	6.95	<.001

parahippocampal gyrus	Hippocampus	L	-28	-16	-16	24	11.95	<.001
lentiform nucleus	Putamen	R	24	6	8	463	11.17	<.001
superior temporal gyrus	BA38	L	-48	8	-26	15	10.9	<.001
thalamus	Pulvinar	R	14	-30	8	94	10.69	<.001
middle temporal gyrus	BA21	L	-46	2	-28	53	10.3	<.001
inferior frontal gyrus	BA46	L	-48	30	18	36	9.14	<.001
superior temporal gyrus	BA22	L	-56	-8	6	93	9.13	<.001
superior temporal gyrus	BA6	L	-20	22	62	302	9.11	<.001
middle frontal gyrus	BA46	L	-50	22	26	13	8.88	<.001
posterior insular cortex	BA13	L	-30	-28	14	18	8.24	<.001
inferior frontal gyrus	BA47	R	30	6	-18	115	8.2	<.001
middle frontal gyrus	BA9	L	-36	30	38	65	8.1	<.001
middle frontal gyrus	BA9	L	-32	38	40	12	8.08	<.001
precentral gyrus	BA6	R	52	-6	52	153	8.01	<.001
middle frontal gyrus	BA6	L	-44	2	54	128	7.9	<.001
superior temporal gyrus	BA41	L	-36	-32	16	10	7.77	<.001
middle frontal gyrus	BA10	L	-32	46	30	76	7.68	<.001
superior temporal gyrus	BA22	R	60	-6	10	28	7.65	<.001
sub-gyral	BA6	L	-20	0	58	12	7.64	<.001
inferior frontal gyrus	BA45	R	52	26	10	11	7.63	<.001
superior frontal gyrus	BA8	R	12	52	46	78	7.63	<.001
superior frontal gyrus	BA8	L	-8	50	46	17	7.49	<.001
middle frontal gyrus	BA46	R	48	36	18	11	7.34	<.001
middle frontal gyrus	BA6	L	-24	-10	48	37	7.32	<.001
parahippocampal gyrus	Hippocampus	R	30	-18	-16	10	7	<.001
anterior insular cortex	BA 13	R	34	24	2	24	6.98	<.001
middle frontal gyrus	BA6	L	-24	-2	48	10	6.78	<.001
middle frontal gyrus	BA6	R	26	20	62	17	6.41	<.001

Significance threshold p < .001. corrected for whole brain FDR. k = 10 voxels for all one-sample t-tests
Abbreviations: ^ = right/ left hemisphere; p.h.g. = parahippocampal gyrus; PTSD = posttraumatic stress disorder group; HC = healthy control group; PAG = periaqueductal grey. FDR = false discovery rate; BA = Brodmann Areal

Table 9. Within-group right amygdala resting state functional connectivity

Brain Regions	BA	r/l^	*x*	*y*	*z*	*k*	*T-value*	*pFDR*
Healthy Controls								
amygdala	p.h.g	R	22	-6	-18	549	18.84	<.001
amygdala	p.h.g	R	30	-4	-20	Of549	17.45	<.001
amygdala	p.h.g	R	28	0	-18	Of549	17.04	<.001
PTSD								
amygdala	p.h.g	R	26	-6	-16	463	31.42	<.001
lentiform nucleus	Putamen	R	22	10	-4	Of463	13.1	<.001
inferior frontal gyrus	BA 47	R	32	16	-18	978	14.38	<.001
superior temporal gyrus	BA 38	R	32	6	-20	Of978	12.89	<.001
posterior insular cortex	BA 13	R	42	-4	0	Of978	11.31	<.001
parahippocampal gyrus	Hippocampus	R	30	-12	-18	15	13.9	<.001
parahippocampal gyrus	BA 35	R	20	-36	-12	1474	11.32	<.001
culmen		R	30	-38	-26	Of1574	10.81	<.001
culmen		R	14	-38	-10	Of1574	10.52	<.001
parahippocampal gyrus	BA 35	R	32	-46	-14	Of1574	10.18	<.001
culmen		R	24	-46	-20	Of1574	10.13	<.001
parahippocampal gyrus	BA 35	L	-10	-40	2	Of1574	9.64	<.001
culmen		R	24	-34	-24	Of1574	9.18	<.001
parahippocampal gyrus	BA 35	L	-22	-28	-16	Of1574	8.97	<.001
thalamus	Pulvinar	L	-16	-28	4	Of1574	8.28	<.001
culmen		L	-10	-42	-10	Of1574	8.19	<.001
superior colliculus. PAG		L	-6	-32	-8	Of1574	7.69	<.001
parahippocampal gyrus	BA 30	R	12	-44	-2	Of1574	7.36	<.001
culmen		L	-20	-34	-22	Of1574	7.32	<.001
fusiform gyrus	BA 36	L	-32	-42	-20	Of1574	6.81	<.001
lentiform nucleus	Putamen	L	-14	6	-8	92	10.79	<.001
lentiform nucleus	Putamen	L	-16	12	-4	11	10.64	<.001
superior temporal gyrus	BA 38	L	-46	10	-28	16	10.2	<.001
precentral gyrus	BA 4	R	52	-10	54	218	8.34	<.001
anterior cingulate cortex	BA 24	L	-2	22	26	4571	9.96	<.001
anterior cingulate cortex	BA 24	R	4	28	18	Of4571	9.12	<.001
midcingulate cortex	BA 24	L	-6	-8	42	Of4571	9.03	<.001
midcingulate cortex	BA 32	R	6	22	30	Of4571	9.02	<.001
medial frontal gyrus	BA 32	L	-8	8	48	Of4571	8.99	<.001
medial frontal gyrus	BA 8	R	6	16	48	Of4571	8.75	<.001
anterior cingulate cortex	BA 32	L	-4	30	26	Of4571	8.71	<.001
anterior cingulate cortex	BA 32	R	8	28	26	Of4571	8.7	<.001
superior frontal gyrus	BA 8	R	10	50	48	Of4571	8.61	<.001
midcingulate cortex	BA 32	L	-8	34	30	Of4571	8.6	<.001
anterior cingulate cortex	BA 32	L	-2	32	-10	Of4571	8.6	<.001
posterior cingulate cortex	BA 24	R	8	-18	44	Of4571	8.52	<.001
medial frontal gyrus	BA 9	R	12	40	18	Of4571	8.5	<.001
midcingulate cortex	BA 24	L	-4	-6	50	Of4571	8.46	<.001
midcingulate cortex	BA 32	R	6	16	34	Of4571	8.33	<.001
posterior cingulate cortex	BA 23	R	0	-48	24	Of4571	8.24	<.001
posterior cingulate cortex	BA 24	L	-6	-20	42	Of4571	8.23	<.001
anterior cingulate cortex	BA 32	R	6	34	-4	Of4571	8.19	<.001
medial frontal gyrus	BA 11	R	2	30	-12	Of4571	8.15	<.001
sub-gyral	Hippocampus	R	32	-22	-10	16	9.82	<.001
posterior insular cortex	BA 13	R	36	-26	16	16	9.47	<.001
thalamus	Pulvinar	R	24	-26	4	79	9.35	<.001

posterior insular cortex	BA 13	L	-46	2	-2	668	9.33	<.001
superior frontal gyrus	BA 8	L	-40	14	54	55	9.15	<.001
middle frontal gyrus	BA 46	R	50	32	18	17	8.84	<.001
superior temporal gyrus	BA 22	R	60	-8	2	26	8.84	<.001
middle temporal gyrus	BA 21	R	46	0	-28	19	8.81	<.001
superior temporal gyrus	BA 38	R	42	12	-32	33	8.73	<.001
parahippocampal gyrus	Hippocampus	L	-30	-16	-14	24	8.35	<.001
Transverse Temporal Gyrus	BA 42	R	60	-14	12	40	7.75	<.001
precentral gyrus	BA 6	L	-54	2	16	61	7.51	<.001
middle frontal gyrus	BA 8	R	26	22	44	11	7.44	<.001
middle frontal gyrus	BA 8	R	50	12	46	14	7.42	<.001
middle frontal gyrus	BA 8	L	-22	22	42	44	7.23	<.001
precentral gyrus	BA 6	L	-56	-2	14	43	7.22	<.001
posterior insular cortex	BA 13	L	-40	-8	10	15	7.21	<.001
superior temporal gyrus	BA 22	R	62	-22	-6	40	7.2	<.001
precentral gyrus	BA 6	R	60	-4	32	12	7.18	<.001
superior frontal gyrus	BA 10	L	-20	58	30	56	7.13	<.001
precentral gyrus	BA 4	R	62	-10	26	14	7.01	<.001
culmen		R	40	-48	-38	11	6.95	<.001
middle frontal gyrus	BA 9	L	-34	26	42	35	6.94	<.001
middle frontal gyrus	BA 46	L	-44	32	18	31	6.9	<.001
inferior frontal gyrus	BA 44	L	-52	10	20	10	6.79	<.001
middle frontal gyrus	BA 6	L	-24	-10	48	13	6.55	<.001

Significance threshold p < .001. corrected for whole brain FDR. k = 10 voxels for all one-sample t-tests
Abbreviations: ^ = right/ left hemisphere; p.h.g. = parahippocampal gyrus; PTSD = posttraumatic stress disorder group; HC = healthy control group; PAG = periaqueductal grey. FDR = false discovery rate; BA = Brodmann Areal

Table 10. Within-group PAG resting state functional connectivity

Brain Regions	BA	r/l^	*x*	*y*	*z*	*k*	*T-value*	*pFDR*
Healthy Controls								
PAG	midbrain	L	-6	-30	0	211	16.28	<.001
thalamus	Pulvinar	L	-4	-22	2	Of211	14.17	<.001
PAG	midbrain	R	4	-28	2	Of211	11.6	<.001
thalamus	anterior	R	8	-4	12	k80	10.02	<.001
PTSD								
PAG	midbrain	L	-6	-30	-2	54407	26.86	<.001
thalamus	Pulvinar	R	4	-32	-4	Of54407	18.64	<.001
PAG	midbrain	R	8	-30	0	Of54407	17.75	<.001
cerebellum	Culmen	L	-14	-42	-12	Of54407	13.03	<.001
midcingulate cortex	BA 24	R	2	-20	36	Of54407	12.48	<.001
cerebellum	Culmen	R	14	-38	-12	Of54407	12.43	<.001
cerebellum	Culmen	R	24	-52	-20	Of54407	12.25	<.001
cerebellar lingual		L	-2	-40	-20	Of54407	12.21	<.001
cerebellum	Culmen	R	8	-42	-10	Of54407	11.54	<.001
dorsal posterior CC	BA 31	R	18	-26	38	Of54407	11.54	<.001
dorsal posterior CC	BA 31	L	-6	-26	38	Of54407	11.32	<.001
anterior cingulate cortex	BA 25	L	-2	2	-8	17	11.01	<.001
superior frontal gyrus	BA 9	R	10	54	44	44	6.92	<.001
posterior insular cortex	BA13	R	38	-36	16	1020	9.4	<.001
posterior insular cortex	BA13	R	34	-30	16	Of1020	6.78	<.001
amgydala		R	28	-18	-16	57	6.91	<.001
cerebellum	Vermis	R	2	-58	-12	19837	11.14	<.001
cerebellum	Vermis	R	8	-42	-10	Of19837	11.54	<.001
putamen	Pulvinar	L	-22	14	-4	23	9.98	<.001
putamen	Pulvinar	R	24	-4	14	1020	7.25	<.001

Significance threshold p < .001. corrected for whole brain FDR. k = 10 voxels for all one-sample t-tests
Abbreviations: ^ = right/ left hemisphere; PTSD = posttraumatic stress disorder group; HC = healthy control group; PAG = periaqueductal grey. FDR = false discovery rate; BA = Brodmann Areal

Table 11. Between-group vmPFC resting state functional connectivity

Brain Regions	BA	r/l^	*x*	*y*	*z*	*k*	*T-value*	*pFDR*
Healthy Controls > PTSD								
non significant clusters								
PTSD > Healthy Controls								
anterior cingulate cortex	BA 3210	R	14	40	14	4979	11.93	<.001
middle cingulate gyrus	BA 24	L	-2	-18	3	Of4979	6.38	<.001
medial frontal gyrus	BA 10	R	6	52	8	Of4979	11.15	<.001
medial frontal gyrus	BA 10	L	-12	48	10	Of4979	10.57	<.001
anterior cingulate cortex	BA 32, 24	R	6	40	0	Of4979	10.08	<.001
medial frontal gyrus	BA 9	L	-16	40	18	Of4979	9.59	<.001
medial frontal gyrus	BA 10	R	8	54	14	Of4979	9.54	<.001
anterior cingulate cortex	BA 32	L	-4	36	30	Of4979	9.01	<.001
lentiform nucleus	Putamen	R	22	14	6	262	9.5	<.001
middle frontal gyrus	BA 46	R	46	40	18	18	8.76	<.001
middle frontal gyrus	BA 10	L	-32	46	30	53	8.37	<.001
middle frontal gyrus	BA 10	R	38	46	28	32	8.16	<.001
anterior insular cortex	BA 13	L	-32	22	14	81	8.15	<.001
precentral gyrus	BA 6	R	44	-10	64	119	7.87	<.001
middle frontal gyrus	BA 8	R	38	28	44	34	7.69	<.001
middle frontal gyrus	BA 46	L	-42	38	18	31	7.68	<.001
middle frontal gyrus	BA 21	R	64	-20	-8	14	7.26	<.001
precentral gyrus	BA 6	L	-42	-6	60	86	7.09	<.001
inferior frontal gyrus	BA 9	R	54	4	32	50	6.97	<.001
parahippocampal gyrus	BA 30	L	-14	-36	-8	20	6.86	<.001
lentiform nucleus	Putamen	R	28	-12	-8	14	6.84	<.001
superior frontal gyrus	BA 8	R	22	22	48	12	6.8	<.001
lentiform nucleus	Putamen	L	-24	4	-6	10	6.79	<.001
Sub-Gyral	BA 6	L	-20	0	60	13	6.73	<.001
middle frontal gyrus	BA 6	R	34	10	62	17	6.66	<.001
thalamus	Pulvinar	L	-18	-30	6	21	6.5	<.001
posterior cingulate cortex	BA 30	R	8	-54	12	12	6.43	<.001
precentral gyrus	BA 6	L	-52	2	32	25	6.2	<.001

Significance threshold p < .001; corrected for whole brain FDR; k = 10 voxels for all two-sample t-tests
Abbreviations: ^ = right/ left hemisphere; PTSD = posttraumatic stress disorder group; HC = healthy control group; vmPFC = ventromedial prefrontal cortex; PAG = periaqueductal grey; FDR = false discovery rate; BA = Brodmann Areal

Table 12. Between-group left amygdala resting state functional connectivity

Brain Regions	BA	r/l^	*x*	*y*	*z*	*k*	*T-value*	*pFDR*
Healthy Controls > PTSD								
n.s.								
PTSD> Healthy Controls								
lentiform nucleus	Putamen	R	22	6	10	323	9.91	<.001
midcingulate cortex	BA 32	R	12	6	44	2647	9.56	<.001
posterior insular cortex	BA 23	R	6	-20	34	Of2647	8.6	<.001
posterior insular cortex	BA 31	L	-8	-28	40	Of2647	8.58	<.001
anterior cingulate cortex	BA 24	R	6	28	18	Of2647	8.55	<.001
midcingulate cortex	BA 24	L	-6	-6	40	Of2647	8.51	<.001
anterior cingulate cortex	BA 24	R	14	38	18	Of2647	8.37	<.001
medial frontal gyrus	BA 32	L	-10	10	48	Of2647	8.13	<.001
midcingulate cortex	BA 32	L	-6	20	46	Of2647	8.12	<.001
midcingulate cortex	BA 24	R	12	-4	48	Of2647	8.04	<.001
anterior cingulate cortex	BA 24	L	-2	28	20	Of2647	8.02	<.001
midcingulate cortex	BA 24	L	-12	-6	46	Of2647	7.9	<.001
midcingulate cortex	BA 24	R	4	2	40	Of2647	7.79	<.001
midcingulate cortex	BA 24	R	8	-18	40	Of2647	7.66	<.001
midcingulate cortex	BA 23	R	4	28	30	Of2647	7.51	<.001
anterior cingulate cortex	BA 24	L	-6	24	26	Of2647	7.51	<.001
anterior cingulate cortex	BA 32	R	8	28	28	Of2647	7.28	<.001
midcingulate cortex	BA 32	R	12	32	32	Of2647	7.23	<.001
anterior cingulate cortex	BA 32	R	-8	38	33	Of2647	7.14	<.001
lentiform nucleus	Putamen	L	-22	6	-6	73	8.87	<.001
anterior insular Cortex	BA 13	L	-40	4	8	155	8.58	<.001
lentiform nucleus	Putamen	L	-20	12	-6	11	8.55	<.001
superior frontal gyrus	BA 8	L	-34	14	54	53	8.08	<.001
anterior insular Cortex	BA 13	L	-28	20	-2	20	8.04	<.001
precentral gyrus	BA 4	L	-62	-12	28	34	7.86	<.001
parahippocampal gyrus	BA 30	L	-16	-32	-4	174	7.79	<.001
thalamus	Pulvinar	L	-20	-28	6	Of174	7.33	<.001
superior frontal gyrus	BA 6	L	-20	22	62	176	7.69	<.001
culmen		L	-22	-36	-24	37	7.48	<.001
inferior frontal gyrus	BA 44	R	58	4	16	17	7.46	<.001
middle frontal gyrus	BA 9	L	-38	30	38	41	7.41	<.001
middle frontal gyrus	BA 46	L	-44	36	18	31	7.35	<.001
thalamus	Pulvinar	R	10	-26	6	38	7.33	<.001
precentral gyrus	BA 6	R	54	-2	46	95	7.14	<.001
parahippocampal gyrus	BA 30	R	14	-36	-4	34	7.03	<.001

Significance threshold p < .001; corrected for whole brain FDR; k = 10 voxels for all two-sample t-tests
Abbreviations: ^ = right/ left hemisphere; PTSD = posttraumatic stress disorder group; HC = healthy control group; PAG = periaqueductal grey; FDR = false discovery rate; BA = Brodmann Areal

