Experimental Investigation of the Role of Slow Wave Sleep in Fear Extinction and Analog Intrusive Re-Experiencing

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Zusammenfassung

Furchtkonditionierung stellt ein wichtiges translationales Modell für die Entwicklung und Aufrechterhaltung pathologischer Furcht dar. Im Kontext der posttraumatischen Belastungsstörung (PTBS) können Wiedererlebenssymptome, wie Intrusionen, als komplexe konditionierte Furchtreaktionen verstanden werden. Furchtextinktion beschreibt den Rückgang konditionierter Furcht während der wiederholten Exposition mit Trauma-assoziierten Reizen in einer sicheren Umgebung und wird als ein grundlegender Mechanismus erfolgreicher Trauma-fokussierter Psychotherapie angenommen. Da Furchtextinktion als eine Form des Lernens betrachtet wird, könnten Interventionen zur Verbesserung von Gedächtnisprozessen die Furchtextinktion stärken und somit die Erfolgsaussichten Trauma-fokussierter Psychotherapie erhöhen. Die bisherige Forschung hat überzeugende Evidenz für eine kausale Rolle von Schlaf in Gedächtnisprozessen erbracht. Auf der Grundlage zweier Theorien wird angenommen, dass Schlaf, insbesondere Tiefschlaf, aktiv an der Konsolidierung und dem Abruf von Gedächtnisinhalten sowie an der Regeneration von Enkodierfähigkeit für die nächste Wachperiode beteiligt ist. Vor diesem Hintergrund zielte die vorliegende Dissertation darauf ab, die Rolle des Tiefschlafs in der Furchtextinktion zu untersuchen, wobei der Schwerpunkt zum einen auf der Tiefschlaf-abhängigen Enkodierung und zum anderen auf der Tiefschlaf-abhängigen Konsolidierung lag. Darüber hinaus war es Ziel dieser Dissertation weitere Erkenntnisse über den Zusammenhang zwischen konditionierter Furcht und der Entstehung von Intrusionen zu gewinnen.

Studie 1 untersuchte die Furchtakquisition und analoge Intrusionen im Kontext erhöhter psychischer Belastung in der Allgemeinbevölkerung durch den Ausbruch der Coronavirus-Krankheit-2019 (COVID-19) zu Beginn des Jahres 2020. Die Ergebnisse zeigen, dass die psychische Belastung durch den COVID-19-Ausbruch mit mehr analogen Intrusionen nach Exposition mit einem aversiven Filmausschnitt während der Furchtakquisition verbunden war. Von besonderer Bedeutung ist dabei, dass dieser Zusammenhang durch die Stärke der konditionierten Furcht mediiert wurde. Dieser Befund stützt die Hypothese, dass prätraumatischer Stress das Risiko für die Entwicklung posttraumatischer Belastungssymptome erhöht, indem er die Verarbeitung von Gedächtnisinhalten aversiver Ereignisse beeinflusst. Darüber hinaus unterstützt Studie 1 mit der Feststellung eines kausalen Zusammenhangs zwischen der assoziativen Stärke konditionierter Furcht und analogen Intrusionen die Konstruktvalidität des Paradigmas, das in der vorliegenden Dissertation zur Untersuchung analoger Intrusionen als Folge von Furchtkonditionierungsprozessen genutzt wurde.

In Studie 2 wurde untersucht, ob Tiefschlaf-reicher Schlaf Extinktionslernen fördert. Analysen polysomnographischer Daten legten eine erfolgreiche Manipulation des Tiefschlafanteils in den experimentellen Bedingungen nahe. Die Ergebnisse wiesen jedoch nicht darauf hin, dass Schlaf in der frühen Nachthälfte, im Vergleich zu Wachheit, vor dem Extinktionstraining das Extinktionslernen und -abruf begünstigt oder zu einer Verringerung von analogen Intrusionen führt. Diese Befunde wurden durch Bayes-Inferenzstatistik gestützt. Im Gegensatz dazu deuteten explorative Zusammenhangsanalysen zu den Anteilen verschiedener Schlafstadien und dem anschließendem Extinktionslernen auf eine Rolle des rapid-eye-movement (REM)-Schlafs hin.

Studie 3 untersuchte die Hypothese, dass Schlaf-gerichtete Hypnose, die darauf abzielt, den Tiefschlaf zu erhöhen, die Konsolidierung und Generalisierung der Furchtextinktion begünstigt. Manipulationschecks ergaben keine Steigerung des Tiefschlafs durch Schlaf-gerichtete Hypnose im Vergleich zu einer Kontrollbedingung. Im Hinblick auf den Extinktionsabruf und dessen Generalisierung zeigten die Ergebnisse keinen Hinweis auf einen Effekt von Schlaf-gerichteter Hypnose. Ebenso wurden keine Effekte in analogen Intrusionen oder Rumination gefunden. Bemerkenswerterweise zeigten die Analysen eine Verbesserung der subjektiven Schlafqualität nach der hypnotischen Suggestion, während die Schlafqualität in der Kontrollbedingung absank. Dies weist darauf hin, dass Schlaf-gerichtete Hypnose zur Verbesserung der Schlafqualität nach einem Trauma beitragen könnte.

Die vorliegende Dissertation ist die erste systematische Untersuchung der Rolle des Tiefschlafs in der Furchtextinktion und analogem intrusiven Wiedererleben. Zusammengefasst stützen die Ergebnisse von Studie 2 und 3 nicht die Annahmen, dass Tiefschlaf Extinktionslernen und –konsolidierung begünstigt und dass diese Effekte sich zu einer Verringerung von analogen Intrusionen übertragen. Diese Forschung trägt wichtige Erkenntnisse zu der bestehenden Befundlage bei, die bisher uneinheitlich ist in Bezug auf den Einfluss von Schlaf auf die Furchtextinktion. So deuten die Ergebnisse von Studie 2 auf eine bedeutsamere Rolle des REM-Schlafs anstelle des Tiefschlafs für das Extinktionslernen hin. Dies steht im Einklang mit aktuellen Theorien, die die Rolle des REM-Schlafs in der Regeneration der Enkodierfähigkeit betonen. In Studie 3 schränkt die nicht-erfolgreiche Manipulation der Tiefschlafmenge durch die Schlaf-gerichtete Hypnose die Interpretation der Gruppeneffekte hinsichtlich des Einflusses von Tiefschlaf ein. Anschließende Korrelationsanalysen deuteten jedoch ebenso auf keinen Zusammenhang zwischen Tiefschlaf und nachfolgendem Extinktionsabruf hin. Weitere Forschung ist notwendig, um die Rolle des Schlafs bei der Furchtextinktion zu untersuchen.

Abstract

The fear conditioning framework is a central translational model for the development and maintenance of pathological anxiety. In the context of posttraumatic stress disorder (PTSD), re-experiencing symptoms, such as intrusions, can be explained as complex conditioned fear responses to trauma-associated stimuli. Fear extinction describes the dissipation of conditioned fear during repeated exposure to trauma-associated stimuli in the absence of current threat and is assumed to underlie successful trauma-focused psychotherapy. Since fear extinction is considered as a form of learning, interventions to improve memory processing could enhance fear extinction and thereby improve success rates of trauma-focused psychotherapy. To date, research has provided compelling evidence for a causal role of sleep in memory processing. Two prominent accounts assume that sleep, and in particular slow wave sleep (SWS), is actively involved in memory consolidation and recall as well as in restoration of encoding capacity during ensuing wakefulness. Motivated by these assumptions, the present dissertation aimed to investigate the role of SWS in fear extinction while focusing either on SWS-dependent encoding or on SWS-dependent consolidation. Furthermore, it was the aim of this dissertation to provide further insights on the link between conditioned fear and intrusion development.