Table 13. Between-group right amygdala resting state functional connectivity

Brain Regions	BA	r/l^	*x*	*y*	*z*	*k*	*T-value*	*pFDR*
Healthy Controls > PTSD								
n.s.								
PTSD> Healthy Controls								
lentiform nucleus	Putamen	R	22	14	6	372	9.71	<.001
lentiform nucleus	Putamen	R	24	0	14	Of 372	9.59	<.001
lentiform nucleus	Putamen	R	30	-4	0	Of 372	8.65	<.001
lentiform nucleus	l.g.p.	R	26	-12	-6	Of 372	7.35	<.001
inferior frontal gyrus	BA 44	R	58	4	16	29	6.67	<.001
midcingulate cortex	BA 32	L	-6	22	44	3055	9.4	<.001
medial frontal gyrus	BA 9	R	12	40	20	Of 3055	9.17	<.001
midcingulate cortex	BA 24	R	-6	-10	42	Of 3055	8.97	<.001
medial frontal gyrus	BA 8	R	6	18	50	Of 3055	8.51	<.001
midcingulate cortex	BA 32	L	-8	6	46	Of 3055	8.5	<.001
anterior cingulate cortex	BA 32	L	-4	36	14	Of 3055	8.44	<.001
midcingulate cortex	BA 32	R	8	20	46	Of 3055	8.2	<.001
anterior cingulate cortex	BA 32	L	-10	42	16	Of 3055	8.19	<.001
midcingulate cortex	BA 24	L	-2	-4	42	Of 3055	7.99	<.001
posterior insular cortex	BA 24	L	-6	-20	40	Of 3055	7.92	<.001
midcingulate cortex	BA 32	R	10	4	42	Of 3055	7.89	<.001
posterior insular cortex	BA 24	R	2	-10	40	Of 3055	7.8	<.001
anterior cingulate cortex	BA 24	L	-2	28	20	Of 3055	7.8	<.001
posterior insular cortex	BA 31	L	-8	-12	48	Of 3055	7.78	<.001
superior frontal gyrus	BA 8	R	6	30	48	Of 3055	7.74	<.001
anterior cingulate cortex	BA 32	R	8	28	28	Of 3055	7.73	<.001
anterior cingulate cortex	BA 32	R	16	44	6	Of 3055	7.72	<.001
midcingulate cortex	BA 32	L	-2	22	32	Of 3055	7.65	<.001
midcingulate cortex	BA 32	R	16	12	38	Of 3055	7.64	<.001
inferior frontal gyrus	BA 47	R	32	18	-8	38	7.64	<.001
superior frontal gyrus	BA 8	L	-40	14	54	43	9.16	<.001
middle frontal gyrus	BA 46	R	50	32	18	14	8.35	<.001
lentiform nucleus	Putamen	L	-22	6	-6	57	8.32	<.001
superior frontal gyrus	BA 9	R	8	52	46	98	8.03	<.001
middle temporal gyrus	BA 21	R	58	-4	-6	12	7.97	<.001
precentral gyrus	BA 4	R	50	-14	58	43	7.94	<.001
middle frontal gyrus	BA 8	L	-24	20	48	44	7.72	<.001
middle frontal gyrus	BA 8	R	24	26	44	31	7.34	<.001
superior frontal gyrus	BA 6	L	-10	32	60	123	7.3	<.001
middle frontal gyrus	BA 9	R	50	12	46	14	7.19	<.001
anterior insular Cortex	BA 13	R	40	8	8	25	7.14	<.001
parahippocampal gyrus	BA 30	R	14	-34	-6	45	7.12	<.001
lentiform nucleus	Putamen	L	-18	10	-6	11	7	<.001
middle frontal gyrus	BA 9	L	-34	26	42	26	7	<.001
posterior insular cortex	BA 13	R	36	-14	22	11	6.98	<.001
posterior insular cortex	BA 13	L	-38	-14	22	27	6.75	<.001
middle frontal gyrus	BA 6	L	-24	-8	48	16	6.61	<.001
inferior frontal gyrus	BA 13	R	36	22	8	15	6.6	<.001
middle frontal gyrus	BA 10	L	-34	46	28	22	6.58	<.001
posterior insular cortex	BA 13	R	44	-8	2	10	6.56	<.001
precentral gyrus	BA 4	L	-58	-4	18	21	6.51	<.001
middle frontal gyrus	BA 46	L	-46	32	18	10	6.19	<.001

Significance threshold p < .001; corrected for whole brain FDR; k = 10 voxels for all two-sample t-tests Abbreviations: ^ = right/ left hemisphere; l.g.p. = lateral globus pallidus; PTSD = posttraumatic stress disorder group; HC = healthy control group; PAG = periaqueductal grey; FDR = false discovery rate; BA = Brodmann Areal

Table 14. Between-group PAG resting state functional connectivity

Brain Regions	BA	r/l^	*x*	*y*	*z*	*k*	*T-value*	*pFDR*
Healthy Controls > PTSD								
non significant clusters								
PTSD > Healthy Controls								
midcingulate cortex	BA 24	L	-2	-18	38	27583	10.46	<.001
midcingulate cortex	BA 24	L	-2	-22	36	Of27583	10.05	<.001
medial frontal gyrus	BA 6	R	6	-18	52	43	9.44	<.001
midcingulate cortex	BA 24	R	0	-10	42	10	9.36	<.001
medial frontal gyrus	BA 32	L	-10	12	48	k10	9.35	<.001
dorsal posterior CC	BA 31	L	-18	-22	42	k10	9.29	<.001
midcingulate cortex	BA 24	L	-6	2	50	k10	9.28	<.001
midcingulate cortex	BA 31	L	-10	-12	48	k10	9.19	<.001
superior frontal gyrus	BA 6	L	-32	12	56	k10	9.13	<.001
precentral qyrus	BA 4	L	-26	-30	54	k10	9.12	<.001
medial frontal gyrus	BA 9	R	8	54	42	43	6.56	<.001
anterior insular cortex	BA13	L	-34	22	12	887	6.63	<.001
anterior insular cortex	BA13	L	-42	6	10	Of887	6.77	<.001
posterior insular cortex	BA13	L	-32	-12	14	Of887	6.69	<.001
cerebellum	Vermis	R	2	-56	-16	975	6.45	<.001
putamen		L	-22	18	0	23	8.44	<.001
putamen		R	22	16	4	369	8.3	<.001
thalamus	Pulvinar	L	-20	-28	4	Of975	6.49	<.001
hippocampus	p.h.g	L	-28	-28	-14	43	6.44	<.001

Significance threshold p < .001; corrected for whole brain FDR; k = 10 voxels for all two-sample t-tests
Abbreviations: ^ = right/ left hemisphere; p.h.g. = parahippocampal gyrus; PTSD = posttraumatic stress disorder group; HC = healthy control group; PAG = periaqueductal grey; FDR = false discovery rate; BA = Brodmann Areal

C3. STUDY III MODIFICATION OF FEAR MEMORY BY PHARMACOOGICAL AND BEHAVIORAL INTERVENTIONS DURING RECONSOLIDATION

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C3.1 Abstract

Background: Dysfunctional fear responses play a central role in many mental disorders. New insights in learning and memory suggest that pharmacological and behavioural interventions during the reconsolidation of reactivated fear memories may increase the efficacy of therapeutic interventions. It has been proposed that interventions applied during reconsolidation may modify the original fear memory, and thus prevent the spontaneous recovery and reinstatement of the fear response.

Methods: We investigated whether pharmacological (propranolol) and behavioural (reappraisal, multisensory stimulation) interventions reduce fear memory, and prevent reinstatement of fear in comparison to a placebo control group. Eighty healthy female subjects underwent a differential fear conditioning procedure with three stimuli (CS). Two of these (CS+) were paired with an electric shock on day 1. On day 2, 20 subjects were pseudo-randomly assigned to either the propranolol or placebo condition, or underwent one of the two behavioural interventions after one of the two CS+ was reactivated. On day 3, all subjects underwent an extinction phase, followed by a reinstatement test. Dependent variables were US expectancy ratings, fear-potentiated startle, and skin conductance response.

Results: Differential fear responses to the reactivated and non-reactivated CS+ were observed only in the propranolol condition. Here, the non-reactivated CS+ evoked stronger fear-potentiated startle-responses compared to the placebo group. None of the interventions prevented the return of the extinguished fear response after re-exposure to the unconditioned stimulus.

Conclusions: Our data are in line with an increasing body of research stating that the occurrence of reconsolidation may be constrained by boundary conditions such as subtle differences in experimental manipulations and instructions. In conclusion, our findings do not support a beneficial effect in using reconsolidation processes to enhance effects of psychotherapeutic interventions. This implies that more research is required before therapeutic interventions may benefit from a combination with reconsolidation processes.

C3.2 Introduction

Fear is an important symptom in many mental disorders such as phobia, generalized anxiety disorder or posttraumatic stress disorder (Schwabe, Nader, & Pruessner, 2014). In a recent concept paper, Lane and co-workers (Lane et al., 2015) emphasized reconsolidation as a central mechanism in treating fear-relevant disorders, irrespective of the psychotherapeutic orientation. The authors proposed that incorporating new emotional experiences into previously reactivated memories might attenuate or actually erase fear by reconsolidating a modified memory trace. The updating of a learned fear memory stands in contrast to the mechanism of extinction learning that forms the basis for exposure-based techniques (Hofmann & Smits, 2008; Norton & Price, 2007; Olatunji et al., 2010). Extinction learning represents 'inhibitory learning', i.e. the formation of a second memory trace, which competes as a 'safety memory' trace with the original fear memory trace (Bouton, 2002; Finnie & Nader, 2012; Milad & Quirk, 2002; Rescorla, 2001). Although extinction learning is a well-established therapeutic intervention, it is well known to every clinician that patients may re-experience fear after exposure therapy: the fear may spontaneously recover over time, or be evoked when exposed to a relevant cue in the same or within a new context (Bouton, 2004; Harris et al., 2000; Myers et al., 2006; Rescorla, 2004). This is explained by a temporary dominance of the fear over the safety memory.

Studies on behavioural and pharmacological interventions targeting fear memory have revealed promising results across species when applied after reactivation of fear memory during the time window of reconsolidation processes (Choi et al., 2010; Corlett et al., 2013; Debiec et al., 2011; Debiec et al., 2002; Hou, Zhao, Zhang, & Ding, 2015; Lee, 2008; Schiller et al., 2013; Soeter & Kindt, 2015b; Tian et al., 2011). Particularly, the administration of the ß-adrenergic receptor antagonist propranolol has consistently been shown to erase fear responses (Kindt et al., 2009; Sevenster et al., 2013, 2014b; Soeter & Kindt, 2010, 2011, 2012a, 2012b). Declarative memory, i.e. the explicit expectation of the occurrence of an aversive event, was not affected by this intervention. However, the fear-potentiated startle response, which involves amygdala engagement, was strongly attenuated during re-extinction and reinstatement tests up to one month later (Soeter & Kindt, 2010). Studies on combining extinction with reactivation of fear memories suggested that a behavioural intervention might be similarly efficient as a pharmacological one (Agren, Engman, et al., 2012; Agren, Furmark, et al., 2012; Oyarzun et al., 2012; Schiller et al., 2013; Schiller et al., 2010; Steinfurth et al., 2014). Behavioural interventions have particularly attenuated skin conductance responses that primarily reflect explicit learning about contingencies between conditioned stimuli and the aversive event (Sevenster et al., 2014a; Warren et al., 2014). However, in contrast to propranolol administration, behavioural interventions were less

efficient in erasing the emotional response as measured by fear-potentiated startle (Golkar & Ohman, 2012; Kindt & Soeter, 2013; Soeter & Kindt, 2011).

In sum, the engagement of reconsolidation processes may indeed be suited to improve therapy of fear-related disorders. This was recently supported by first studies in samples with clinical features (James et al., 2015; Soeter & Kindt, 2015a). Nevertheless, a growing body of work has failed to replicate the original findings for both the pharmacological intervention (Bos et al., 2014; see also Bos et al., 2012) as well as the behavioural intervention (Golkar & Ohman, 2012; Kindt & Soeter, 2013; Klucken et al., 2016; Soeter & Kindt, 2011). This suggests that further studies in healthy volunteers by independent research groups are required before these approaches can be translated into clinical practice (Golkar & Ohman, 2012).

Dialectical Behaviour Therapy for Posttraumatic Stress Disorder (DBT-PTSD) has been established as an intervention for PTSD following childhood sexual abuse (Bohus et al., 2013). In recent years, exposure-based techniques have been combined with reappraisal and multimodal sensory stimulation to diminish the influence of dissociative symptoms, which often hamper learning in this clinical group (see skills-assisted exposure Görg et al., 2016). Reappraisal aims at focusing attention on the emotion-eliciting event, rather than avoiding it, while simultaneously providing new information about the fear-associated cue and thus neutralizing its emotional impact (Ochsner et al., 2002; Ray et al., 2005; Ray et al., 2008). Multimodal sensory stimulation ranks among 'grounding skills' (Bohus et al., 2013; Courtois & Ford, 2009; Jeffries & Davis, 2013). Thus, external sensory information such as haptic, acoustic and visual stimuli is used to block dissociative symptoms, i.e. the disruption and fragmentation of usually integrated functions of consciousness (Frewen & Lanius, 2014). An enhanced integration of external and internal stimuli is assumed to promote memory encoding (Powers, Cross, et al., 2015; van Heugten-van der Kloet, Giesbrecht, & Merckelbach, 2015).

The present study aimed at 1) replicating the erasure of fear memory by propranolol by an independent research group, and 2) testing whether established therapeutic approaches may benefit from a preceding reactivation of fear memory, to modify fear memory by induction of reconsolidation processes.

We hypothesized that propranolol administration as well as behavioural interventions, i.e. reappraisal and sensory stimulation, attenuate fear memory, restricted to the reactivated fear memory.

C3.3 Methods

C3.3.1 Participants

A total of 80 female participants participated in the study. Subjects were recruited via a call for participants on the website of the Central Institute of Mental Health, Mannheim as well as via flyers. Participants were informed about electric stimulation and potential drug administration. Subjects underwent a psychiatric and medical interview by a trained psychologist and physician to ensure mental and physical health. In case of any medical condition that contraindicated the intake of propranolol, subjects were excluded from further participation. The study was approved by the ethical committee of the Medical Faculty Mannheim/Heidelberg University. Written informed consent was obtained from each subject before participating in the study. Participants received a reimbursement for participation.

Subjects filled in self-report questionnaires, to assess trait and state anxiety (German version of the State-Trait Anxiety questionnaire, STAI Laux et al., 1981; Spielberger, Sydemann, Owen, & Marsh, 1999), spider (German version of the fear of spiders questionnaire, FAS, Rinck et al., 2002) as well as snake anxiety (German version of the snake questionnaire, SNAQ, Klorman, Hastings, Weerts, Melamed, & Lang, 1974). For further details on these questionnaires see C3.7.1.

Table 15. Sociodemographic and physiological sample characteristics study III

	Placebo (n=19)	**Propranolol (n = 20)**	**CRA (n = 20)**	**MMSS (n=20)**	**F**	***p***
Sociodemographics						
age (*mean/SD)*	23.89 (3.06)	25.50 (3.71)	24.80 (6.15)	26.65 (7.42)	0.97	.442
years of education *(mean/SD)*	11.78 (.63)	11.90 (.45)	11.60 (.82)	11.45 (.99)	1.13	.251
US characteristics						
Shock Intenstity (mA) *(mean/SD)*	15.73 (8.67)	13.60 (7.27)	17.30 (7.21)	17.20 (8.14)	0.97	.411
Trait Anxiety Assessment						
Spider Fear *(mean/SD)*	5.21 (8.21)	7.65 (8.49)	7.50 (11.19)	8.70 (12.26)	0.4	.753
Snake Fear *(mean/SD)*	5.00 (5.02)	4.20 (3.16)	3.55 (2.94)	5.25 (3.14)	0.89	.446
Trait Anxiety *(mean/SD)*	29.11 (5.09)	31.70 (5.85)	30.45 (5.78)	31.45 (5.94)	0.83	.479
US Evaluation						
Day 1 *(mean/SD)*	-2.78 (1.68)	-3.50 (1.05)	-3.05 (1.76)	-3.30 (1.26)		
Day 3 *(mean/SD)*	-2.94 (1.22)	-2.45 (1.63)	-2.45 (1.79)	-2.80 (0.95)		
State Anxiety Assessment						
day 1: state anxiety pre	29.16 (4.72)	32.52 (6.26)	31.70 (4.69)	32.50 (6.27)		
day 1: state anxiety post	31.63 (10.1)	35.35 (8.91)	33.20 (7.73)	32.40 (6.56)		
day 2: state anxiety pre	30.05 (6.28)	32.70 (8.19)	30.40 (5.24)	32.00 (6.74)		
day 2: state anxiety post	28.52 (4.71)	31.80 (6.21)	28.25 (6.27)	30.60 (6.23)		
day 3: state anxiety pre	29.62 (7.04)	34.15 (8.79)	31.60 (7.71)	31.35 (7.82)		
day 3: state anxiety post	30.42 (7.17)	33.75 (7.06)	31.85 (9.41)	33.70 (8.37)		

C3.3.2 Procedure

The experimental procedure was adapted from the protocol by Kindt and co-workers (see Kindt, Soeter, & Sevenster, 2014). On three consecutive days, participants underwent a fear acquisition phase (day 1), a memory reactivation phase combined with one of the four interventions (day 2), and a test phase during which retention, extinction and reinstatement of fear were assessed (day 3). See Figure 10 (for further information see Figure 12).

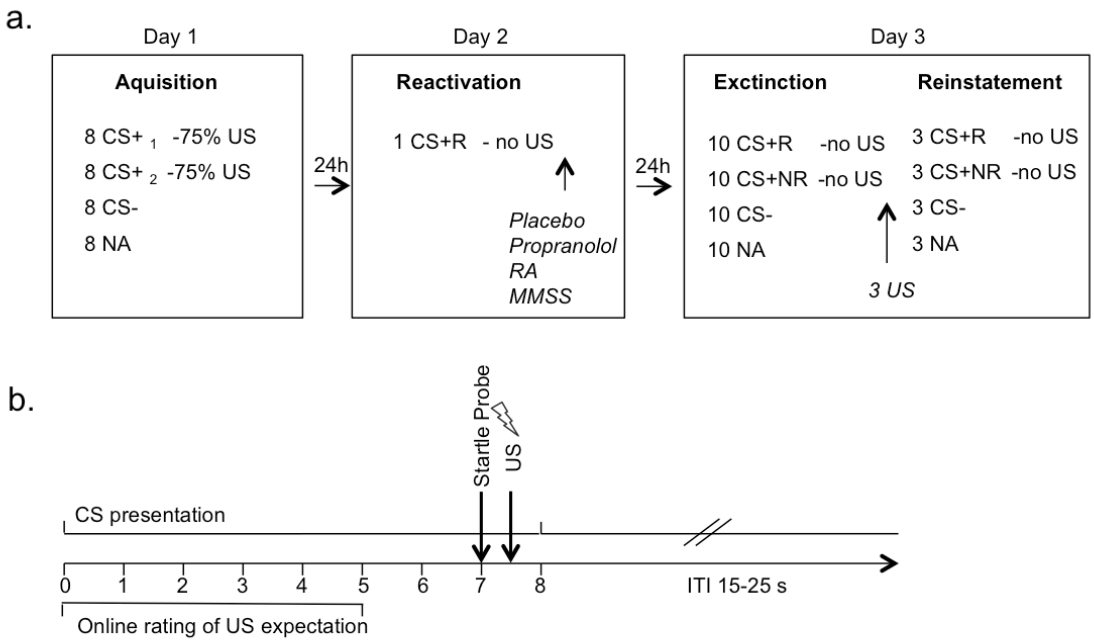

Figure 10: a) Schematic illustration of the experimental design b) A conditioning trial of a reinforced stimulus presentation (stimulus duration 8s (within the first 7s US expectancy rating), startle probe 7s after CS onset, US 500ms after startle probe onset (electric shock for 2ms with an individually determined intensity).

Interventions during reconsolidation:

During the reconsolidation time window, subjects underwent one of four interventions:

1) In the Propranolol condition, subjects received an oral dose of 40 mg propranolol similar as in previous studies (see Kindt et al., 2009; Sevenster et al., 2013, 2014b; Soeter & Kindt, 2010, 2011, 2012a, 2012b, 2015b).

2) In the Placebo condition, subjects received a placebo capsule, which was identical in size, shape and colour to the propranolol capsule. Both placebo and propranolol capsules were prepared and blinded by the pharmacy of the University Hospital Heidelberg.

3) In the Reappraisal (RA) condition, neutral information about the reactivated stimulus was presented for 15 minutes binaurally via headphones. For further details, see C3.7.1.