Study 1 examined fear acquisition and analog intrusions in the context of increased psychological distress in the general population due to the coronavirus disease 2019 (COVID-19) outbreak in early 2020. Results show that COVID-19-related distress was associated with more analog intrusions after exposure to an aversive film clip during fear acquisition. Importantly, this relationship was mediated by the strength of conditioned fear. This supports the hypothesis that pretrauma stress could increase the risk for posttraumatic symptom development by affecting memory processing of aversive events. Furthermore, by establishing a causal relationship between the associative strength of conditioned fear and analog intrusions, Study 1 provides support for the construct validity of the paradigm used in the present dissertation to examine analog intrusions as a phenomenon deriving from fear conditioning.

In Study 2, it was investigated whether sleep rich of SWS promotes extinction learning. Analyses of polysomnographic recording indicated successful manipulation of SWS amounts in the experimental conditions. However, results did not suggest that early night sleep, in contrast to wakefulness, prior to extinction training facilitates extinction learning and recall or diminishes analog intrusions. These findings were supported by Bayesian inference. In contrast, exploratory analyses on associations between sleep stage amounts and subsequent extinction learning suggested a role of rapid eye movement (REM) sleep in extinction learning.

Study 3 tested the hypothesis that sleep-directed hypnosis, designed to boost SWS, facilitates consolidation and generalization of fear extinction. Manipulation checks did not establish increased SWS by sleep-directed hypnosis in comparison with a control condition. With regard to extinction recall and generalization, results did not suggest an effect of sleep-directed hypnosis. Similarly, no effects were found in analog intrusions and rumination. Notably, analyses showed that subjective sleep quality increased after the hypnotic suggestion but decreased in the control condition, suggesting that sleep-directed hypnosis may be beneficial for improving sleep quality after trauma.

This dissertation is the first systematic investigation of the role of SWS in fear extinction and analog intrusive re-experiencing. Overall, the results from Study 2 and 3 did not support the assumptions that SWS facilitates extinction learning and consolidation and that these effects transfer to fewer analog intrusions. The present research adds important insights to existing evidence, which has been mixed in terms of sleep effects on fear extinction. In particular, the findings from Study 2 suggest REM sleep rather than SWS to be important for subsequent extinction learning, which aligns with current accounts proposing a more dominant role of REM sleep in restoring encoding capacity. With regard to the findings of Study 3, the failed manipulation of SWS amounts by sleep-directed hypnosis limits the interpretation in terms of SWS effects. However, subsequent correlation analyses also did not indicate an association between SWS and subsequent extinction recall. Further research is needed to investigate the role of sleep in fear extinction.

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I General Introduction

Worldwide, about 70% of the population experiences at least one traumatic event across their lifespan (Kessler et al., 2017). Trauma is defined as an extremely stressful event that includes actual or possible serious injury, death and sexual violence and is accompanied by a normative reaction of existential fear and despair (APA, 2013; WHO, 2019). Such an experience has the potential to affect its survivors permanently and a prominent example of this is posttraumatic stress disorder (PTSD). Ehlers and Clark (2000) describe PTSD as a psychological disorder that is hallmarked by the persistent appraisal of the environment as threatening and insecure. This ongoing feeling of impending danger is assumed to originate from the nature of traumatic memories and related cognitions, feelings, and behaviors. Accordingly, several theoretical accounts highlight the role of learning and memory in the etiology of PTSD (see Brewin, 2001a; Ehlers & Clark, 2000; Elzinga & Bremner, 2002; Foa & Kozak, 1986). One important form of learning assumed to play a role in PTSD development is the acquisition of conditioned fear, which describes the associative binding between an aversive event and temporally related stimuli which, by that, obtain the potential of eliciting responses as if an aversive event is happening (Michael, 2017; Zuj & Norrholm, 2019). Research of almost a century has provided evidence for fear conditioning processes explaining the development and maintenance of pathological fear after trauma (e.g., Dunsmoor et al., 2022; Norrholm & Jovanovic, 2018; Zuj & Norrholm, 2019). A recently developed experimental paradigm, moreover, allows for specifically investigating the role of conditioned fear in the development of pathological re-experiencing memories of the trauma (Ney et al., 2022; Wegerer et al., 2013). Processes of fear extinction, i.e., the gradual decline in conditioned fear after repeated exposure to conditioned fear-eliciting stimuli without an aversive event to occur, are widely considered as one of the key mechanisms underlying evidence-based psychotherapy for PTSD (Craske et al., 2018). Therefore, a line of research with the aim of improving treatment efficacy focusses on enhancing these learning processes (Craske et al., 2014; Dunsmoor et al., 2015; Lipp et al., 2020) and special interest is given to potential modulators of fear extinction (Lonsdorf & Merz, 2017; Zuj, Palmer, Lommen et al., 2016).

A particularly promising field of investigation in this context is sleep. Research has shown that sleep is actively involved in learning and memory consolidation (Rasch & Born, 2013). Specifically, empirical findings suggest that sleep supports memory encoding during subsequent wakefulness, as well as consolidation of previously encoded material and later memory recall (Hu et al., 2020; Newbury et al., 2021). Prominent theoretical accounts explaining these effects highlight the role of slow wave sleep (SWS) in sleep-dependent learning and memory consolidation (Diekelmann & Born, 2010; Tononi & Cirelli, 2003). This is important to note since the majority of PTSD patients report sleep problems (Maher et al.,

2006), and research on objective sleep parameters demonstrates alterations in sleep physiology (including reduced SWS) associated with PTSD (Zhang et al., 2019). Based on these findings, it has been hypothesized that disturbances in sleep-dependent learning and memory consolidation impede recovery by interfering with underlying learning and memory processes (Colvonen, Straus et al., 2019; Germain et al., 2017). To date, a number of studies have investigated the impact of sleep in contrast to wakefulness on fear extinction of which some reported a beneficial effect of sleep while clear evidence is currently lacking (Davidson & Pace-Schott, 2020; Pace-Schott, Germain, et al., 2015; Pace-Schott et al., 2023; Schenker et al., 2021). Another approach could be to manipulate sleep and test whether such intervention affects fear extinction processes. If such studies show that sleep interventions facilitate processes underlying conditioned fear reduction, this could bring important implications for further research on the role of sleep in fear memory processing and may enhance psychotherapy for PTSD patients.

The scope of this dissertation was, first, to investigate sleep's role in fear extinction while focusing on the one hand, on sleep-dependent encoding and, on the other hand, on sleep-dependent consolidation. The second aim was to provide further insights into the development of posttraumatic re-experiencing symptoms by investigating its relationship to the acquisition of conditioned fear. In the following (Chapter I.1), theoretical accounts and empirical evidence on memory processes linked to PTSD are introduced, focusing on mechanisms of fear conditioning. Thereafter (Chapter I.2), current findings on the relationship between PTSD and sleep disturbances are presented. Subsequently, two prominent accounts on the role of sleep in memory processing are introduced, and a brief overview of empirical findings from research on fear conditioning and sleep are presented (Chapter I.3). Finally, the research objectives of the present dissertation are outlined (Chapter I.4). Chapter II, III and IV enclose the unchanged manuscripts of Study 1, 2 and 3, which were carried out for this dissertation and have been published as articles in international peer-reviewed journals. The findings deriving from these studies are conjointly discussed and implications for further research are provided in Chapter V.