4) The Multimodal Sensory Stimulation (MMSS) condition provided multiple sensory stimulation to each subject for 15 minutes: optic stimuli were applied by a fantasy movie

trailer (e.g. “The Hobbit” by Peter Jackson, Warner Home Video; “Avatar” by James Cameron, Twentieth Century Fox) projected on a 150 x 150 cm (Lavolta, HD) screen (distance 270 cm); haptic stimulation by an massage chair providing intensive massage of the back area, and acoustic stimulation by a sample of daily noises (e.g. “Voice of America part 3/ LEGS” by Fred Frith, Step across the border, RecRec Music) presented binaurally via headphones. For further details, see C3.7.1.

Subjects were assigned randomly to the intervention conditions. Placebo and Propranolol were assigned in a double-blind design.

Experimental Procedure:

At each of the three testing sessions, participants were seated in a darkened room 80 cm in front of a computer screen. Each session started with a 5-minute resting period during which subjects watched an animal movie (“Winged Migration”, by Jacques Cluzaud, Michel Debats, Studiocanal) to allow habituation to the testing situation. Each day, throughout testing a 70 dB(A) broadband white noise was used as background noise. Testing started with a presentation of 10 startle probes to reduce initial startle reactivity. On each day, subjects rated state of anxiety (STAI-S, Laux et al., 1981; Spielberger et al., 1999) before and after testing. Blood pressure was measured at the start of each session as well as 90 minutes post intervention at day 2 (sphygmomanometer SBC 23, Sanitas). Subjects evaluated the US at the end of the session on day 1 and 3 on an 11-point rating scale ranging from -5 (unpleasant) to 5 (pleasant).

Day 1: Acquisition Phase: Three types of visual stimuli were presented 8 times each. Two fear-relevant stimuli were used as CS+ (spider and snake, IAPS, numbers 1220 and 1052) (Lang, Bradley, & Cuthbert, 2008). CS+ were linked in 75% of trials to an unpleasant, but not painful electric stimulation (US, duration 2ms, intensity individually adjusted). A fear-irrelevant stimulus served as a CS- (mug, IAPS number 7009) (Lang et al., 2008) and was never associated with an aversive event. Each CS presentation was coupled with a startle probe (duration of CS presentation 8s, onset of startle probe 7.5s after CS onset). For reinforced CS+ trials, the startle probe was followed after 500ms by the presentation of the US. In addition, 8 startle probes were presented alone (noise alone, NA). Inter-trial intervals (ITI) varied between 15, 20 and, 25 s (mean 20 s) (see Figure 10; for detailed description of stimuli and US characteristics see C3.7.1). Experimental trials were presented in a pseudo-random order with counterbalancing the position of the CS and NA trials. In each sequence, the first and last presentation of both CS+ were unreinforced to prevent that the reminder trial on day 2 results in extinction learning (LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998).

Subjects were instructed to learn to predict which of the pictures will be followed by an electric shock. Before the start of the testing, they were told that two pictures would be followed by an electric stimulus (US) in most of the cases, whereas a third picture would

never be followed by the US. Immediately after onset of each stimulus, subjects were asked to rate how strongly they expected that an US would occur. At the end of the acquisition phase, subjects were explicitly instructed to remember what they had learned to enhance retention of the CS-US contingency on the following days (Norrholm et al., 2006).

Day 2: Memory Reactivation Phase and Intervention: To ensure consolidation of the acquired fear memory, an interval of 24 hours was inserted. After electrode attachment, participants were instructed to remember what they had learned the day before, and told that the same pictures would be presented again. During testing, one of the CS+ (CS+R) was presented to reactivate fear memory. The presentation of the CS+R was followed by one NA trial. The non-reactivated CS+ (CS+NR) served as a fear-conditioned control stimulus on day 3, to test whether effects of the interventions depend on reactivation, i.e. whether they selectively affect the fear response to the CS+R, but not the CS+NR (see for similar design Soeter & Kindt, 2011, 2012b). The assignment of the two CS+ to the reactivation condition was counterbalanced.

One of the four interventions was administered 5 minutes post reactivation. To standardize the experimental setting, participants of the placebo and propranolol condition were sitting in front of a black computer screen for 15 minutes. Participants of the RA and MMSS condition were exposed to the specific intervention, respectively (for details see C3.7.1). Afterwards, electrodes were detached and participants were seated in a waiting room for about 60 minutes. Blood pressure was measured for 90 min after the onset of the intervention.

Day 3: Test Phases: Twenty-four hours after memory reactivation, participants underwent extinction training and reinstatement testing. Participants were told that the same three pictures provided on day 1 would be presented again. During the extinction phase, CS+R, CS+NR and CS-, as well as NA trials were presented 10 times, respectively. Subsequently, fear memory was reinstated by presenting three unsignalled reminder shocks (time interval between the last trial of the extinction phase and the first US: 19 s). In the reinstatement test phase, 3 CS and NA each were presented in a pseudo-randomized order. The first trial started 15s after the last unsignalled US.

Measurement Parameters:

Fear response was assessed by three dependent variables, i.e. US online expectancy ratings, fear potentiated startle amplitude and skin conductance response.

US online expectancy (OE-R): With each CS+ and CS- onset, subjects were asked to rate their expectancy of an electric shock (11 point-Likert scale, ranging from -5: sure no shock to +5: sure a shock). The rating scale was displayed on the bottom of the screen and choices were selected by moving a cursor with a pen on a graphical tablet (Wacom intuos5 touch pen tablet, (PTH 850 IT)). Responses had to be done within a 5 s interval after stimulus onset. Missing values were replaced by means of moving average interpolation within each subject,

stimulus type and experimental phase, except for the first and the last trial of fear acquisition and extinction learning, the reactivation trial and reinstatement testing. Regarding the first and last trial of fear acquisition and extinction learning, missing values were replaced by means of nearest neighbour interpolation.

Fear Potentiated Startle (FPS): The conditioned fear response was measured via the potentiation of the eye-blink startle reflex to a loud noise by electromyography (EMG) of the left orbicularis oculi muscle. The acoustic startle reflex is a specific measure of fear (Hamm & Weike, 2005), and is modulated by the amygdala (Davis, 2006). Two electrodes with a diameter of 13 mm each, filled with electrolyte gel (Synapse, Costumer Kinetics) were positioned approximately 1 cm under the pupil and 1 cm below the lateral canthus (Blumenthal et al., 2005). The eye-blink EMG activity was measured with an EMG amplifier (Varioport, Becker Meditec, input resistance of 500 MΩ, bandwidth of 19–500 Hz (-3dB), sampling rate 1024Hz). EMG data were pre-processed using in-house software (MatLab 2011b, MathWorks) following a standard procedure (Blumenthal et al., 2005). Raw data were filtered (50Hz notch filter, 28-Hz high-pass filter, 4th order Butterworth filter), rectified and smoothed (low-pass filter 50Hz). Startle amplitude was measured as the maximum peak within a time window of 20-150ms following the onset of the startle probe referenced to mean baseline level (500ms before onset of the startle probe). Outliers were defined ($Z > 3$) and replaced by the maximum z-score. Missing values were replaced by means of nearest-neighbour interpolation within each subject, stimulus type and experimental phase, except the reactivation trial. To normalize the data and to reduce the influence of between-subjects variability, startle amplitudes across all phases of the study were standardized together using within-subject t-score conversion (Bos et al., 2012; Golkar & Ohman, 2012).

Skin Conductance Response (SCR): Electrodermal activity was measured using an electrodermal response amplifier (Varioport, Becker Meditec) by applying a DC voltage of 0.5 Volt. Data was collected with a bandwidth of 0 – 50 micro Siemens (µS) and a solution of 0.002 µS. Two electrodes with a diameter of 13 mm were attached to the ball of the thumb on the non-preferred hand. Analogous to Kindt and colleagues (Kindt & Soeter, 2013; Kindt et al., 2009; Sevenster et al., 2014a), SCR elicited by the CS was determined by taking the peak-to-baseline difference within the 1 to 7 s window following stimulus onset. A minimum response criterion was set to 0.02 µS and filtered with 1 Hz. All other responses were scored as zero and included in the analyses (Soeter & Kindt, 2010). Raw SCR scores were square-root-transformed to normalize distributions (Golkar & Ohman, 2012; Schiller et al., 2013; Schiller et al., 2010; Steinfurth et al., 2014).

C3.3.3 Statistical Analyses

Sociodemographic variables (age, years of education), trait anxiety, spider and snake phobia characteristics and the intensity chosen for the electrical shock were analysed in separate

one-factorial variance-analytical designs (ANOVA) with ‘type of intervention’ as between-subjects factor. To examine differences in state anxiety between intervention groups over the course of testing, a 4 x 3 x 2 repeated measure ANOVA (rmANOVA) was applied with the between-subjects factor ‘type of intervention’ (Placebo vs. Propranolol vs. RA vs. MMSS) and the within-subject factors ‘experimental phase’ (acquisition, reactivation and test phase, i.e. day 1, 2 and 3) and ‘time’ (pre- vs. post-testing). In addition, evaluation of the US over the course of testing was assessed with a 4 x 2 rmANOVA with the between-subjects factor ‘type of intervention’ and the within-subject factor ‘day’ (day 1 and day 3).

To ensure comparability with previous studies and simultaneously reduce the complexity of the statistical designs, we compared each of the three active interventions (propranolol, RA, MMSS) to the placebo control condition in separate analyses. The effect of the intervention group on systolic and diastolic blood pressure on day 2 was analysed with a 2 x 2 rmANOVA, with the between-subject factor ‘type of intervention’ (placebo vs. propranolol) and the within-subject factor ‘time’ (pre-testing day 2 vs. 90 min post intervention day 2).

Fear response was assessed by three dependent variables (OE-R, FPS, SCR) and analysed for fear acquisition, retention, extinction learning and reinstatement, respectively.

We run separate rmANOVAs with the between-subject factor ‘type of intervention’ (Placebo vs. Propranolol/ RA/ MMSS) and the within-subject factors ‘stimulus type’ (CS-, CS+R, CS+NR) and ‘time’. The factor ‘time’ was calculated as following a) for the acquisition of fear: the 8 trials of the acquisition phase on day 1 averaged over two consecutive trials resulting in a 2 x 3 x 4-design, b) for the retention of fear: the average of the last 2 trials of the acquisition phase on day 1 and the average of the first two trials of the extinction phase on day 3 resulting in a 2 x 3 x 2-design, c) for extinction learning: the average of the first two trials and the last two trials of the extinction phase on day 3 (2 x 3 x 2-design), and d) for reinstatement: the average of the last two trials of the extinction phase and the first reinstatement test trial after the presentation of three reminder shocks on day 3 (2 x 3 x 2-design). For further description of statistical effects, post-hoc comparisons were calculated as appropriate by sub-designs of the main design or pairwise comparisons (Bonferroni adjusted for multiple testing).

Statistical significance was set to $p < .05$. All analyses were performed using SPSS (version 22; SPSS Inc., USA).

C3.4 Results

C3.4.1 Sample description

The four intervention groups were comparable in age ($F(3,75) = .91$, $p = .442$), years of education ($F(3,75) = 1.39$, $p = .251$), trait anxiety ($F(3,75) = .83$, $p = .479$), snake ($F(3,75) = .89$, $p = .446$) and spider phobia ($F(3,75)= .94$, $p = .753$). Moreover, intervention groups did not differ in their objectively selected electric shock intensity ($F(3,75) = .97$, $p = .411$) (see Table 15). US evaluation differed over time depending on the intervention (intervention x time: $F(1,75) = 2.89$, $p = .041$) with a reduction of unpleasantness over time for the propranolol, RA and MMSS groups compared to the placebo group. Consistent with other studies (e.g. Soeter & Kindt, 2010), intervention groups were comparable in their state anxiety over the course of testing ($F(6,148) = 1.06$, $p = .389$). For further details on sample characteristics see Table 15.

C3.4.2 Manipuation check propranolol

Systolic or diastolic BP as well as HR did not decrease in the propranolol as compared to the placebo group on day 2 (systolic BP: $F(1,37) = 2.02$, $p = .164$, diastolic BP: $F(1,37) = .024$, $p = .878$, HR: $F(1,36) = 2.78$, $p = .102$). For means and SD see Table 18.

C3.4.3 Experimental tasks

Results of the ANOVAs are reported in Table 16 and 17. Mean US expectancy ratings and fear potential startle amplitudes are displayed for the four intervention groups in Figure 11. Since statistical analyses revealed no differences for the behavioural interventions (RA, MMSS) as compared to the placebo condition (see Table 16, 17), we restrict the results description to the analyses of propranolol as compared to the placebo condition. For further information on the analyses for RA and MMSS, see C3.7.2.

Fear Acquisition Propranolol compared to Placebo:

To test for the successful acquisition of fear, we analysed the change of the dependent variables over the course of the acquisition phase. Differences between both CS+ compared to the CS- in the linear trend as well as increased responses to both CS+ as compared to the CS- at the end of fear acquisition phase are indicative of successful fear acquisition.

US Online Expectancy Ratings (OE-R): OE-R differed between stimulus types depending on time ($F(6,222) = 67.43$, $p < .001$; see Table 16, Figure 11). This effect was not influenced by the intervention condition (intervention x stimulus x time: $F(6,222) = 1.10$, $p = .362$). The linear trend over time differed for both the CS+R and the CS+NR compared to the CS- (post-hoc contrasts: CS+R: $F(1,36) = 100.69$, $p < .001$; CS+NR: $F(1,36) = 191.92$, $p < .001$). A direct comparison of the OE-R between CS+R and CS+NR revealed no differential change over time (2x4-ANOVA sub-design: stimulus x time: $F(3,114) = .71$, $p = .546$). Post-hoc tests revealed that at the end of the acquisition phase the OE-R was higher for CS+R and CS+NR

as compared to CS- (both $p < .001$), while no differences were found between both CS+ ($p > .1$).

Fear Potentiated Startle (FPS): FPS differed between stimulus types depending on time ($F(6,216) = 3.05$, $p = .007$; see Table 17, Figure 11). This effect was not influenced by the type of intervention (intervention x stimulus x time: $F(6,216) = 0.65$, $p = .663$). The linear trend over time differed for both the CS+R and the CS+NR compared to the CS- (post-hoc contrasts: CS+R: $F(1,36) = 5.71$, $p = .022$; CS+NR: $F(1,36) = 4.59$, $p = .039$). In addition, the change in FPS change over time was different between CS+R and CS+NR (2x4-ANOVA sub-design: stimulus x time: $F(3,111) = 3.03$, $p = .033$). While there were no differences in the linear trend between both conditions ($F(1,36) = 0.41$, $p = .527$), post-hoc contrasts revealed a differential quadratic trend ($F(1,36) = 7.01$, $p = .012$). This suggests that the interaction effect was caused by a stronger change in CS+NR as compared to the CS+R at the start of the acquisition phase. However, at the end of the acquisition phase FPS was higher for CS+R and CS+NR as compared to CS- (both $p < .003$) and there was no difference between both CS+ ($p > .1$).

Skin Conductance Response: Overall analysis of variance did not reveal significant fear acquisition (stimulus x time: all F's < 1.81, all *p's* > .099). Therefore, no further data on SCR are reported.

Retention Propranolol compared to Placebo:

The retention of fear is measured as the strength of the fear response at the start of the extinction phase compared to the end of the acquisition phase. A stronger reduction of fear in response to the CS+R as compared to the CS+NR and a lower fear response to the CS+R compared to the CS+NR at the start of extinction, indicate a fear attenuation effect, which is specific for the reactivated CS+.

US Expectancy Ratings (OE-R): OE-R differed between stimulus types depending on time ($F(2,74) = 7.86$, $p = .001$; see Table 16, Figure 11) without an influence of the intervention condition (intervention x stimulus x time: $F(2,74) = .24$, $p = .792$). The OE-R change from the end of the acquisition phase to the start of extinction differed for both the CS+R and the CS+NR as compared to the CS- (post-hoc contrasts: all *p*'s < .015). No difference was found in OE-R between CS+R and CS+NR depending on time (2x2-ANOVA sub-design: stimulus x time: $F(1,38) = 1.45$, $p = .236$). Post-hoc tests revealed that OE-R dropped for both CS+ from the end of acquisition to the start of the extinction phase (both $p < .05$) while there was no change in O-ER for CS- ($p = .780$). Nevertheless, OE-R was higher in response to the CS+R and the CS+NR compared to the CS- (both $p < .001$) without a difference between OE-R of both CS+ at the start of the extinction phase ($p > .1$).

Fear Potentiated Startle (FPS): FPS differed between the two intervention conditions depending on stimulus type and time (intervention x stimulus x time: $F(2,72) = 3.77$, $p = .028$;

see Table 17, Figure 11). Intervention conditions differed in change of FPS over time when comparing the CS+NR to the CS- ($F(1,36) = 6.39$, $p < .016$), but not when comparing the CS+R to the CS- ($F(1,36) = 0.36$, $p = .551$). A direct comparison of both CS+ with an additional ANOVA sub-design revealed that intervention conditions differed in FPS change also on a trend-level for CS+R and CS+NR (2x2x2-ANOVA sub-design: intervention x stimulus x time: $F(1,36) = 3.94$, $p = .055$). At the start of the extinction phase, FPS was higher in response to the CS+NR as compared to the CS- as well as to the CS+R in the propranolol condition (both $p <.011$), while FPS did not differ between the three stimulus types in the placebo condition (all $p > .411$).

Extinction learning Propranolol compared to Placebo:

To test effects during extinction learning, dependent variables were contrasted for the start to the end of the extinction phase.

US-Expectancy Ratings (OE-R): OE-R differed between stimulus types depending on time ($F(2,74) = 267.51$, $p < .001$; see Table 16, Figure 11). This effect was not influenced by the intervention condition (intervention x stimulus x time: $F(2,74) = .06$, $p = .944$). The OE-R change from the start to the end of the extinction phase differed for both the CS+R and the CS+NR as compared to the CS- (post-hoc contrasts: all p's $< .001$). No difference was detected in OE-R between CS+R and CS+NR depending on time (2 x 2-ANOVA sub-design: stimulus x time: $F(1,38) = .77$, $p = .386$). Post-hoc tests revealed lower OE-R to both CS+ during the end as compared to the start of extinction learning (both $p < .001$), while only a trend was found for CS- between phases ($p = .086$). At the end of the extinction phase, OE-R was still higher for both CS+ compared to the CS- (both $p < .013$), while there was no difference between both CS+ ($p > .1$).

Fear potentiated startle (FPS): FPS differed between stimulus types depending on time without an influence of the intervention condition (stimulus x time: $F(2,68) = 3.37$, $p = .040$; intervention x stimulus x time: $F(2,68) = .64$, $p = .533$; see Table 17, Figure 11). While no differential change over time was revealed by post-hoc contrasts for both CS+ compared to the CS- (both p's $> .114$), a direct comparison between both CS+ revealed a stronger decrease of FPS from the start to the end of the extinction phase for CS+NR than for CS+R (2x2-ANOVA sub-design: stimulus x time: $F(1,36) = 7.04$, $p = .011$).

Reinstatement Propranolol compared to Placebo:

The reinstatement of fear is measured as the strength of the fear response at the end of the extinction phase compared to the first trial upon the unsignalled US presentations. A stronger increase of fear in response to the CS+NR as compared to the CS+R and a lower fear response to the CS+R compared to the CS+NR in response to the reinstatement test trial, indicate the prevention of fear memory recovery, which is hypothesized to be specific for the reactivated CS+.