1. Memory Processes underlying Posttraumatic Stress Disorder: the Role of Fear Conditioning

1.1 Posttraumatic Stress Disorder

While initial posttraumatic stress symptoms can be considered a normative response to trauma, the majority of trauma-exposed individuals show no significant psychological impairment or recover from these transient symptoms (Bonanno, 2004; Diamond et al., 2022; Galatzer-Levy et al., 2018; King et al., 2003). The remaining individuals, however, suffer from a variety of trauma-related psychological disorders and decrements in well-being and social functioning that can persist chronically (Kessler et al., 2017; Morina et al., 2014). PTSD emerges from trauma with an average conditional risk of 4% though the risk can differ greatly between trauma types, e.g., 0.3% following natural disaster vs. 19% following rape (Kessler et al., 2017). One of the core symptoms of PTSD are re-experiencing phenomena that vary widely in their content and quality (APA, 2013; WHO, 2019). They range from the feeling of distress to strong physical reactions during exposure with trauma-related stimuli to reliving of traumatic memories (i.e., intrusive re-experiencing) to partly or fully re-experiencing episodes of the trauma including a dissociative distortion of reality (i.e., flashbacks). Nightmares, as another manifestation of re-experiencing, are also frequently observed in PTSD and extend the phenotype of re-experiencing with regard to the state of consciousness during which PTSD patients can be afflicted by their past. Since confrontation with traumatic memories or trauma-related stimuli is highly aversive, PTSD patients attempt to avoid situations, conversations and even thoughts or emotions that are linked to trauma and could increase the risk of re-experiencing. PTSD is further characterized by increased startle reactivity, hypervigilance, sleep problems and other symptoms resulting from generally increased arousal (APA, 2013; WHO, 2019). In addition, negative alterations in cognitions and affect are also considered characteristic for PTSD (APA, 2013). These symptoms are associated with severe suffering and global functioning impairment in the affected individuals and constitute a significant burden to society (Davis et al., 2022; Kessler, 2000; Kessler et al., 2009). Therefore, it is of high importance to provide therapy to individuals with PTSD (Kessler et al., 2017).

Based on empirical evidence (e.g., Bisson et al., 2013; Cusack et al., 2016; Lewis, Roberts, Andrew, et al., 2020), clinical practice guidelines on treatment of PTSD strongly recommend trauma-focused psychotherapies including Prolonged Exposure, Cognitive Processing Therapy, trauma-focused cognitive behavioral therapy and, in most guidelines, Eye Movement Desensitization and Reprocessing (Hamblen et al., 2019). With that, there is a high consistency between guidelines in recommending treatments that focus re-processing of the individual traumatic memories by cognitive, emotional or behavioral techniques (Schnurr, 2017). One of the core components underlying all of these therapies is the use of exposure

(McLean et al., 2022; VA/DoD, 2017). This involves either imaginal exposure to the traumatic event(s) that may additionally comprise the creation of a written trauma narrative or in-vivo, and nowadays also in-virtuo, exposure to trauma-related cues (Schnurr, 2017). Despite proven effectiveness of exposure-based therapies, not all PTSD patients show significant progress after treatment, and improvements are urgently needed to increase treatment respondence (Cusack et al., 2016; Schottenbauer et al., 2008). In particular, studies suggesting that about a third of the treated patients still reports substantial PTSD symptoms (Bradley et al., 2005). One line of research aimed at improving trauma-focused psychotherapy outcomes focuses on directly augmenting memory processes during and after exposure (e.g., Craske et al., 2014; Lipp et al., 2020; Pittig et al., 2016) or supporting these processes by adjunctive treatments (e.g., Fitzgerald et al., 2014; Michael et al., 2019). Such approaches deliver promising new perspectives on interventions and treatments for trauma-exposed individuals and highlight the importance of investigating learning and memory processes to understand the etiology of PTSD and to improve PTSD therapy.

1.2 Basic Concepts of Human Memory

Memory reflects a number of different abilities and the act of remembering is supposed to rely on three sequential stages of memory processing: encoding, consolidation and retrieval (McDermott & Roediger, 2020). Information that has been initially registered (i.e., encoded) is supposed to be formed to a representation in the neuronal system (termed as engram or memory trace) during consolidation that lasts until it is reconstructed during retrieval. Consolidation can be further divided into short-term or ‘synaptic’ consolidation and long-term or ‘systems’ consolidation, both supporting the progressive stabilization of information to a permanent memory (Dudai, 2004; Dudai et al., 2015). Synaptic consolidation refers to the local strengthening of memories that usually takes minutes to be accomplished and is supposed to be universal for all types of memory. Systems consolidation, on the other hand, refers to the redistribution of memories between neuronal circuitries that can take weeks, months or even years to accomplish. It is currently debated whether systems consolidation is similarly universal or rather unique to specific memory systems (Dudai, 2004; Dudai et al., 2015).