US Expectancy Ratings (OE-R): OE-R differed between stimulus types depending on time ($F(2,70) = 15.31$, $p < .001$; see Table 16, Figure 11). This effect was not influenced by the intervention condition (intervention x stimulus x time: $F(2,70) = .78$, $p = .462$). The OE-R change from the end of the extinction phase to reinstatement differed for both the CS+R and the CS+NR as compared to the CS- (post-hoc contrasts: all p's < .002). No difference was found in OE-R change between CS+R and CS+NR (2x4-ANOVA sub-design: stimulus x time: $F(1,36) = 2.22$, $p = .145$). Post-hoc tests revealed higher OE-R to both CS+ at reinstatement testing as compared to the end of extinction learning (both $p < .001$), while change over time regarding the CS- was only a trend ($F(1,36) = 3.25$, $p = .094$). At reinstatement testing, OE-R was higher to both CS+ compared to the CS- (both $p < .020$), with no difference between both CS+ ($p > .1$).

Fear Potentiated Startle (FPS): FPS increased over time ($F(1,34) = 22.49$, $p < .001$; see Table 17, Figure 11), independently of the intervention condition and the stimulus type (intervention x stimulus x time: $F(2,68) = .24$, $p = .786$; stimulus x time: $F(2,68) = .15$, $p = .829$). In general, FPS differed between stimulus types ($F(2,68) = 11.97$, $p < .001$). Post-hoc tests revealed a larger FPS to both CS+ as compared to the CS- overall (both $p < .001$), with no differences between CS+ ($p > .1$).

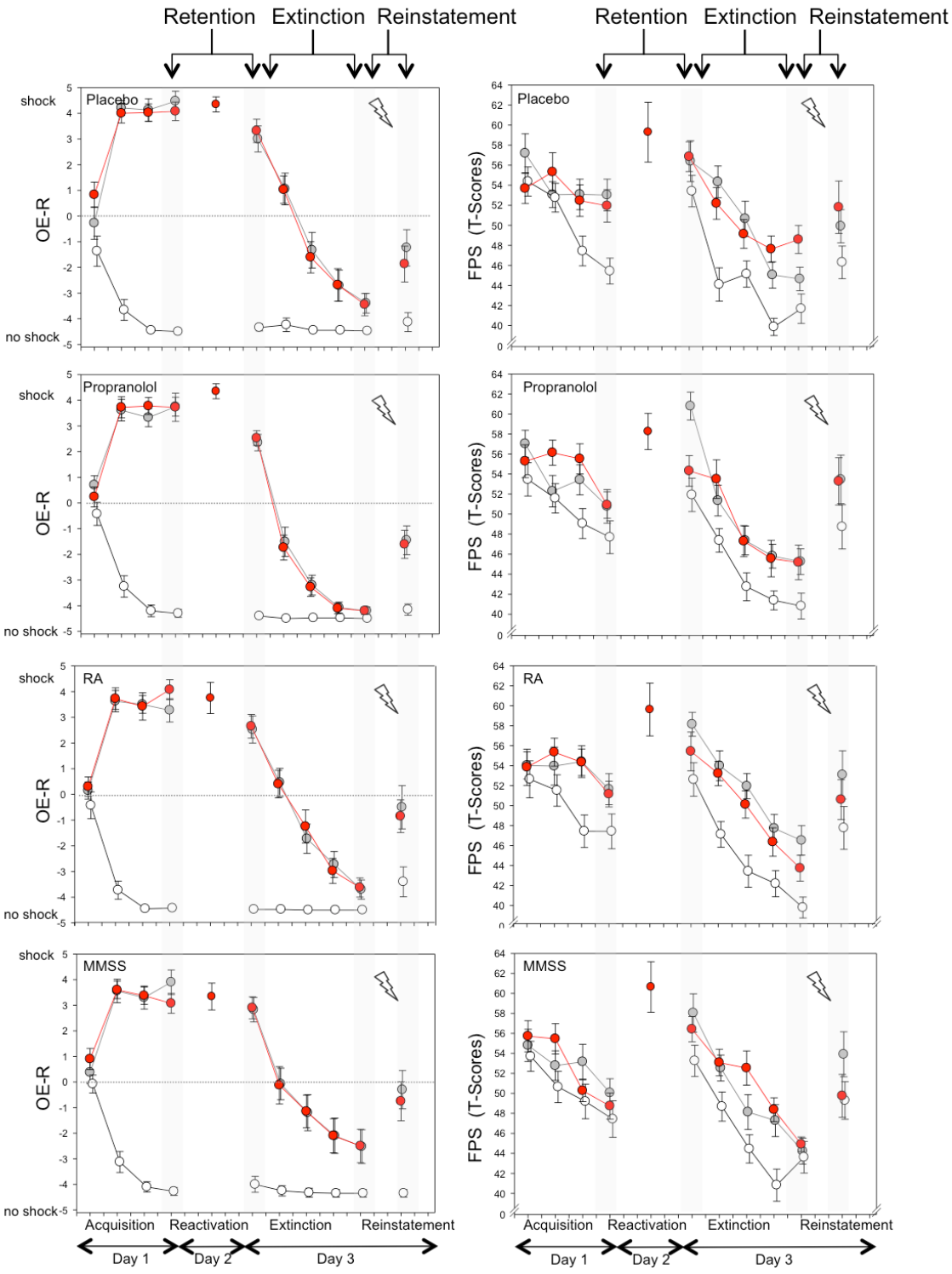

Figure 11: US online expectancy ratings (OE-R, left column) and fear potentiated startle (FPS, right column) for the four intervention conditions (placebo, propranolol, cognitive reappraisal (RA), multisensory stimulation (MMSS)) and the three types of stimuli (white circles: CS-, red circles: reactivated CS+, grey circles: non reactivated CS+) for the different phases of the experimental procedure (please note, data corresponds to averages across two consecutive trials, except for reinstatement, which displays the first trial after reinstatement)

Table 16. Summary of rmANOVAs testing US-E separate for each experimental phase. Intervention groups are compared to placebo condition, respectively.

	Propranolol			**CRA**			**MMSS**		
	F	p		F	P		F	p	
Acquisition									
Intervention	0.14	.712		0.49	.484		0.15	.698	
Stimulus Type	462.74	<.001	*	548.04	<.001	*	446.46	<.001	*
Time	15.544	<.001	*	18.58	<.001	*	13.89	<.001	*
Intervention x Stimulus Type	1.78	.175		1.46	.240		3.12	0.5	*
Intervention x Time	1.05	.372		1.98	.121		2.64	.053	*
Stimulus Type x Time	67.44	<.001	*	77.51	<.001	*	68.56	<.001	*
Intervention x Stimulus Type x Time	1.1	.362		1,018	.414		0.21	0.98	
Retention									
Intervention	2.6	.115		1.67	.205		0.89	.350	
Stimulus Type	707.74	<.001	*	576.81	<.001	*	483.28	<.001	*
Time	12.65	<.001	*	13.69	.001	*	5.76	.022	*
Intervention x Stimulus Type	1.46	.239		1.16	.318		1.55	.219	
Intervention x Time	0.21	.647		0.02	.901		0.75	.391	
Stimulus Type x Time	7.87	.001	*	7.24	.001	*	8.15	.001	*
Intervention x Stimulus Type x Time	0.24	.792		2.03	.139		0.21	.815	
Reinstatement									
Intervention	0.24	.627		0.33	.567		1.29	.262	
Stimulus Type	29.68	<.001	*	18.98	<.001	*	31.87	<.001	*
Time	42.14	<.001	*	55.22	<.001	*	27.88	<.001	*
Intervention x Stimulus Type	0.23	.794		0.08	.920		1.52	0.23	
Intervention x Time	1.6	.214		4.66	.038	*	0.01	.946	
Stimulus Type x Time	15.31	<.001	*	6.54	.002	*	10.65	<.001	*
Intervention x Stimulus Type x Time	0.78	.462		.094	.910		0.18	.837	

Table 17. Summary of rmANOVAs testing FPS separate for each experimental phase. Intervention groups are compared to placebo condition, respectively.

	Propranolol			**CRA**			**MMSS**		
	F	p		F	P		F	p	
Acquisition									
Intervention	0.08	.781		0.03	.876		0.37	.549	
Stimulus Type	13.69	<.001	*	14.21	<.001	*	12.56	<.001	*
Time	12.73	<.001	*	8.89	<.001	*	14.48	<.001	*
Intervention x Stimulus Type	0.67	.515		0.15	.858		0.68	.508	
Intervention x Time	0.59	.623		0.7	.553		.190	.903	
Stimulus Type x Time	3.05	.007	*	2.99	.008	*	1.88	.085	
Intervention x Stimulus Type x Time	0.65	.691		0.72	.637		1.53	.169	
Retention									
Intervention	0.02	.889		0.02	.892		0.38	.542	
Stimulus Type	14.79	<.001	*	12.89	<.001	*	9.71	<.001	*
Time	20.22	<.001	*	15.94	<.001	*	24.97	<.001	*
Intervention x Stimulus Type	0.99	.377		0.35	.705		0.81	.448	
Intervention x Time	0.03	.854		.001	.970		0.48	.492	
Stimulus Type x Time	0.88	.418		0.62	.538		0.21	.814	
Intervention x Stimulus Type x Time	3.77	.028	*	1.24	.297		1.68	.194	
Reinstatement									
Intervention	0.63	.433		0.04	.841		0.15	.703	
Stimulus Type	11.97	<.001	*	10.88	<.001	*	4.46	.015	*
Time	22.48	<.001	*	24.47	<.001	*	21.49	<.001	*
Intervention x Stimulus Type	0.62	.539		2.34	.103		2.26	.111	
Intervention x Time	2.28	.140		1.36	.252		0.94	.340	
Stimulus Type x Time	.148	.862		0.25	.776		2.05	.136	
Intervention x Stimulus Type x Time	0.24	.786		0.23	.793		0.34	.713	

C3.5 Discussion

The objective of the present study was to investigate whether different interventions are suited to alter or erase fear memory by targeting reconsolidation processes. We aimed at a) replicating the fear-erasing effect of propranolol in disrupting reconsolidation processes, and b) testing effects of reappraisal and sensory stimulation on fear memory, when applied after reactivation of a fear-associated stimulus during the time window of reconsolidation. As expected, during retention testing we observed 1) comparable fear responses for the reactivated fear-conditioned stimulus and the non-fear associated stimulus and 2) stronger fear responses to the non-reactivated fear-conditioned stimulus. However, these effects could not be explained by an erasure of fear for the reactivated CS+, but instead by a stronger fear response to the non-reactivated CS+ as revealed by the placebo control condition. Thus, we were not able to replicate an erasure of fear by the administration of propranolol. In contrast to our hypotheses, RA and MMSS did not result in an attenuation of fear for the reactivated fear-conditioned stimulus. Instead, we observed a similar fear response during retention and reinstatement testing for all stimulus types, suggesting a generalization of fear to the neutral control stimulus.

Several studies by Kindt and co-workers have demonstrated a beneficial effect of propranolol on fear memory. This led to increasing hopes for a successful translation of this approach to the treatment of fear in mental disorders (Kindt et al., 2009; Sevenster et al., 2013, 2014b; Soeter & Kindt, 2010, 2011, 2012a, 2012b). A precondition for this effect is the reactivation of the fear-associated stimulus: In the studies by Kindt and co-workers, fear was selectively reduced for the reactivated CS+, but not for the non-reactivated CS+ suggesting a potential specificity for targeting pathological fear responses (Soeter & Kindt, 2011, 2012b). Semantic instead of perceptual differences between fear-associated stimuli appear to be essential to trigger differential disruption of reconsolidation processes (Soeter & Kindt, 2015b). In variations of their experimental setups, Kindt and co-workers consistently demonstrated that propranolol reduced fear-potentiated startle responses when the substance was effective during the time window of reconsolidation, i.e. when propranolol was applied between 90 min before (Kindt et al., 2009; Soeter & Kindt, 2010, 2011, 2012b) to 5 min after reactivation (Sevenster et al., 2013, 2014b; Soeter & Kindt, 2012a, 2012b). Beneficial effects were observed both during retention and reinstatement testing for FPS, as well as during a follow-up one month later, suggesting that fear memory was not only attenuated but also actually erased (Soeter & Kindt, 2010). These effects were observed for FPS. In contrast, contingency learning, i.e. measurements of declarative memory such as online ratings of the expectation of the aversive event, as well as skin conductance response were not influenced by a propranolol administration (Bos et al., 2012, 2014; Kindt et al., 2009; Sevenster et al., 2013, 2014b; Soeter & Kindt, 2010). One explanation for these differential effects on

emotional and declarative fear memory is that propranolol blocks ß-adrenergic receptors within the basolateral amygdala, which are needed for long-term potentiation and thus specifically disrupts the emotional expression of fear (Huang & Kandel, 2007; Hurlemann et al., 2010; Kindt et al., 2009; Soeter & Kindt, 2010; van Well, Visser, Scholte, & Kindt, 2012). In line with these studies, we found no effects of propranolol administration on the cognitive level of fear memory, i.e. in online expectancy ratings, but differences in the emotional fear response during retention testing, depending on a reactivation of the fear-associated stimulus. Retention of fear measured by FPS was stronger for the non-reactivated CS+ as compared to the CS- and the reactivated CS+. Contrasting these changes with those observed after placebo administration revealed that fear response did not differ for the CS- and the reactivated CS+, but only for the non-reactivated CS+. This suggests that differences between stimulus types were not actually explained by an erasure of fear towards the reactivated CS+, but by a stronger fear response to the non-reactivated CS+. In line, reinstatement testing did not reveal a differential effect of propranolol upon the different stimulus types suggesting that indeed fear was not erased but generalized to the previously neutral CS-.

Our findings are in line with previous studies that failed to replicate beneficial effects of a pharmacological or behavioural intervention during the time window of reconsolidation. A recent study of the research group of Kindt could not replicate the otherwise often demonstrated erasure of fear after propranolol administration without identifying the conditions that may have prevented the beneficial effect (Bos et al., 2014). The present study, which similarly found no fear-erasing effect of propranolol, was to the best of our knowledge the first attempt to replicate the effects of propranolol by an independent research group. In contrast to the pharmacological intervention with propranolol, there exist several studies by independent groups that aimed at replicating the effects of behavioural interventions as first described by Schiller and co-workers (Schiller et al., 2010). Some of these confirmed a superior fear attenuation of extinction when applied during reconsolidation (Agren, Engman, et al., 2012; Agren, Furmark, et al., 2012; Oyarzun et al., 2012), however, several others did not replicate this effect (Golkar & Ohman, 2012; Kindt & Soeter, 2013; Klucken et al., 2016; Soeter & Kindt, 2011).

These inconsistent findings have recently been discussed in the context of so-called boundary conditions that may restrict the induction of reconsolidation processes, and as a consequence, the potential to actually modify a consolidated memory trace (Bos et al., 2012; Finnie & Nader, 2012; Golkar & Ohman, 2012; Schwabe et al., 2014).

Boundary conditions comprise e.g. features of the experimental procedures, which can affect the memory strength during acquisition and the updating of a memory trace. Moreover, characteristics of the memory itself such as its age as well as features of the enrolled

participants may influence findings. However, none of these boundary conditions appear to be able to explain our propranolol findings. Regarding experimental features, we aimed to closely follow the experimental protocol of the studies of Kindt and co-workers (Kindt & Soeter, 2014; Soeter & Kindt, 2011, 2012b). For example, a higher number of CS-US pairings, as well as a higher US reinforcement rate have been linked to stronger fear memories, which are particularly resistant to modification during reconsolidation (Oyarzun et al., 2012; Suzuki et al., 2004; Wang, Ostlund, Nader, & Balleine, 2005). Both CS-US pairings as well as reinforcement rates in our study were comparable to those used in previous experiments (e.g. number of CS-US pairings = 6, similar to Kindt et al., 2009; Soeter & Kindt, 2010); reinforcement rate = 75%, similar to Kindt et al., 2009; Soeter & Kindt, 2010). Memory updating may also be hampered if the memory retrieval trial does not present novel or relevant information. Instead, the reminder trial has to generate a mismatch between what is expected and what actually happens (Sevenster et al., 2012, 2013, 2014b). However, the expectancy rating as well as the FPS in response to the reminder stimulus on day 2 indicated a high expectation of the US, as well as an emotional fear response, suggesting the occurrence of the mismatch required for memory updating (see Figure 11, C3.7.2) (Sevenster et al., 2012, 2013, 2014b). Moreover, the age of the acquired fear memory is in line with previous studies, i.e. reactivation was done 24 h after fear acquisition (Kindt et al., 2009; Schiller et al., 2013; Schiller et al., 2010; Sevenster et al., 2012, 2013, 2014b; Soeter & Kindt, 2010, 2011). Finally, fear erasure is less efficient in subjects high in trait anxiety (Soeter & Kindt, 2013). However, an additional analysis of the potential link between trait anxiety and retention of fear revealed no association, suggesting that trait anxiety does not contribute to our findings (see C3.7.2).

Similarly to the failure of propranolol to erase fear memory, our data does not support beneficial effects of the combination of established therapeutic techniques and reconsolidation processes. Neither reappraisal nor multisensory stimulation resulted in an attenuation of fear, not to mention an erasure of fear. This was true for both contingency learning, as well as the emotional fear response measured by FPS. While the mentioned boundary conditions affect pharmacological as well as behavioural interventions, the choice of the selected stimulus material may have particularly contributed to our findings regarding reappraisal or multisensory stimulation. Most studies confirming a beneficial effect of behavioural interventions, i.e. extinction training during reconsolidation, associated the fear response to neutral stimuli such as coloured geometrical shapes (Agren, Engman, et al., 2012; Agren, Furmark, et al., 2012; Oyarzun et al., 2012; Schiller et al., 2013; Schiller et al., 2010; Steinfurth et al., 2014). In contrast, we used fear-relevant stimuli paired with an electric shock (see for similar design Soeter & Kindt, 2011, 2012b) and these are assumed to be more resistant to extinction learning. Therefore, this experimental feature may have

contributed to the missing effect of reappraisal or multisensory stimulation. However, Golkar and co-workers (Golkar & Ohman, 2012) targeted the fear-relevance of the applied stimuli and failed to replicate fear attenuation after a behavioural intervention with both fear-relevant and fear-irrelevant stimuli.

Irrespective of the intervention group, we observed a generalization of the emotional fear response to the CS- during both, retention and reinstatement testing. Although generalization of fear is observed in many studies (Ghirlanda & Enquist, 2006; Lissek et al., 2008; Shepard, 1987) and is discussed as an important factor in the development of fear-related mental disorders (Dymond, Dunsmoor, Vervliet, Roche, & Hermans, 2015), the exact underlying mechanism is still under debate (Dunsmoor & Murphy, 2015). Generalization of fear has been related to many different processes ranging from the perception of stimuli features (Lissek et al., 2008; Lissek et al., 2010) over category induction, comprising pre-existing knowledge about the nature of a relationship (Dunsmoor & Murphy, 2015), to new category learning (Vervoort, Vervliet, Bennett, & Baeyens, 2014). Moreover, subject characteristics such as the level of trait anxiety or the affective mood modulate generalization processes (Geschwind, Meulders, Peters, Vlaeyen, & Meulders, 2015). In studies on pharmacological and behavioural interventions during reconsolidation, generalization of fear to the non-fear-conditioned control stimulus have been observed simultaneously with a failure to erase fear (e.g. Bos et al., 2012, 2014; Golkar & Ohman, 2012; Kindt & Soeter, 2013). Golkar et al. (Golkar & Ohman, 2012) observed a generalization of fear during reinstatement in response to fear-relevant, but not to fear-irrelevant stimuli, while Kindt and colleagues (2013) linked a generalization of fear during reinstatement to subjects' trait anxiety. In line with that, worrying about feared outcomes resulted in an enhanced FPS to the CS- (Gazendam, Kamphuis, & Kindt, 2013). A recent study by Geschwind et al. (Geschwind et al., 2015) suggests that the affective state after learning modifies safety learning and the generalization of fear. Similarly, Onat & Büchel (Onat & Buchel, 2015) emphasized the relevance of ambiguity-based uncertainty and threat identification processes when building a flexible and adaptive fear response.

Based on our data, we cannot identify factors responsible for the observed generalization effect. However, exploratory analyses of our data revealed that trait anxiety is not sufficient to explain the generalization of fear (see C3.72). Overall, generalization is a complex phenomenon. Further studies are needed that investigate in detail which factors may contribute to generalization in standard procedures for studying modifications of fear memory in the context of reconsolidation processes.

Finally, some limitations of the present study have to be addressed. First of all, the physiological effect of propranolol was not confirmed by heart rate and blood pressure decreases. However, the mean BP of our sample points to a floor effect: Baseline BP level in

our sample equaled that observed after propranolol administration in previous studies (Bos et al., 2012; Soeter & Kindt, 2010, 2012b) (see Table 18). Moreover, we included only female subjects. While this resulted in a highly homogenous sample, it limits the generalizability of the present findings. Since female participants were overrepresented in recent publications (Kindt et al., 2009; Soeter & Kindt, 2010, 2011, 2012a, 2012b), it appears to be unlikely that our findings can be explained by this sample characteristic. Nevertheless, further studies are required that investigate potential gender effects on the studied processes. Finally, in contrast to declarative memory, emotional fear learning was supported statistically only on a trend-level for the multisensory intervention condition. Thus, findings on this intervention have to be interpreted with caution. Nevertheless, we observed discrimination between stimulus types at the end of fear learning in FPS. In addition, FPS as well as US expectation in response to the reactivated conditioned stimulus on day 2 suggests that at least the reactivated CS+ evoked a fear response. Finally, we were not able to investigate potential effects of our interventions on SCR since this parameter did not reveal fear acquisition. While studies by Kindt and co-workers (Kindt et al., 2009; Sevenster et al., 2014b; Soeter & Kindt, 2010, 2011, 2012a, 2012b) suggest that propranolol administration had no effect on SCR, behavioural interventions have affected particularly this variable (Agren, Engman, et al., 2012; Agren, Furmark, et al., 2012; Schiller et al., 2013; Schiller et al., 2010; Steinfurth et al., 2014). While previous studies on behavioural interventions (Schiller et al., 2013; Schiller et al., 2010; Steinfurth et al., 2014) have excluded up to one third of the studied sample to restrict analyses to only those subjects that exhibited higher SCR to CS+ compared to CS-, a similar procedure in the present study would have resulted in too small

C3.6 Conclusion

Reconsolidation research points to an efficient mechanism, which could be used for the treatment of anxiety disorders. Indeed, first investigations revealed promising results (James et al., 2015; Soeter & Kindt, 2015a): combining reactivation with a pharmacological agent in spider-fearful participants (Soeter & Kindt, 2015a) or a visuo-spatial task in subjects exposed to experimentally induced “trauma” (James et al., 2015) attenuated fear memory and prevented fear-related behaviour. Yet, an increasing number of studies – including our experiments – suggest difficulties in triggering reconsolidation processes. Although many boundary conditions for inducing reconsolidation have been described in the past years, these are not sufficient to explain the failure of replications. Moreover, the age of fear memories, as well as a higher anxiety in clinical samples may hamper the use of reconsolidation processes in the treatment of mental disorders. Thus, further basic research is needed to deepen our understanding of reconsolidation processes, before this approach can efficiently be translated into the clinical practice of treating anxiety disorders.

C3.7 Supplemental Material

C3.7.1 Supplemental Methods

Subjective Assessment:

The STAI (Laux et al., 1981; Spielberger et al., 1999) is a 40 item questionnaire, with 20 items assessing trait anxiety (STAI-T) and 20 items measuring state anxiety (STAI-S). Each item is rated on a 4-point intensity scale. The questionnaire is characterized by a high degree of internal reliability (STAI-S: Cronbachs alpha = .92; STAI-T: Cronbachs alpha = .90), and discriminant validity in differentiating between anxiety and non-anxiety disorder groups (Kabacoff, Segal, Hersen, & Van Hasselt, 1997).

The FAS (Rinck et al., 2002) is an 18 item self-report measurement, comprising spider-anxiety related items. Each item is rated on a 7 point likert scale ranging from 0 (not true) to 6 (true), with a maximum score of 108. The questionnaire reached excellent internal reliability (Cronbachs alpha = .96) and retest reliability (rtt = .95). Moreover, the instrument is proven to discriminate appropriately between subjects with and without spider phobia (non overlapping distributions: non spider anxiety 0.6, spider anxiety 15-92; mean spider anxiety = 58.7) (Rinck et al., 2002).

The SNAQ (Klorman et al., 1974) is a 30 items questionnaire to assess fear of snakes. Subjects are instructed to state whether each item is true or not, with true answers forming the sum score (0-30). The questionnaire has shown good test-retest variability (rtt = .78) and internal consistency (Cronbachs alpha = .89) (Klorman et al., 1974). However the discriminant validity seems to be controversial, since high SNAQ scores (> 13) do not necessarily reflect avoidance behavior (Klieger, 1987).

Interventions during reconsolidation:

Cognitive Reappraisal: Depending on the reactivated CS+ on day 2, either a neutral narrative about spiders or snakes were presented binaurally via headphones.

Spider. Spiders are very important animals, which are home in all ecological systems. They contribute to biodiversity und take a regulatory function in the habitat. For some habitats, more than a million spiders per hectare were estimated, which eat around 50 tons of prey per year – or far more than one million animals. They mostly consume insects. Doing that, they pay an important contribution to the maintenance of the natural equilibrium. Their body consists of two parts. On the upper body they have two chelicerae, two little feelers, eight legs and mostly eight eyes. On the lower body, the spider warts are located, in which die spider silk is produced. Worldwide exist more than 38 000 kinds of spiders. Of these, only twenty are dangerous for humans. None of them lives in central Europe. In Germany live cerca 1004 different, but harmless kinds of spiders. One very interesting spider is the water spider: The water spider is the only spider, which lives undersea. How does she manage not to choke? Basically, she does is very similar to scuba drivers. She always has a

supply of oxygen stored. If she needs oxygen, she sticks her abdomen out of the water and pulls it back under water very quickly. In doing so, little air bubbles get stuck in the hair of her abdomen and hold onto it. The water spider then brings the air bubbles to her self-yearned diving bell under water, whereby an oxygen store is created. She only rarely stays at the water surface. In her driving bell she does not only store oxygen – in that place she recovers, eats and watches her babys while hatching. Furthermore spiders are very useful animals. On one hand there are useful insect eaters. Aphids, moths, flies and other arthropods are welcome delicacies on their menu. Doing this, they contribute to the balance of the ecosystem. Thus the night active eight-legged animals are important for the agriculture. The spiders help eliminating the pest in farming. Also in medicine, the poison of the spider finds application. Using a bird spider's poison, a new medicament against heart failure was developed. For many people, the spider's web is a fascinating artwork. They produce threads as safety rope, for building up cocoons, as ballooning and especially as catching device that means webs. The threads consist of protein, because of that the orb-weaver spider can eat her old web, when building a new one. The physical processes of the thread production are still not completely understood. But it is known, that the thread consists of liquid protein, in which protein crystals are stored. Spiders own a sortiment of spinneret, which produce threads with different qualities for different purposes. Depending on the purpose the thickness of the threads lays around a thousandth part of a millimeter. Many kinds of spiders besides produce special fine threads of a hundred-thousandth part of a millimeter. Interestingly, the spider threads are as tear-proof as nylon und simultaneous as double stretchable. Therefore, there were especially many efforts to use spiders' threads for the production of textiles. The undertaking failed basically because the spiders needed to be held alone and this was too costly. Today, there are trials intending to let bacteria or dwarf goats produce the spiders' silk by implanting the genome of spiders. Until now, they do produce the right protein, but the connection of the threads was not accomplished yet. Furthermore, spiders are mostly loner. Although there are a series of exceptions: freshly hatched spiders stay a few days or weeks with their siblings together. In some species they are guarded by the mother, wolf spiders carry their babies on their back und some species even feed them with predigested food. Another species of spiders of a subtropical kind builds a catching web together and share their prey.

Snake. The evolution of the snakes begun many million years ago, a lot earlier than the evolution of the humans. Fossil discoveries from cretaceous age from around 95-100 million years ago indicate that. Thus, Snakes are real survival fighters. For example they can get along until 24 month without food, by strongly downregulating their metabolism. Snakes have the ability to feel vibrations on the ground very sensitively to protect them from enemies, compensating their blindness. Snakes do have a nose, with which they are able to smell, but

their tongue supports them regarding odors closely to the ground. How do they do that? They pick up little odorous substances with their tongue and transport them to their mouth. In the front of the snake's palate there are recesses – the so called Jacobson-Organ. Exactly here odorous substances are processed and therefore can be perceived. The perception works very similar to the perception in the nose. Although the Jacobson-Organ is a lot more sensitive. Furthermore snakes belong to the cold-blooded animals. That means that they cannot regulate their body temperature by using their metabolism. But how do they regulate their temperature instead? They do this, rolling up or moving to a cooler place, that means they use the outdoor temperature to compensate their body temperature. Because of that, it is possible that snakes fall into torpidity at lower temperatures. This can already happen at outdoor temperatures from 1°C to 9°C. To prevent torpidity or to counteract against it, they can move very elegant in smooth waveforms over the ground. Scientists have been very fascinated by this form of movement for a long time und try to simulate this smooth kind of movement. In general it could not be found out how the animals move that elegant on smooth surfaces. On rough surfaces, this ability goes back on their scalelike body. In Germany there are only two poisonous kinds of snakes: the common viper and the asp viber. Both kinds are strictly protected animals by nature conservation and are listed on the red list as threatened to extinction. Because of the rarity of the animals bite accidents are relatively rare. But in the last 60 years, there was no single case of death in the last 60 years related to a snake bite. The viper (Colubridae) has no poisonous fangs and is harmless. The viper snakes differ from the native poisonous snakes regarding their round pupils. Snakes have always been fascinating to humans. Because of that, they play a big role in cultural history and mythology. For example in ancient Greece, snakes were considered as sacred. Why? Because of the fact that snakes often peel off their skin, humans mad them to a symbol of re-renewal and immortality. Furthermore, snakes were thought to have healing powers. This also leaded to the snake being a symbol for the status of doctors. Unit today the snake is still in the sign of the staff of Aesculapius, which can be found in simplified form in some signs of pharmacies. Snakes were also suggested to have the ability of clairvoyance, therefore they were the animals of the goddess Gaia. According to Hesiod Gaia Pelope was one of the many names of the earth goddess Gaia. In the Oracle of Delphi snake priests (Pythea) were in service of Gaia. Not only in the christian-jewish tradition existed a tree protected by snakes. In the ancient Greek imagination there was a life spending apple tree in the garden of the Hesperides, which is guarded by the snake Ladon and was given as a present to the goddess Hera by Gaia.

Multimodal Sensory intervention (MMSS): The visual stimulation comprised toneless video trailers of the following fantasy movies: "The Hobbit" (Peter Jackson, Warner Home Video), "Avatar" (James Cameron, 20th Century Fox Home Entertainment), "Wizard of Oz" (Sam

Raimi, Walt Disney), “Pans Labyrinth” (Javier Navarrete, Universum Film GmbH), “Epic” (Danny Elfman, 20th Century Fox Home Entertainment), and “Jack and the Giants” (Bryan Singer, Warner Home Video). At the same time, subjects listen binaurally via headphones to music by Fred Frith (e.g. “Voice of America part 3/ LEGS” by Fred Frith, Step across the border, RecRec Music). Individuals were further sitting on a massage chair, which provided haptic stimulation by a intensive massage of the back area (Medisana MCN Shiatsu massage seat, program: whole back).

Experimental Procedure:

Day 1	Day 2	Day 3
Pre Testing STAIT/ FAS/ SNAQ STAI-S Blood Pressure	Pre Testing STAI-S Blood Pressure	Pre Testing STAI-S Blood Pressure
Resting Period psychophysiological recording 5 min	Resting Period psychophysiological recording 5 min	Resting Period psychophysiological recording 5 min
Testing: Habituation 70 db(A) background noise 10 NA trials	Testing: Habituation 70 db(A) background noise 10 NA trials	Testing: Habituation 70 db(A) background noise 10 NA trials
Testing: Acquisition 70 db(A) background noise 6 CS+R + US 6 CS+NR + US 2 CS+R 2 CS+NR 8 CS- 8 NA	Testing: Reactivation 70 db(A) background noise 1 CS+R 1 NA	Testing: Extinction 70 db(A) background noise 10 CS+R 10 CS+NR 10 CS- 10 NA
	5 min post Testing: Intervention propranolol/ placebo/ RA/ MMSS	Testing: Reinstatement 70 db(A) background noise 3 unsignaled US followed by 3 CS+R 3 CS+NR 3 CS- 3 NA
Resting Period psychophysiological recording 5 min	Resting Period psychophysiological recording 5 min	Resting Period psychophysiological recording 5 min
Post Testing STAI-S US evaluation	90 min post intervention STAI-S Blood pressure	Post Testing STAI-S US evaluation

Figure 12. Detailed description of the experimental procedure over three consecutive days

Stimuli Characteristics:

Conditioned stimuli (CS): Two fear-relevant stimuli were used as CS+ (spider and snake, IAPS numbers 1220 and 1052), as well as a fear-irrelevant stimulus as CS- (mug, IAPS number 7009) (Lang et al., 2008). Analogous to Kindt and colleagues (Soeter & Kindt, 2011, 2012a), we chose fear-relevant stimuli, since these have been shown to be particularly resistant to extinction learning and ecologically valid, as they have been linked to fear responses in clinical samples (see also Ohman & Mineka, 2001). One of the two CS+ (CS+R) was reactivated during the memory reactivation phase on day 2 while the other

served as a control CS+ (CS+NR). Assignment of the pictures as CS+R and CS+NR was counterbalanced across participants. The fear-irrelevant stimulus (CS-) was never associated with an aversive event. The CS- provides a baseline since it should not elicit a fear response. All pictures were presented at the center of a 17'' computer screen (resolution 1024 x 786 x 32 pixel, picture size 600 x 450 pixel).

Unconditioned stimulus (US): As US an electric stimulation of 2 ms was applied to the wrist of the non-preferred arm. Delivery of electric stimulation was controlled by the Digitimer DS7A constant current stimulator (Digitimer, Herfordshire, UK) via a bar stimulating electrode with two durable stainless steel disk electrodes (8 mm diameter, distance 30 mm) placed on the upper wrist of the non-preferred hand and fixated with a Velcro strap. Electrodes were filled with conductive gel (Signa Gel, Parker). Shock intensity was determined individually for each participant on day 1 before the start of testing. Starting at an intensity of 1 mA, the electric stimulus was delivered to the non-preferred hand and gradually increased (2mA steps), until subject rated it as "very unpleasant, but not painful" (see e.g. Soeter & Kindt, 2010, 2012b). Participants were instructed that the individually selected intensity remained set during all three days.

Startle probe: The startle probe consisted of a burst of white noise (40 ms, 95 dB, bandwith of 20 Hz – 20 kHz) and was presented during each CS presentation, as well as during habituation and noise alone trials, binaurally via headphones (Sennheiser HD 25-1-II).

C3.7.2 Supplemental Results

Fear Acquisition:

US Online Expectancy Ratings (OE-R)

RA compared to Placebo: Comparing RA to placebo revealed similar effects as the analyses of propranolol and placebo: OE-R differed between stimulus types depending on time (stimulus x time: $F(6,216) = 77.51$, $p < .001$; see Table 16, Figure 11) with no influence of the intervention condition (intervention x stimulus x time: $F(6,216) = 1.02$, $p = .414$). OE-R change could be confirmed for both CS+ as compared to the CS- (post hoc contrasts: CS+R: $F(1,36) = 158.07$, $p < .001$; CS+NR: $F(1,36) = 207.48$, $p < .001$). No differences were confirmed between both CS+ (2x4-ANOVA sub-design: stimulus x time: $F(3,111) = 1.72$, $p=.168$). Post-hoc tests revealed higher OE-R to both CS+ as compared to the CS- at the end of fear learning (both $p<.001$), while no differences were confirmed between both CS+ ($p > .1$).

MMSS compared to Placebo: OE-R differed between stimulus types depending on time ($F(6,222) = 68.56$, $p < .001$; see Table 16, Figure 11) without an influence of the intervention conditions (intervention x stimulus x time: $F(6,222) = .21$, $p = .975$). OE-R change differed between all three stimulus types (post-hoc contrasts: CS+R: $F(1,36) = 128.85$, $p < .001$; CS+NR: $F(1,36) = 210.49$, $p < .001$; 2x4-ANOVA sub-design with CS+R and CS+NR:

stimulus x time: F(3,114) = 4.37, *p* = .006; linear contrast: F(1,37) = 13.14, *p* < .001). At the end of the acquisition phase, post-hoc tests revealed higher OE-R to both CS+ as compared to the CS- (both *p* < .001) and no differences between both CS+ (*p* > .1). In addition, OE-R differed as a trend between intervention conditions depending on the stimulus type (intervention x stimulus: F(2,74) = 3.12, *p* = .050; post-hoc linear trend: CS+R: F(1,36) = 5.46, *p* = .025; CS+NR: F(1,36) = 2.57, *p* = .117; 2x2x4-ANOVA sub-design with CS+R and CS+NR: intervention x stimulus: F(1,37) = .19, *p* = .664) and time (; (intervention x time: (F(3,111) = 2.64, *p* = .053, post-hoc linear trend: F(1,37) = 3.63, *p* = .064): OE-R to the CS- in the placebo was lower as compared to MMSS condition (post hoc: *p* = .040, both other *p* > .1).

Fear Potentiated Startle (FPS)

RA compared to Placebo: The comparison of RA and placebo revealed similar results as the analysis contrasting the propranolol intervention with placebo (see Table 17, Figure 11): FPS differed between stimulus types depending on time without an influence of the intervention condition (stimulus x time: F(6,222) = 2.99, *p* = .008; intervention x stimulus x time: F(6,222) = 0.71, *p* = .637). The linear trend over time differed for both the CS+R and the CS+NR compared to the CS- (post-hoc contrasts: CS+R: F(1,36) = 7.94, *p* = .008; CS+NR: F(1,36) = 7.86, *p* = .008). A direct comparison of FPS between both CS+ revealed no differences in FPS between these stimulus types over the course of the acquisition phase (2x4-ANOVA sub-design: stimulus x time: F(3,111) = 1.31, *p* = .274). At the end of the acquisition phase, FPS was higher to both CS+ as compared to the CS- (both *p* < .001), but not significantly different between both CS+ (*p* = 0.557).