A widely accepted nomenclature of long-term memory separates declarative from non-declarative memory systems (Squire, 1992). Declarative memory comprises semantic knowledge (i.e., facts) and episodic memories (i.e., events) and is also referred to as ‘explicit’ memory system since it should require conscious awareness for retrieval. Non-declarative memory is also termed as ‘implicit’ memory system as it should not require conscious awareness during retrieval and comprises a number of subdivisions such as procedural memories (i.e., skills and habits), as well as classical conditioning and priming (Squire, 1992). Despite this theoretical distinction, memory systems are assumed to work in concert with

overlapping brain circuitry (Dudai et al., 2015; Henke, 2010) and this should evidently be the case for memories of a traumatic event.

1.3 Memory Characteristics of Posttraumatic Stress Disorder

PTSD has been frequently considered as a ‘disorder of memory’ (Brewin, 2001b; Elzinga & Bremner, 2002; McNally, 2006; van der Kolk et al., 1989). This is based on observations of memory retrieval in PTSD patients, which concluded in two general hypotheses. The first hypothesis is that PTSD is associated with difficulties in deliberately retrieving the traumatic experience and fragmented, less coherent narratives of the trauma (Brewin, 2014; Ehlers & Clark, 2000). Accordingly, several investigations on trauma narratives reported higher disorganization or fragmentation of trauma memories in PTSD patients compared to non-traumatic memories and to trauma-exposed individuals without PTSD (Halligan et al., 2003; Jelinek et al., 2009). Furthermore, the amount of memory disorganization was found to be predictive for the course of PTSD (Ehring et al., 2008; Halligan et al., 2003). However, it is important to note that there are also findings challenging the assumption of impaired intentional retrieval of trauma memories in PTSD patients (see Mattsson et al., 2021). The second hypothesis, to date, found much more widespread agreement (Brewin, 2014) and states that PTSD is associated with frequent involuntary intruding memories of the trauma involving intense reliving and strong emotions (Brewin, 2001a; Ehlers & Clark, 2000). Intrusive re-experiencing characteristically consists of spontaneously triggered, brief memory fragments that are of mostly sensory, in particular visual, quality though they are also described as feeling, thought or action and not uncommonly multimodal (Ehlers et al., 2004; Ehlers et al., 2002; Hackmann et al., 2004; Michael, Ehlers, Halligan, et al., 2005). While intrusions are not a phenomenon that is restricted to PTSD (Brewin et al., 2010), the repetitiveness, vividness and high distress accompanying intrusions, as well as the lack of temporal contextualization of the memory, are considered highly specific to PTSD (Brewin et al., 2010; Ehlers et al., 2004; Michael, Ehlers, Halligan, et al., 2005). The latter is assumed to explain the perception of reliving the memory as if it happens ‘here and now’, which was found to be associated with higher PTSD symptom severity (Ehlers et al., 2004; Michael, Ehlers, Halligan, et al., 2005). Intrusions are assumed to occur in response to a wide range of cues that perceptually match stimuli, which were present during trauma, while the individual is often unaware of this contingency (Brewin, 2001a; Ehlers & Clark, 2000; Ehlers et al., 2002). Since intruding memories are proposed to rely primarily on implicit memory processes, their retrieval is assumed to be less controllable than other memories of past episodes (Brewin, 2001a; Ehlers & Clark, 2000). PTSD patient’s attempts to suppress those memories intentionally, or avoid stimuli that could elicit intrusive re-experiencing, were shown to be related to higher PTSD symptom severity including more frequent intrusions (Steil & Ehlers, 2000). Investigations on

intrusive memories provided important insights into memory alterations in PTSD patients that have strongly influenced psychological theories of PTSD.