MMSS compared to Placebo: Statistical analyses revealed a change of FPS over time that was different between stimulus types statistically only as a trend (F(6,222) = 1.88, *p* = .085; intervention x stimulus x time: F(6,222) = 1.53, *p* = .169; see Table 17, Figure 11). The linear trend over time differed for the CS+NR, but not for the CS+R as compared to the CS- (post-hoc contrasts: CS+R: F(1,36) = 2.11, *p* = .154; CS+NR: F(1,36) = 5.83, *p* = .021). However, a direct comparison of FPS between both CS+ revealed no differences in FPS between these stimulus types over the course of the acquisition phase (2x4-ANOVA sub-design: stimulus x time: F(3,111) = 2.06, *p* = .110). Nevertheless, at the end of the acquisition phase, FPS was higher to both CS+ as compared to the CS- (both *p* < .005), but not significantly different between both CS+ (*p* = .395).

Retention:

US Online Expectancy Ratings (OE-R)

RA compared to Placebo: Comparing RA to placebo revealed similar effects as the analyses of propranolol and placebo: OE-R differed between stimulus types depending on time without a modulating effect of the intervention condition (F(2,74) = 7.24, *p* = .001;

intervention x stimulus x time: F(2,74) = 2.03, *p* = .139; see Table 16, Figure 11). OE-R change could be confirmed to both CS+ as compared to the CS- (post-hoc contrasts: all *p*'s < .003), while no differences were confirmed between both CS+ (2x2-ANOVA sub-design: stimulus x time: F(1,38)< .01, *p* > .1). Post-hoc tests revealed a reduction of OE-R for both CS+ from end of acquisition to the start of the extinction phase (both *p* < .005), while there was no change in OE-R for CS- (*p* = .458). OE-R was higher in response to both the CS+R and CS+NR compared to the CS- (both *p* < .001) without a difference between OE-R of both CS+ (*p* > .1) at the start of the extinction phase.

MMSS compared to Placebo: OE-R differed between stimulus types depending on time without an influence of the intervention condition (F(2,74) = 8.15, *p* = .001; (intervention x stimulus x time: F(2,74) = .21, *p* = .815; see Table 16, Figure 11). The OE-R change from end of the acquisition to start of extinction phase differed for the CS+R as compared to the CS- (post hoc contrast: *p* < .001). However, OE-R change for the CS+NR differed from CS- only as a trend (post hoc contrast: *p* = .085) and was less pronounced than OE-R change to the CS+R (2x2-ANOVA sub-design: stimulus x time: F(1,38) = 4.63, *p* = .038). Post-hoc tests revealed lower OE-R to the CS+NR during retention testing as compared to the end of fear learning (*p* = .001), while no differences were confirmed for CS+R and CS- between phases (*p* > .156). However, OE-R to both CS+ was higher than to the CS- at the start of the extinction phase (*p*<.001), without a difference between OE-R of both CS+ (*p* > .1).

Fear Potentiated Startle (FPS)

RA compared to Placebo: FPS increased over time (F(1,37) = 15.94, *p* < .001; see Table 17, Figure 11). However, this change was neither influenced by the stimulus type, nor by intervention condition (stimulus x time: F(2,74) = 0.62, *p* = .538, intervention x stimulus x time: F(2,74) = 1.24, *p* = .297). In general, FPS was higher to both CS+ as compared to the CS-, with no differences between both CS+ (stimulus: F(2,74) = 12.89, *p* <.001; post-hoc tests: CS+R vs. CS-: *p* = .002; CS+NR vs. CS-: *p* <.001; CS+R vs. CS+NR: *p* > .1).

MMSS compared to Placebo: Comparing MMSS to placebo revealed similar effects as the analyses of RA and placebo: FPS increased over time (time: F(1,37) = 24.97, *p* < .001; see Table 17, Figure 11) without an influence of the stimulus type or the intervention condition (stimulus x time: (F2,74) = .221, *p* = .814; intervention x stimulus x time: F(2,74) = 1.68, *p*=.194). In general, FPS was higher to both CS+ as compared to the CS-, with no differences between both CS+ (stimulus: F(2,74) = 9.71, *p* < .001; post-hoc tests: CS+R vs. CS-: *p* = .005; CS+NR vs. CS-: *p* = .001; CS+R vs. CS+NR: *p* > .1).

Extinction learning:

US Online Expectancy Ratings (OE-R)

RA compared to Placebo: Comparing RA to placebo revealed similar effects as the analyses of propranolol and placebo: OE-R differed between stimulus types depending on time

(F(2,74) = 179.13, *p* < .001; see Table 16, Figure 11), without an influence of the intervention condition (intervention x stimulus x time: F(2,74) = .14, *p* = .870). OE-R change differed for both CS+ as compared to the CS- (post hoc contrasts: all *p*'s < .001), while there was no difference between OE-R change between both CS+ (2x2-ANOVA sub-design: stimulus x time: F(1,38) = .38, *p* = .540). Post-hoc tests revealed lower OE-R to both CS+ during the end as compared to the beginning of extinction learning (both *p* < .001), while no differences were confirmed for CS- between phases (*p* = .153). At the end of the extinction phase, OE-R was still higher to both CS+ compared to the CS- (both *p* < .005).

MMSS compared to Placebo: Comparing MMSS to placebo revealed similar effects as the analyses of the propranolol and RA interventions compared to placebo: OE-R differed between stimulus types depending on time (F(2,74) = 116.43, *p* < .001; see Table 16, Figure 11), but independent of the intervention condition (intervention x stimulus x time: F(2,74) = 1.86, *p*=.164). OE-R change differed to both CS+ as compared to the CS- from the beginning to the end of the extinction phase (post-hoc contrasts: all *p*'s <.001), while no differences were confirmed in OE-R change between both CS+ (2x2-ANOVA sub-design: stimulus x time: F(1,38) = .53, *p* = .473). Post-hoc tests revealed lower OE-R to both CS+ during the end as compared to the beginning of extinction learning (both *p* < .001), while OE-R decreased only as a trend for CS- between phases (*p* = .092). At the end of the extinction phase, OE-R was still higher to both CS+ compared to the CS- (both *p* < .001).

Fear Potentiated Startle (FPS)

RA compared to Placebo: FPS decreased over time (F(1,36) = 96.77, *p* <.001; see Table 17, Figure 11) independent of the intervention condition and the stimulus type (intervention x stimulus x time: F(2,72) = .56, *p* = .576; stimulus x time: F(2,72) = .99, *p* = .376). However, FPS differed between intervention conditions depending on the stimulus types (intervention x stimulus: F(2,72) = 3.56, *p* = .040). While pairwise comparison of the intervention conditions for the stimulus types revealed, as a trend, only a higher FPS to CS+R during placebo compared to RA (*p* = .053), an explorative analyses of mean FPS suggests that this difference may be attributable particularly to differences at the end of the extinction phase (start extinction: *p* = .072, end extinction *p* = .020).

MMSS compared to Placebo: FPS decreased over time (F(1,36) = 125.84, *p* <.001; see Table 17, Figure 11), without an influence of the intervention condition or the stimulus type (intervention x stimulus x time: F(2,72) = 1.77, *p* = .177; stimulus x time: F(2,72) = 1.69, *p* = .192). In general, FPS was higher to the CS+R as compared to the CS-, with no differences between CS+NR and CS- or both CS+ (stimulus: F(2,72) = 5.03, *p* < .001; post-hoc tests: CS+R vs. CS-: *p* = .012; CS+NR vs. CS- *p* = .120; CS+R vs. CS+NR: *p* > .1).

Reinstatement:

US Online Expectancy Ratings (OE-R)

RA compared to Placebo: OE-R differed between stimulus types depending on time ($F(2,70) = 6.54$, $p = .002$; see Table 16, Figure 11). While OE-R change over time differed for both CS+ compared to the CS- (post hoc contrasts: all p's < .024), it was not distinguishable between both CS+ (2x2-ANOVA sub-design: stimulus by time: $F(1,36) = 1.12$, $p = .275$). In general, OE-R decreased stronger in the RA than in the placebo condition (intervention x time: $F(1,35) = 4.66$, $p = .038$). At reinstatement testing, OE-R was higher to both CS+ compared to the CS- (both $p < .009$), with no difference between both CS+ ($p > .1$).

MMSS compared to Placebo: Comparing MMSS to placebo revealed similar effects as the analyses of propranolol and placebo: OE-R differed between stimulus types depending on time independent of the intervention condition (stimulus x time: $F(2,74) = 10.65$, $p <. 001$; intervention x stimulus x time: $F(2,74) = .178$, $p = .837$; see Table 16, Figure 11). The OE-R change from the end of the extinction phase to reinstatement differed for both the CS+R and the CS+NR as compared to the CS- (post hoc contrasts: $p < .001$), while there was no difference in OE-R between the two CS+ (2x2 ANOVA sub-design: stimulus x time: $F(1,38) = 1.75$, $p = .193$). At reinstatement testing, OE-R was higher to both CS+ compared to the CS- (both $p < .001$), with no difference between both CS+ ($p > .1$).

Fear Potentiated Startle (FPS)

RA compared to Placebo: Comparing RA to placebo revealed similar effects as the analyses of propranolol and placebo: FPS increased over time ($F(1,36) = 24.48$, $p < .001$; see Table 17, Figure 11), independent of the intervention condition and stimulus type (intervention x stimulus x time: $F(2,72) = .23$, $p = .793$; stimulus x time: $F(2,72) = .25$, $p = .776$). In general, FPS differed between stimulus types ($F(2,72) = 10.88$, $p < .001$). Post hoc tests revealed a larger FPS to both CS+ as compared to the CS- overall (CS+R vs. CS-: $p = .002$; CS+NR vs. CS-: $p < .001$), with no differences between CS+ ($p > .1$).

MMSS compared to Placebo: Comparing MMSS to placebo revealed similar effects as the analyses of the other intervention conditions: FPS increased over time ($F(1,36) = 21.49$, $p < .001$; see Table 17, Figure 11) independent of the intervention condition and stimulus type (intervention x stimulus x time: $F(2,72) = 34$, $p = .713$; stimulus x time: $F(2,72) = 2.05$, $p = .136$). In general, FPS differed between stimulus types ($F(2,72 = 4.46$, $p = .015$). Post hoc tests revealed a larger FPS to the CS+R as compared to the CS- ($p = .043$), a marginal significant effect comparing CS+NR to CS- ($p = .061$) and no differences between both CS+ ($p > .1$).

Prediction error:

To assess the degree of a prediction error on day 2 (Sevenster et al., 2013, 2014b), a 2 x 2 rmANOVA with the between-subjects factor 'type of intervention' and the within-subject factor 'time' (end of acquisition, reactivation trial).

US Online Expectancy Ratings (OE-R)

Propranolol compared to Placebo: OE-R did not differ between the end of acquisition and reactivation (F(1,36) = .31, *p* = .583), and there was no influence of the intervention conditions (intervention x time: F(1,36) = .63, *p* = .433).

RA compared to Placebo: Comparing RA to placebo revealed similar effects as the analyses of propranolol and placebo: OE-R did not differ between the end of acquisition and reactivation (F(1,36) = .28, *p* = .599), and there was no influence of the intervention conditions (intervention x time: F(1,36) = .07, *p* = .796).

MMSS compared to Placebo: Comparing MMSS to placebo revealed similar effects as the analyses of propranolol and placebo: OE-R did not differ between the end of acquisition and reactivation (F(1,35) = .01, *p* = .908), and there was no influence of the intervention conditions (intervention x time: F(1,36) = .14, *p* = .708).

Fear Potentiated Startle (FPS)

Propranolol compared to Placebo: FPS increased over time (F(1,35) = 13.07, *p* = .001), while this effect was independent of the intervention condition (intervention x time: F(1,35) <.001, *p* = .996).

RA compared to Placebo: Comparing RA to placebo revealed similar effects as the analyses of propranolol and placebo: FPS increased over time (F(1,36) = 16.26, *p* < .001), while this effect was independent of the intervention condition (intervention x time: F(1,36) = .09, *p* = .773).

MMSS compared to Placebo: Comparing MMSS to placebo revealed similar effects as the analyses of propranolol and placebo: FPS increased over time (F(1,34) = 18.24, *p* < .001), while this effect was independent of the intervention condition (intervention x time: F(1,34) = .92, *p* = .344).

Trait anxiety and effects of propranolol on fear memory reconsolidation:

FPS Retention analyses controlled for trait anxiety:

To assess, whether trait anxiety might impact the observed effects within the propranolol intervention condition, we reran the analyses with trait anxiety as a covariate. FPS still differed between the two intervention conditions depending on stimulus type and time (intervention x stimulus x time: F(2,70) = 5.71, *p* = .005). Intervention conditions differed in FPS change over time when comparing the CS+NR to the CS- (F(1,35) = 8.51, *p* = .006), but not when comparing the CS+R to the CS- (F(1,35) = .095, *p* = .759). A direct comparison of both CS+ with an additional ANOVA sub-design revealed that intervention conditions differed in FPS change also for CS+R and CS+NR (2x2x2-ANOVA sub-design: intervention x stimulus x time: F(1,35) = 8.00, *p* = .008). At the start of the extinction phase, FPS was higher in response to the CS+NR as compared to both the CS- as well as to the CS+R in the propanol condition (both *p* <. 005), while FPS did not differ between the three stimulus types

in the placebo condition (all $p > .684$). Thus, controlling for trait anxiety supports the observed effects.

Generalization to the control stimulus:

To test whether the observed generalization to the control stimulus during retention and reinstatement testing was associated with trait anxiety, we run Pearson correlations between a) the change in FPS of the CS- regarding retention testing (CS- start extinction minus CS- end acquisition) and b) reinstatement testing (CS- end extinction minus CS- reinstatement trial) overall subjects. We did not observe a significant association (Retention: r = .01, p = .928; Reinstatement; r = -.05, p = .685).

Table 18. Mean values (SD) of systolic and diastolic blood pressure (in mmHg) and HR pre and 90 minutes post propranolol administration during memory reactivation on day 2.

	Pre-pill intake	Post-pill intake
Placebo		
Systolic BP (mean/SD)	109.16 (13.15)	111.68 (14.02)
Diastolic BP (mean/SD)	66.21 (6.47)	69.16 (10.99)
HR (mean/SD)	77.89 (12.17)	67.89 (10.47)
Propranolol		
Systolic BP (mean/SD)	108.16 (12.79)	106.47 (13.62)
Diastolic BP (mean/SD)	65.94 (7.02)	68.73 (12.38)
HR (mean/SD)	79.89 (12.27)	64.37 (8.19)

D. GENERAL DISCUSSION

The present doctoral thesis aimed at gaining a deeper understanding of alterations in emotional reactivity in PTSD. Herein, underlying mechanisms were studied, these are, disturbances in memory functioning and emotion regulation. In addition, it was also tested whether an experimental approach, in which reconsolidation is combined with therapeutical techniques, is successful in targeting emotional memory and its associated emotional response. Thus, three studies have been conducted. Specifically and with respect to alterations in memory processes, study I focused on fear memory (over-) generalization in PTSD. Experimentally it has been investigated whether PTSD individuals are characterized by stronger subjective (explicit memory) and physiological responding, as well as alterations in response times (implicit memory) to stimuli that have not been presented during fear conditioning, but perceptually resemble the conditioned danger cue. Study II focused on the neurobiological underpinnings of emotion regulation, by trying to identify an aberrant interaction between the brain and the autonomic nervous system in PTSD. Thus, the association between HRV and its neuronal representation (i.e. central autonomic network) during resting state was investigated. Study III extends both investigations by testing an experimental paradigm that may alter memory and its associated emotional reaction. The therapeutical techniques applied during fear memory reconsolidation are hypothesized to attenuate the prior learned emotional response. Herein, this aims at testing whether therapeutical techniques may be more effective when applied during reconsolidation.

In the following section, results of all three studies will be discussed and related to each other: Specifically, section D1. provides a summary of the included experiments and presents the results with respect to the a-priori hypotheses. Subsequently, in section D2. the results will be integrated and discussed in terms of general effects found across studies (in relation to emotional reactivity), as well as in terms of study specific effects. Methodological limitations will be summarized with respect to each study (section D3.) and findings will be concluded with emphasis on implications for future studies in PTSD (section D4.).

D1. SUMMARY OF STUDY RESULTS

D1.1 Summary of study I

In study I, a female sample of 30 PTSD subjects, 30 trauma exposed healthy controls (TC), as well as 30 non-trauma exposed healthy controls (HC) performed a fear conditioning and generalization paradigm. The task comprises three phases: pre-acquisition, fear acquisition, and generalization testing. Conditioned and generalization stimuli comprised 10 circles (differing in size), with either the largest or smallest one representing the conditioned danger or safety cue (counterbalanced across subjects). The remaining 8 stimuli formed a continuum of similarity between the danger and safety cue, and thus fear responding to those cues is indicative for the amount of fear transfer from the danger cue. Fear potentiated startle response (FPS) and reaction times (RT, both implicit memory), as well as online risk ratings (ORR, explicit memory) served as dependent variables.

D1.1.1 Hypothesis 1: Enhanced responding during baseline testing in PTSD

It was hypothesized that PTSD patients were characterized by enhanced baseline responding, especially with respect to implicit memory processes (FPS) compared to both TC and HC subjects.

We did observe increased responding during baseline testing (pre-acquisition) in PTSD, when no US was presented. However, this effect was observed only with respect to explicit memory (ORR). Specifically, PTSD patients overall subjectively expected more risk of an US, irrespective of the displayed stimulus compared to both control groups.

Contrary to our hypothesis and with respect to implicit memory, PTSD patients did not differ in their FPS during baseline testing from both control groups.

Overall, no differences between trauma and healthy controls were observed.

D1.1.2 Hypothesis 2: Alterations in fear learning in PTSD

It was hypothesized that PTSD patients would show alterations in fear learning with respect to implicit memory.

In line with our hypothesis, PTSD patients showed alterations on implicit measurements during fear acquisition. As such, PTSD patients exhibited a lower FPS in response to the danger cue compared to healthy controls, pointing towards a reduced differentiation between danger and safety in PTSD. Moreover, PTSD patients showed an altered RT pattern when evaluating the risk of an US associated with the danger and safety cue compared to HCs. Specifically, PTSD patients were faster in response to the danger and slower in response to the safety cue. This pattern was reversed in HCs. Importantly, TC subjects did not differ with respect to their FPS compared to both HC and PTSD subjects, while TC individuals did mirror the RT pattern in PTSD and herein also differed from HCs.

We further observed alterations regarding explicit memory processes, while those were not stimulus specific: PTSD patients overall expected heightened risk of an US while evaluating both cues compared to HCs. No differences were observed between PTSD and TC or between TC and HC subjects regarding the latter reported effect.

D1.1.3 Hypothesis 3: Overgeneralization of fear in PTSD

We hypothesized that PTSD subjects were characterized by a wider fear transfer to stimuli resembling the danger cue, with respect to both, implicit and explicit memory.

The hypothesis was partly confirmed regarding implicit memory: Alterations in generalization were found with respect to an implicit behavioral measurement. Herein, PTSD individuals compared to HCs were characterized by an altered pattern of RT when evaluating the risk of an US associated to the GS. In PTSD, the longest RT was observed for GS of moderate similarity to the danger cue. In contrast, HCs showed the longest RT in response to those stimuli most similar to the danger cue. No differences were observed with respect to FPS between groups. Importantly, TC subjects mirrored the mentioned RT pattern of PTSD subjects compared to HC, but less pronounced, as this effect was observed on a marginal significant level only.

With respect to explicit memory processing during generalization testing we did not observe a stimulus specific effect, but instead a stimulus unspecific effect in PTSD: PTSD subjects were characterized by an increased expectation of risk compared to HCs, as well as on a trend level compared to TC subjects. No differences were observed between TC and HC subjects with respect to the latter effect.

D1.1.4 Hypothesis 4: Overgeneralization is related to alterations during baseline testing and fear learning

Moreover, we hypothesized that alterations in fear generalization would be related to alterations during baseline responding (=pre-acquisition) and fear acquisition.

With respect to group specific generalization effects within implicit memory, we found a negative relationship between the altered pattern of RT during generalization testing and ORR during fear acquisition in PTSD. This association was also observed in TC subjects, but not in HCs.

With respect to group specific generalization effects within explicit memory, ORR during generalization testing was positively related to ORR during fear acquisition in all groups, as well as during pre-acquisition in HCs. The latter effect was also observed in PTSD, but on a marginal significant level. Additionally, ORR during generalization testing was negatively related to the differential FPS response during fear acquisition solely in PTSD.

D1.2 Summary of study II

In study II, 57 PTSD individuals and 41 HC subjects underwent six minute resting state functional magnetic resonance imaging (fMRI). Simultaneously, cardiac responding was recorded. Subjects were instructed to relax and let their mind wander.

D1.2.1 Hypothesis 5: Reduced HRV in PTSD

We hypothesized that PTSD patients would exhibit lower resting HRV compared to HC subjects.

This hypothesis was confirmed, as PTSD subjects showed diminished HRV with respect to all parameters (RMSSD, LF HRV, HF HRV) compared to HCs.

D1.2.2 Hypothesis 6: Altered connectivity pattern of key CAN regions in PTSD

We hypothesized that PTSD patients show an altered functional connectivity pattern between key CAN regions (vmPFC, amygdala, PAG) and cortical as well as subcortical structures.

This hypothesis was confirmed, since HCs only engaged a localized activation pattern (vmPFC to anterior cingulate, and medial frontal gyrus; amygdala within seed itself; PAG to thalamus and seed itself). In stark contrast, PTSD patients were characterized by a widespread activation pattern: PTSD individuals engaged brain regions associated with emotional reactivity (all seed regions to insula, vmPFC), motor readiness (all seed regions to the precentral gyrus, PAG to cerebellum), and salience processing (all seed regions to anterior insula and dorsal ACC).

D1.2.3 Hypothesis 7: Reduced relationship between CAN connectivity and HRV in PTSD

It was hypothesized, that the relationship between CAN connectivity and HRV is reduced in PTSD compared to HCs.

This was not confirmed. Contrary, in PTSD, HRV scores did not significantly predict increased functional connectivity between any of the CAN related brain regions. However, in HC subjects, HRV predicted increased functional connectivity between a) the vmPFC and the insula, as well as between b) the left amygdala and the PAG, and between c) the PAG and the dorsal cingulate cortex, medial and superior frontal cortex, and the thalamus.

D1.3 Summary of study III

In study III, 80 female healthy individuals underwent a differential fear conditioning paradigm: On day 1, two stimuli were associated with an aversive event (CS+), while one was never followed by an aversive event (CS-). Twenty-four hours later, pharmacological (propranolol) and behavioural (reappraisal, multimodal sensory stimulation) intervention protocols were applied upon memory reactivation (reconsolidation disruption) of one of the two CS+ (CS+Reac) and contrasted to a placebo control condition. The second conditioned stimulus

was not reactivated (CS+Non-Reac). On a third day, effects of the interventions on reconsolidation of fear memory were tested during extinction and reinstatement testing. Dependent variables comprised fear potentiated startle (FPS), skin conductance response (SCR) and online risk ratings (ORR). Since all groups did not acquire fear with respect to SCR, findings are discussed with respect to FPS and ORR.

D1.3.1 Hypothesis 8: Propranolol administration during reconsolidation attenuates emotional memory

It was hypothesized that propranolol administration upon memory reactivation would result in an attenuation of the prior acquired fear response with respect to FPS. Herein, in a first testing phase a) (start of extinction) a lower FPS to the CS+Reac compared to the CS+Non-Reac during the first trials during extinction testing would be indicative for the latter effect. This needed to be supplemented by a lower FPS to the CS+Reac during the first trials of extinction testing compared to the end of fear acquisition. Moreover, in a second testing phase b) (reinstatement testing) fear response was hypothesized to selectively increase to the CS+Non-Reac upon the presentation of the US: This would be indicated by a selective increase of FPS to the CS+Non-Reac when comparing the end of extinction testing to the first trial upon US presentation. Contrary, FPS to the CS+Reac was hypothesized not to differ with respect to the end of extinction learning and the first trial upon US presentation.

These hypotheses were not confirmed. In the following, results are presented with respect to FPS only, as with respect to FPS, group specific effects were observed (no group differences were observed with respect to ORR): Regarding the first testing phase a), we did observe a differential effect in FPS responding to the CS+Reac and CS+Non-Reac at the start of extinction testing, with lower FPS to the CS+Reac. However, this effect was not related to a reduction in FPS to the CS+Reac, but rather to an enhanced FPS to the CS+Non-Reac, when contrasting the end of the acquisition phase to the start of extinction testing. This pattern was confirmed when compared to the placebo control group. Moreover, with respect to the second testing phase b), FPS increased unspecificly to all stimuli (CS+ Reac, CS+ Non-Reac, CS-) upon US presentation.

D1.3.2 Hypothesis 9: Therapeutical techniques during reconsolidation attenuate emotional memory

Hypotheses were comparable to those listed for propranolol.

The hypotheses were not confirmed. Both groups did not differ from the placebo group regarding both testing phases. Specifically, with respect to testing phase a) neither FPS, nor ORR was selectively attenuated during the first trials during extinction testing to the CS+Reac. Moreover, regarding testing phase b) FPS responding increased to all stimuli when comparing the end of extinction learning to the first trial upon US presentation, while

ORR increased to both CS+Reac and CS+Non-Reac. This pattern was not significantly different from the placebo group.

D2. INTEGRATION INTO PREVIOUS RESEARCH

"Being traumatized means continuing to organize your life as if the trauma were still going on
– unchanged and immutable –
as every new encounter or event is contaminated by the past"

- van der Kolk, 2012, p.53

With respect to the overall aim of gaining a better understanding of emotional reactivity in PTSD and testing a memory based experimental approach aiming at attenuating emotional reactivity, the above-mentioned quote highlights certain aspects, which are affected by enhanced emotional reactivity in PTSD. Those will be put in context while discussing the study results.

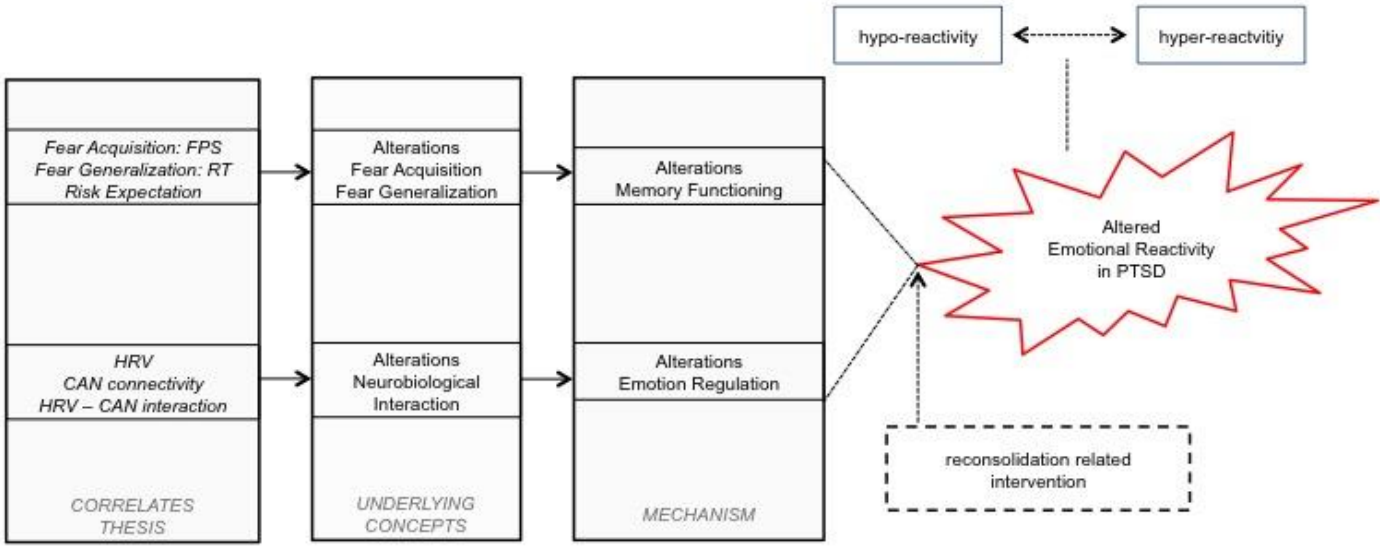

Figure 13. Conceptual framework of the doctoral thesis and related findings.
Framework is extended by including PTSD related correlates identified in the doctoral thesis.
FPS = fear potentiated startle, RT = reaction time, HRV = heart rate variability, CAN = central autonomic network

D2.1 Emotional reactivity and impaired memory functioning in PTSD

"Being traumatized means continuing to organize your life
as if the trauma were still going on"

- van der Kolk, 2012, p.53

This part of the quote implies important problems PTSD patients are facing, which as how distressing intrusive memories or flashbacks of the traumatic experience(s) (= re-experiencing) dominate the present, while the latter is simultaneously counteracting the feeling of being in the present. This highlights the caused distress and enhanced negative emotional reactivity in PTSD. Learning theoretical approaches describe the phenomenon of re-experiencing by means of associative learning processes. For example, a situation comprises a variety of neutral cues that are thought to be associated with the aversive events (e.g. traumatic event) and bear the opportunity to elicit emotions associated with the aversive event. In turn, re-experiencing symptoms are thought to reflect overgeneralization processes, as this association between neutral and trauma associated cues is stated to be exaggerated, meaning that associations are established between more and more cues following traumatization.

Study I provided experimental evidence towards alterations in memory processes, which are hypothesized to underlie emotional reactivity (see Figure 13). Specifically, alterations in fear generalization with respect to implicit memory were observed in PTSD, i.e. alterations in reaction times towards generalization stimuli. From a theoretical perspective, increased reaction times have been linked to higher uncertainty about the threat information of a given stimulus (Kaczkurkin et al., 2016; Kaczkurkin & Lissek, 2013; Lissek et al., 2014; Lissek et al., 2010). Generalization stimuli comprise less threat information as compared to both, safety and danger cues. Therefore, it was hypothesized that increased reaction times to generalization stimuli would indicate that subjects differentiate between generalization stimuli and the danger and safety cue. Importantly, prolonged reaction times to generalization stimuli with a moderate similarity to the danger cue have been observed in PTSD. Contrary, healthy control individuals showed the slowest reaction times towards the most similar generalization stimuli to the danger cue. As PTSD individuals did not differ in their reaction times to the latter mentioned closest approximation, this pattern provides evidence towards a shift in uncertainty to more dissimilar generalization and thus safer stimuli in PTSD. Importantly, the present thesis did not observe generalization stimuli modulated alterations with respect to the subjective expectancy of risk or FPS, which are directly related to fear processing. Contrary, we observed alterations regarding an implicit measurement, i.e. reaction times. Yet, studies investigating fear generalization in PTSD are sparse, with no

study focusing on PTSD related to childhood maltreatment. Two investigations did focus on combat exposure and hinted towards alteration in fear generalization in PTSD: While one study found fear overgeneralization across a range of dependent variables (neuronal activity, subjective risk expectation) (Kaczkurkin et al., 2016), Morey et al. (2015) observed alterations in fear generalization on a neuronal level only (for preliminary results also see Lissek & van Meurs, 2015). Thus, further studies are needed to disentangle affected processes related to fear generalization in PTSD, i.e. implicit and explicit memory correlates, which might be modulated by the type of the trauma history. Apart from fear memory generalization, further evidence of affected generalization processes in PTSD comes from studies applying reward and punishment learning tasks: Within these studies foreground objects and backgrounds are associated to a specific outcome ("win"/"loose") in the first phase. Subsequently, the rule is reversed. Interestingly, PTSD patients showed specific impairments in reversing the negative background to a positive outcome, while they did not differ regarding the foreground objects or positive backgrounds (Levy-Gigi, Szabo, Richter-Levin, & Keri, 2015). Adding to this, a recent study extended the reasoning of the prior mentioned paradigm by adding new stimuli during a test phase and showed that selectively female PTSD patients did not differentiate between positive, negative or new backgrounds (Radell, Beck, Gilbertson, & Myers, 2017). Thus, subjects did not seem to transfer prior learned rules to stimuli associated to a specific outcome or new ones. Altogether, based on different paradigms, evidence hints towards altered generalization processes in PTSD: While the tendency to explicitly overgeneralize newly learned fear on direct fear measurements was not found consistently, implicit memory seems to be affected herein. Additionally, studies point towards difficulties in processing especially contextual information in PTSD. **Study I** further revealed alterations in fear acquisition on an implicit level: FPS to the danger cue was less potentiated in PTSD, hinting towards a reduced discrimination between threat and safety. Moreover, we also observed stimulus unspecific alterations regarding explicit memory, pointed to a tendency to expect heightened risk of an aversive event in response to both danger and safety cues. The latter finding was further observed and extended to additional stimuli resembling the danger cue, but decreasing in their similarity. In line with a heightened uncertainty when evaluating the safety cue during fear acquisition, as indicated by increased response times in PTSD, perceiving safety might be challenged in PTSD. One may hypothesize that this contributes to altered emotional reactivity, as it points towards the fact that trauma survivors are in a constant hypervigilant state.

Thus, coming back to the above-mentioned quote, PTSD patients are haunted by re-experiencing symptoms, while they are simultaneously trying to avoid trauma reminders to escape from the distressing past. Thus, it is plausible, that trauma survivors are mostly in a

hypervigilant state, scanning the environment for possible threats, and thus more prone to experiencing changes in their affective state (i.e. alterations in emotional reactivity).

Adding to this, **study II** hints towards a state of enhanced emotional reactivity in PTSD patients, as reflected by their neuronal response pattern during rest (see Figure 13). We observed increased connectivity between key nodes of the central autonomic network (i.e. the vmPFC, the amygdala and the PAG to several cortical and subcortical structures). Herein, particularly the PAG connectivity pattern is important to mention, as the PAG has been associated with specific parts of the defense cascade (Satpute et al., 2013): One subdivision, the dorsolateral PAG has been associated to elicit active defense strategies, while the ventrolateral PAG has been related to passive coping strategies (Bandler, Keay, Floyd, & Price, 2000; Behbehani, 1995). In the present investigation, the PAG showed enhanced recruitment with the dorsal ACC in PTSD. The dorsal ACC has been associated with processing contextual information of a situation with respect to its safety (Medford & Critchley, 2010; Mobbs et al., 2007; Shackman et al., 2011). With further increased connectivity between the PAG and regions associated with motor responses (i.e. the precentral gyrus), such a connectivity pattern points towards enhanced emotional reactivity and readiness to react. Moreover, we also observed enhanced connectivity between the amygdala and the medial prefrontal cortex in PTSD. Interestingly, alterations in the latter mentioned connectivity has also been associated with aberrant threat processing in various paradigms in PTSD (e.g. Gilboa et al., 2004; Jin et al., 2014; Stevens et al., 2013). Importantly, Rabellino et al. (2016) found an opposing connectivity pattern of subdivisions of the amygdala complex during conscious and subconscious threat processing. This demonstrates that enhanced connectivity between the centromedial amygdala and the superior frontal gyrus has been observed during subconsciousness threat processing. This result has been interpreted as contributing to a dysregulation of the fear network. Thus, in line with this reasoning, the neuronal findings altogether seem to reflect a state of enhanced emotional reactivity and motor readiness in PTSD during a resting state, in which they have been instructed to relax and let their mind wander.

Both studies provide evidence for alterations in emotional reactivity in PTSD, albeit based on different levels: implicit memory processes (**study I**) and a neuronal response pattern during rest (**study II**). Overall, it is important to consider, that trauma exposure per se partly contributed to the observed effects, as the observed pattern of implicit memory processes during generalization testing was also found in trauma control subjects, although less pronounced, i.e. on a statistical trend level (**study I**). Thus, trauma exposure might lead to a higher proneness to changes in emotional reactivity, however future research is needed to confirm this observation.

D2.2 Emotional reactivity and disturbances in emotion regulation in PTSD

"– unchanged and immutable – "

- van der Kolk, 2012, p.53

Emerging focus has been made on difficulties in emotion regulation (ER) in PTSD (Badour & Feldner, 2013; Barlow, Turow, & Gerhart, 2017; Cloitre, Miranda, Stovall-McClough, & Han, 2005; Powers, Cross, et al., 2015; Powers, Etkin, et al., 2015; Tull, Barrett, McMillan, & Roemer, 2007; Weiss, Tull, Dixon-Gordon, & Gratz, 2013). Accordingly, while these studies in general reported reduced ER skills in PTSD, they further elucidated difficulties in specific abilities, such as disturbances in accepting negative emotions, increased use of avoidant strategies, and difficulties in describing and distinguishing between emotions (Badura, 2003; Cloitre et al., 2005; Gratz & Roemer, 2004; Hyer, Woods, Summers, Boudewyns, & Harrison, 1990; Tull et al., 2007). Importantly, difficulties in emotion regulation have also been strongly associated with PTSD symptom severity (Cloitre et al., 2005; Tull et al., 2007; Weiss et al., 2013), as well as being specifically linked to childhood maltreatment (Burns, Jackson, & Harding, 2010; Powers, Cross, et al., 2015; Tull et al., 2007). Thus, disturbances in emotion regulation ability are closely linked to alterations in emotional reactivity, as emotional undermodulation leads to states of heightened emotional reactivity, while emotional overmodulation results in detachment of emotional experiences, both which are frequently reported in PTSD patients (Figure 13, Lanius, Frewen, et al., 2010; Lanius, Vermetten, et al., 2010; Nicholson et al., 2015; Wolf et al., 2014). Therefore, studies begun to characterize the neuronal underpinning of disturbed emotion regulation (Felmingham et al., 2008; Lanius et al., 2011; Lanius et al., 2015; Sadeh et al., 2015). **Study II** aimed at extending previous findings, as we combined neuronal responses with HRV. HRV has been considered as a biomarker of top-down self-regulation (Porges, 2011; Thayer et al., 2009; Thayer & Lane, 2000). In line with the prior mentioned ER difficulties in PTSD, **study II** provided evidence of reduced HRV in PTSD (see Figure 13). Our result of a blunted HRV is in line with recent theoretical models, such as the neurovisceral integration model (Beauchaine & Thayer, 2015; Thayer et al., 2009). This model has postulate top-down regulatory processes of the prefrontal cortex on CAN related brain structures, which in turn affect vagal input on the sinoarterial node of the heart, allowing a complex variability of HR time series. Here, reduced HRV is indicative for autonomic rigidity and an inability to alter physiological and emotional responses in a synchronized manner to environmental demands. A recent study applying ecological momentary assessment provided further hints towards a close relationship between enhanced negative affective arousal and PTSD severity, as negative affective arousal was strongly related to 24-hour HRV recordings. Thus, an increased affective state is

related to reduced HRV, pointing to the potential in linking HRV to emotion regulation (Dennis, Kimbrel, et al., 2016). Importantly, while in healthy controls HRV was positively related to connectivity between key regions of the CAN to subcortical and cortical structures, no such associations have been observed in PTSD. Thus, one may hypothesize, that this reflects a relative uncoupling of the ANS from the CAN and points to a lack in top-down modulation of cardiac function by higher-order brain regions in PTSD. So far, beside HRV related brain response, difficulties in top-down modulation on a neuronal basis have been found in PTSD across a variety of emotion inducing paradigms (Cohen et al., 2013; Etkin & Wager, 2007; Mickleborough et al., 2011; Reiser et al., 2014; Shin, Rauch, & Pitman, 2006; van Wingen et al., 2011; see also Lanius et al., 2012; Lanius et al., 2015). One recent study associated instantaneous HR to regional cerebral blood flow (positron emission tomography) in response to trauma and neutral scripts in traumatized individuals with and without PTSD (Barkay et al., 2012): Overall, they found increased HR during trauma scripts in PTSD individuals. Further, instantaneous HR was associated with the left orbitofrontal region (OFC), right occipital and precentral region in PTSD, but not in trauma controls. The authors argue that activation of the OFC may reflect emotional control, while activation in the precentral and occipital region may reflect a physical response to traumatic stimuli, with a combination of all reflecting top-down regulation. However, it was not specified whether the correlation with brain response was observed during a specific phase of the experiment nor have the phases been contrasted or the direction of the correlation been specified. Nevertheless, this study provides interesting preliminary findings in showing a relation between autonomic response and brain responses within a context of symptom provocation (although it might be intermixed with neutral contents). Thus, future studies are needed, comparing autonomic and neural activity during rest and in response to stressors to gain further insights into the biological underpinnings of emotion regulation contributing to emotional reactivity.