1.4 The Role of Intrusive Re-Experiencing: the Cognitive Model of Posttraumatic Stress Disorder

An important account of PTSD is the cognitive model by Ehlers and Clark (2000), which proposes that the way a traumatic event is encoded and linked to other autobiographical memories is central for explaining PTSD symptomatology. By drawing on the approach of transfer-appropriate procedures (Roediger, 1990), memory processing is supposed to be dissociated into data-driven and conceptually-driven processing and retrieval depends on which operating mode was active during encoding. Data-driven encoding refers to processing stimuli based on their perceptual features independent of higher-order operating systems and supports automatic stimulus-driven retrieval. Conversely, conceptually-driven encoding is assumed to support elaborated, attention-based processing of information and its context in a meaning-based way. According to Ehlers and Clark (2000), conceptually-driven processing is necessary for the integration of new information into the structure of autobiographical knowledge, thereby supporting its intentional retrieval. However, traumatic stress is proposed to shift information processing towards data-driven processing. This should enhance encoding of stimuli that were temporally related to the trauma, which, on the one hand, reduces the perceptual threshold for these stimuli, i.e., perceptual priming. On the other hand, it facilitates their conjunctive processing with the trauma, i.e., stimulus-stimulus or stimulus-response associative learning (also referred to as fear conditioning; see Michael, 2017). As result of associative binding, trauma-related stimuli may automatically trigger memories and emotions of the trauma. With that, the high frequency of intrusive memories can be explained by effects of priming and the cue-driven nature by mechanisms of fear conditioning. As another consequence of strong data-driven encoding, the cognitive model suggests that the memory of the traumatic event is poorly contextualized into time, place and other knowledge. Therefore, intruding trauma memories are proposed to be fragmented, mainly sensory, and accompanied by a strong ‘here and now’ quality that facilitates misinterpretation of the reactivated memories and emotions as signs of actual threat.

It is important to note that intrusive memories can emerge frequently in the immediate aftermath of trauma irrespective of whether the individual develops PTSD (Ehlers & Clark, 2000; Michael, Ehlers, Halligan, et al., 2005). Several theoretical accounts propose that intrusions, at least in the early period after trauma exposure, serve important functions (e.g., Brewin, 2001a; Ehlers et al., 2002; Krans et al., 2009). One hypothesis is that intrusive memories of the trauma signal a potential threat. In line with basic assumptions on fear conditioning (see Rescorla, 1988), Ehlers and Clark (2000) emphasize that stimuli, which are

bound to the traumatic event, have a predictive meaning due to their temporal relationship. Observations of intrusions have shown that they often represent an event or stimulus that was present before the most distressing and threatening aspect of the trauma, rather than this aspect itself (Ehlers et al., 2002; Hackmann et al., 2004; but see Grey & Holmes, 2008; Holmes et al., 2005, for opposing evidence). Therefore, it is suggested that the content of intrusions could have acquired the function of a 'warning signal' with the potential to elicit a strong perception of impending danger and psychological and physical alertness (Ehlers et al., 2002). While the initial associative binding is not necessarily supposed to be maladaptive, strong perceptual priming may enhance generalization towards a wide range of potential triggers, thus, increasing the likelihood of intrusions and inappropriate fear responses. Furthermore, the implicit nature of intrusions being triggered by cues could support the misinterpretation as signal of current threat. The specific features of intrusive memories in PTSD patients (i.e., high vividness, lacking contextualization, 'here and now' quality, strong negative emotions) are assumed to increase the individual's appraisal of actual danger. With repeatedly having such intrusive memories, new negative appraisals about the individual's self as helpless, unworthy or insane are assumed to emerge and add to symptom chronification. PTSD patients, therefore, commonly exercise several strategies to control intrusions by, e.g., avoiding reminders of the trauma. However, avoidance is assumed to maintain PTSD as it prevents change in memory and cognitions and can also perpetuate intrusions. For instance, ruminative thoughts about the trauma and its consequences occur frequently in response to intrusions (Holz et al., 2017; Laposa & Rector, 2012) and can be considered a form of cognitive avoidance (Ehlers & Clark, 2000). As such, rumination was shown to further trigger intrusive re-experiencing and maintain PTSD (Laposa & Rector, 2012; Michael, Ehlers, Halligan, et al., 2005; Michael et al., 2007). Together, according to the cognitive model of PTSD, it is assumed that the nature of traumatic memories promotes excessive intrusive re-experiencing in response to trauma-related cues (Ehlers & Clark, 2000). The intense reliving of traumatic memories, combined with negative appraisals and maladaptive coping, strengthens their (re)consolidation, leading to a vicious circle of distressing intrusions and the perception of current threat (de Quervain et al., 2009; Ehlers & Clark, 2000).