Interestingly, upcoming evidence is further linking individual differences in fear response magnitude to HRV, with lower HRV leading to increased fear responding and thus linking memory processes and emotion regulation (Gorka, 2016; Melzig et al., 2009; Ruiz-Padial & Thayer, 2014). Yet, with respect to fear acquisition, the few studies focusing on this aspect did not find differences between subjects with low and high HRV regarding fear learning (Sevenster, Hamm, Beckers, & Kindt, 2015; Wendt et al., 2015). However, interesting associations have been found between HRV and safety learning (Pappens et al., 2014; Wendt et al., 2015): Pappens and colleagues (2014) found that solely subjects with higher resting HRV learned that a stimulus was never followed by an aversive event, while subjects with lower resting HRV did not show a reduction in FPS response over the course of learning. Mirroring these findings, Wendt et al. (2015) revealed in a different paradigm, that

only subjects with a high resting HRV successfully inhibited the fear response during the presentation of a stimulus compound including a safety cue and solely showing heightened FPS to the danger cue. Since learning alterations in PTSD are stated, a further relationship to HRV seems plausible. Indeed, we did observe alterations in fear learning and generalization with respect to implicit memory in PTSD, as mentioned in D2.1 (**study I**). Studies in PTSD also addressing safety processing in a fear conditioning context, also provided evidence of a deficient fear inhibition to safety cues in a comparable paradigm as the one presented by Wendt et al. (2015) (e.g. Jovanovic et al., 2010; Jovanovic, Sakoman, et al., 2013; for review see also Jovanovic, Kazama, Bachevalier, & Davis, 2012).

Thus, findings regarding disturbances in emotion regulation were observed on a neuronal level: Resting HRV was reduced and not significantly associated to its hypothesized neuronal response pattern. This contrasts the observations found in healthy controls (**study II**). These findings may contribute to alterations in threat expectation and increased uncertainty when evaluating safe cues in PTSD (**study I**). A combination of this pattern could partly underlie the feeling *"as if the trauma were still going on – unchanged and immutable – "* (van der Kolk, 2014), thus pointing towards an important contribution of emotion dysregulation to altered emotional reactivity.

D2.3 Targeting emotional reactivity: Reconsolidation and its relation to PTSD

> *"as every new encounter or event is contaminated by the past"*
>
> - van der Kolk, 2012, p.53

A conceptual framework to address intense emotional states was based on the fear network (initially proposed by Foa & Kozak, 1986; Foa, Steketee, & Grayson, 1985), covering all information and responses central to the individuals' fear. This maladaptation of the fear structure arises when "1) associations among stimulus elements do not accurately represent the world, 2) physiological and escape avoidance responses are evoked by harmless stimuli, 3) excessive and easily triggered response elements interfere with adaptive behaviour, and 4) harmless stimulus and response elements are erroneously associated with threat meaning" (Gillihan, Cahill, & Foa, 2016). Associations to this theory can partly be drawn based on the findings of the included studies within the thesis. For example, **study I** found that harmless stimuli were judged with heightened risk harmless stimuli were judged with heightened risk (4), while further alterations in response times needed in response to the safety cue during fear acquisition (3). **Study II** further hints towards intense physiological responses in a safe situation, as indexed by the neuronal activation pattern of PTSD patients (2).

To overcome or reduce intense emotions, Foas' theory further proposes the importance to 1) reactivate certain memories, and 2) integrate information into these memories, that are incompatible with its prior association. More specifically, a certain memory, which elicits strong anxiety is thought to be reactivated in a safe situation covering new information contradicting the initial emotional response. This new information is thus encoded and stated to result in reducing the distressing emotional response.

From a mechanistic perspective, the integration of new information into an existing memory trace is referred to as reconsolidation. Kindt and colleagues recently stated the opportunity of propranolol in boosting therapy effects in PTSD (Elsey & Kindt, 2017; Kindt & van Emmerik, 2016). Although beneficial effects of the experimentally tested reduction of fear have been observed in samples suffering from spider anxiety (Bjorkstrand et al., 2016, 2017; Soeter & Kindt, 2015a), PTSD is a complex disorder that goes beyond targeting of a specific fear. Yet, a few studies tested the effect of propranolol on trauma memory recall, while protocols are varying in the amount of session (one vs. six) in which propranolol is combined with script driven memory recall: Two studies observed reduced psychophysiological responding during post testing (one session and six sessions). It is important to note that only one of these investigations included a placebo control group, while the data of this placebo group was included in the analyses of the second investigation (Brunet et al., 2008; Brunet et al., 2014). Three further investigations reported symptom improvement during post testing (all studies: six sessions), while none of the studies included a control group (Brunet et al., 2011; Mahabir, Ashbaugh, Saumier, & Tremblay, 2016; Poundja et al., 2012; but also see Wood et al., 2015), reported three investigations failing to reduce symptoms physiological responding). As the majority of studies did not include control groups, observed effects might not be specifically related to the propranolol administration. Moreover, studies did report either effects on physiological responding or symptom improvement exclusively, challenging the idea for an overall symptom improvement in PTSD. Herein, it is also important to keep in mind, that experimental studies testing reconsolidation disruption by an propranolol administration in healthy individuals only found effects on the emotional expression of fear (i.e. fear potentiated startle) (Kindt et al., 2009; Sevenster et al., 2013, 2014a; Soeter & Kindt, 2010, 2011, 2012a, 2012b, 2015b). However, with respect to **study III**, we could not replicate these beneficial effect - that is fear memory attenuation - upon a combination of memory reactivation and propranolol administration (for null findings also see Bos et al., 2012, 2014; Fricchione et al., 2016; Golkar & Ohman, 2012; Kindt & Soeter, 2013; Klucken et al., 2016; Meir Drexler et al., 2014; Soeter & Kindt, 2011; Warren et al., 2014).

Beyond the administration of a pharmacological agent, the idea of targeting reconsolidation mechanism during therapy to achieve positive effects might provide an opportunity to get further insights into therapy–related mechanisms. Yet, **study III** did not provide evidence

towards fear reduction after subjects were exposed to a combination of memory reactivation and a therapeutical technique. This contrasts a recently published study by Agren et al. (2017), who found a reduction of fear responding (SCR) by combining memory reactivation and in sensu stimulus imagination. We followed a different protocol and thus, studies are not exactly comparable. Nevertheless, a better understanding of boundary conditions needed for reconsolidation to occur is necessary, in addition to simultaneously investigating effective therapeutic techniques that may benefit from reconsolidation processes. With respect to the present doctoral thesis, it seems to be important to offer techniques that increase the feeling of safety within the time window of reconsolidation (see Figure 13). The findings in **study I** point towards difficulties in perceiving safety in PTSD, which contribute to a state of enhanced emotional reactivity. Moreover, evidence from **study II** supplements this finding, as it shows disturbances of the interaction of neurobiological regulation mechanism, pointing to disturbances in emotion regulation at rest. Thus, a facilitation of strategies that help to feel safe due to reconsolidation might allow for “a real change to take place” (…) and that “the body” (…) learns “that the danger has passed and to live in the reality of the present” (van der Kolk, 2014).

D3. METHODOLOGICAL LIMITATIONS

The following limitations are important to consider: Firstly, **study I** and **II** only included female participants, limiting the generalizability of the data to male subjects. Further, the observed effects during generalization testing in **study I** is restricted to behavioral measurements, while no effects have been observed regarding fear potentiated startle. One explanation might be the psychotropic medication in the PTSD group, as antidepressants are known to dampen fear potentiated startle (Arnone et al., 2009). Another methodological issue is that the perceptual discrimination ability test was applied after the conditioned-generalization paradigm in **study I**. As mentioned earlier, fear conditioning might alter perceptual discrimination (Laufer et al., 2016; Resnik et al., 2011; Schechtman et al., 2010). However, we did not find differences in perceptual discrimination. Nevertheless, to better address this issue and to rule out group differences, a combined approach in assessing perceptual discrimination and fear generalization simultaneously might help shed light on potential group differences. It is also important to note, that overgeneralization of fear has been found in panic and generalized anxiety disorders and in obsessive-compulsive traits (similar paradigm) (Kaczkurkin & Lissek, 2013; Lissek et al., 2014; Lissek et al., 2010), as well as partly in social anxiety disorder (Ahrens et al., 2016). This points to the question, whether overgeneralization might be a transdiagnostic factor or whether disorder-specific differences in overgeneralization patterns (behavioral, physiological) might exist.

With respect to **study II**, it must be noted that we did not include trauma exposed healthy control subjects. Thus, we cannot rule out potential effects of traumatization vs. diagnosis. Additionally, as it is a cross-sectional study, the present results cannot explain whether a reduced HRV is a pre-existing risk factor in the current PTSD population or caused *due to* traumatization. As the present study investigated the combination of HRV and CAN related connectivity patterns under resting state, we cannot address the question of whether there was a sufficient or insufficient self-regulatory capacity towards an actual stressor. Therefore, this needs to be addressed in future studies.

Moreover, with respect to **study III** the FPS fear memory acquisition within the multimodal sensory intervention group was observed on a marginally significant level only. Therefore, study results within this condition must be interpreted with caution. Finally, with respect to skin conductance response, we did not observe successful fear conditioning across all groups and thus, the effects of memory reconsolidation cannot be addressed regarding this parameter. Recent investigation excluded up to one third of the sample based on successful skin conductance fear conditioning (Schiller et al., 2013; Schiller et al., 2010; Steinfurth et al., 2014). However, a similar procedure would have led to a too small sample size in the present investigation.

D4. CONCLUSIONS AND FUTURE DIRECTIONS

This thesis aimed at gaining a deeper understanding of alterations in emotional reactivity in PTSD, with an additional focus on an experimental approach whether reconsolidation combined with therapeutical techniques is successful in targeting memory and its associated emotional response.

Alterations in PTSD patients' emotional reactivity were hypothesized to lie partly in alterations in memory processes. We indeed found evidence towards alterations in the generalization of fear with respect to the certainty of stimulus evaluation in PTSD. Moreover, PTSD individuals were characterized by an overall heightened risk expectation of safe stimuli. Together, with alterations during baseline responding and fear acquisition, **study I** provided evidence for alterations in implicit and explicit memory processes, which are stated to underlie alterations in emotional reactivity in PTSD. Nevertheless, it is important to note that traumatization, irrespective of a mental disorder did partly contribute to these effects, as trauma control individuals were also characterized by a similar pattern of alterations in their certainty. Moreover, alterations in emotional reactivity have been related to emotion regulation disturbances. With respect to emotion regulation, **study II** revealed a psychophysiological-neuronal profile in PTSD, which is thought to contribute to emotion regulation difficulties. Quite specifically, PTSD patients were characterized by lower HRV, while HRV was not associated with neuronal activation in the central autonomic network, pointing to a desynchronized pattern. Since enhanced emotional reactivity constitutes an important factor in PTSD, we tried to attenuate emotional memory with an experimental approach by combining reconsolidation with therapeutical techniques in **study III**. However, we did not find a beneficial effect by combining reconsolidation with either a pharmacological agent (propranolol) or therapeutical techniques on a prior established fear memory in healthy individuals.

The present doctoral thesis provided first evidence on generalization processes in a sample of PTSD subjects related to adverse childhood experiences, with hints towards alterations in emotional reactivity. Yet, alterations in generalization were only evident with respect to implicit memory processing. A possible explanation for this restriction could be that fear is not the target emotion in PTSD. Therefore, research is needed to focus on emotions other than fear. Importantly, PTSD is increasingly associated with a wide range of aversive emotions (e.g. disgust, anger, shame, and guilt) (Badour et al., 2015; Coyle et al., 2014). Investigating generalization of these emotions would help to characterize the emotional responding in general, as well as alterations in thresholds of emotional responding in PTSD. Thus, an alteration of the current experimental approach, which is based on fear conditioning procedures, is needed to shift a learned association from fear to other target emotions in PTSD.

With respect to the underlying neuronal and psychophysiological mechanism of emotion regulation, extending the combination of both biomarkers in response to emotion provoking studies would provide further insight into the respective pathomechanism. Herein, it is also important to differentiate between the newly introduced dissociative subtype of PTSD (DSM 5; American Psychological Association, 2013) and those without the dissociative subtype, since increasing evidence points to behavioral, as well as physiological and neuronal distinct symptom patterns of these subtypes (Figure 13; Frewen, Brown, Steuwe, & Lanius, 2015; Harricharan et al., 2016; Nicholson et al., 2015; Nicholson et al., 2016; Steuwe, Lanius, & Frewen, 2012). Thus, considering specific subtypes in relation to the respective neuronal-psychophysiological profile (as investigated in the current study) in response to emotion provoking paradigms, would provide important information on specific altered emotion regulation mechanism and its associated contrasting states of emotional reactivity in PTSD. Moreover, relating these biomarkers to a paradigm that studies threat and safety processing could further help clarify the proposed contribution of HRV (and its neuronal representation) more closely.

The recently suggested translation of reconsolidation related experimental research into therapy (Elsey & Kindt, 2017; Kindt & van Emmerik, 2016) should be considered with caution. There is upcoming evidence, which did not replicate beneficial effects, pointing to boundary conditions restricting reconsolidation to occur. Nevertheless, a detailed understanding of reconsolidation as a mechanism would indeed help to identify the mechanistic underlying therapeutical change, as this has also been stated in a recent concept paper (Lane et al., 2015). Yet, studies that actually investigated therapy related techniques and reconsolidation processes are sparse (present investigation, (Agren et al., 2017). Therefore, more research is needed to identify required conditions in order for reconsolidation to occur. Additionally, precise characterizations of successful reconsolidation-interference protocols need to be tested (pharmacological vs. behavioral). Moreover, since a therapeutical context is far more complex compared to an experimental set up, the feasibility in translating these approaches needs to be considered. With respect to PTSD, a better understanding whether reconsolidation dependent processes could be utilized during trauma-related treatment would be helpful and thereby focusing on strategies that promote safety processing during a time window of reconsolidation. This in turn may improve the feeling of safety and may help to improve the capacity to distinguish between the present and the past. Thus, it could help in adding to our understanding in how to integrate new information into episodic memory and thus, reduce the intensity of trauma related emotions.

E. SUMMARY

The symptom pattern of posttraumatic stress disorder (PTSD) comprises four clusters: “involuntary distressing memories”, “persistent avoidance of stimuli related to the traumatic event”, “negative alterations in cognition and mood”, and “in arousal and reactivity” (DSM 5, American Psychological Association, p.271). Increasing evidence points towards enhanced emotional reactivity as an underlying mechanism of the latter mentioned symptom pattern in individuals with PTSD. From a process oriented perspective, enhanced emotional reactivity has been linked to aberrant fear conditioning processes. It is important to note that the diagnostic criteria of PTSD state that emotional responses in PTSD tend to spread to a variety of stimuli, resembling the traumatic event, which is referred to as overgeneralization. Yet, research mainly focused on classical fear conditioning paradigms, which are restricted to two conditioned cues and thus, cannot investigate the transfer of emotional responses to other cues. Therefore, extending the classic paradigms by including a range of cues is important to ensure a better understanding of the respective pathomechanism. On a neurobiological level, enhanced emotional reactivity has been associated with elevated cardiovascular activity and decreased neuronal activity in prefrontal regions, while simultaneously activity of limbic regions has been found to be increased. This pattern is referred to as decreased top-down regulation. Thus, aberrant neurobiological emotional processing in PTSD points to difficulties in regulating emotional states and thus, alterations in emotional reactivity. Importantly, heart rate variability (HRV) is stated to be a biomarker of emotion regulation, since a high HRV has been associated with one’s regulatory capacity. Importantly, HRV has been found to be lower in PTSD. Yet, the relation between HRV and the neuronal response pattern associated with autonomic functioning has not been studied in PTSD. Investigating both parameters simultaneously is hypothesized to help gain a better understanding of PTSD patients’ capacity to regulate emotional responses. Altogether, emotion overreactivity is a key facet of PTSD. Therefore, one aim of therapeutical attempts is to attenuate strong emotional memory. Interestingly, upcoming evidence from experimental research points to a promising technique, which might provide the opportunity to modify consolidated memory permanently and thus, may be beneficial with respect to therapy. That is, upon retrieval of consolidated memories, these memories must once again stabilize, in order to persist. This process of re-stabilization is known as reconsolidation. Herein, pharmacological, as well as behavioral intervention protocols have been shown to successfully attenuate prior learned emotional responses, when applied during reconsolidation. This has led to an increasing hope in transferring this approach to clinical practice, as it is thought to provide a beneficial therapeutical effect. However, studies are sparse in testing whether therapeutical interventions in combination with reconsolidation provide a beneficial effect on emotional memories. Altogether, the present thesis investigated

underlying mechanisms of heightened emotional reactivity in PTSD. Moreover, an experimental approach aiming at attenuating a newly formed aversive emotional memory was tested, to provide further insights into processes that may contribute to overcome strong negative emotional states.

The first two studies extended prior investigations on emotional reactivity. Results showed that PTSD individuals exhibited altered emotional reactivity to safe stimuli resembling the danger cue, as indexed by alterations in fear generalization with respect to the certainty of stimulus evaluation. Together with increased subjective risk perception and alterations in baseline responding and fear learning, these findings provide further evidence for a correlate of altered emotional reactivity in PTSD. Moreover, study II hints towards a psychophysiological-neuronal profile, contributing to emotion regulation difficulties in PTSD. Thus, while PTSD individuals exhibited lower resting HRV, the latter was not associated with the central autonomic network, pointing to a desynchronized pattern. Both studies implicate the importance of emotional (over-) reactivity in PTSD in contributing to the defined symptom pattern of PTSD. However, an attempt to experimentally target emotional memories did not show a beneficial effect by combining reconsolidation with either a pharmacological agent (propranolol) or behavioural therapeutical techniques on a prior established fear memory. Future research should focus on the combination of the mentioned investigation on emotional reactivity and regulation in PTSD. This would provide a broader picture of the complex interplay between both concepts and their associated behavioral und psychobiological profile. Possible implications for PTSD psychotherapy include strategies that reduce uncertainty in save situations. Although more fundamental research is needed to investigate boundary conditions for reconsolidation to occur, a better understanding of the respective mechanism may help to improve therapeutical strategies.

F. LIST OF FIGURES

G. LIST OF TABLES

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