To date, several empirical findings have provided support for the assumptions of the cognitive model of PTSD. For instance, trauma-related data-driven encoding was associated with more frequent intrusions in clinical samples (Halligan et al., 2003; Murray et al., 2002) and in analog experiments (Halligan et al., 2002; Kindt et al., 2008). Similarly, investigations on trauma-exposed individuals showed that enhanced perceptual priming for trauma-related stimuli predicted PSTD symptom development (Ehring & Ehlers, 2011; Michael, Ehlers, & Halligan, 2005) and experimental analog studies reported more frequent intrusions linked to stronger priming (Ehlers et al., 2006; Michael & Ehlers, 2007). Finally, research of the past

century has provided convincing evidence for a role of fear conditioning processes in PTSD etiology (for reviews, see e.g., Lissek & Van Meurs, 2015; Norrholm & Jovanovic, 2018; Rothbaum & Davis, 2003; Zuj & Norrholm, 2019). The translational value of the fear conditioning framework and its experimental paradigms are described in the following chapters.

1.5 The Fear Conditioning Framework

The capacity to build implicit associative networks by seeking for logical and perceptual relations among stimuli enables an individual to form a sophisticated representation of the environment and, with that, to behave adaptively (Rescorla, 1988). In accordance with the fear conditioning framework[1] (Lonsdorf et al., 2017; Michael, 2017; Pavlov, 1927), an unconditioned stimulus (US) is an innately aversive stimulus that evokes an unconditioned, i.e., automatic, threat response (UR). Neutral stimuli (NS) that are encoded in contingency with the US can be processed and consolidated in conjunction. As a result, the NS, now considered as conditioned stimulus (CS), elicits a conditioned threat response (CR) as an anticipatory reaction to the reactivated US memory engram. This is referred to as (conditioned) fear acquisition and is assumed to rely on associative (i.e., CS-US) binding[2]. When the CS is repeatedly present in absence of the US, the CR may decline gradually, which is supposed to rely on (conditioned fear) extinction (Lonsdorf et al., 2017; Michael, 2017; Pavlov, 1927). According to the retrieval model of extinction (Bouton, 2002; Bouton, 2004), the omission of the US during exposure to the CS violates the individual's expectation based on previous knowledge and initiates the acquisition of a new inhibitory (i.e., CS-noUS) association (Bouton, 2004; Vervliet et al., 2013). This inhibitory memory trace prevents excitation of the US memory engram and, thus, the occurrence of the CR. Since both the acquisition and the extinction memory traces are considered to coexist, the CS can elicit recall of each of the competing associations and their corresponding behavioral outcomes. Therefore, CRs may reoccur after initial extinction, referred to as return of fear (ROF). Which of the two memory traces is reactivated, is assumed to depend on the context during retrieval. The inhibitory memory trace is supposed to be strongly linked to the context in which extinction learning originally took place. Accordingly, extinction is considered much more context-specific than fear acquisition. After extinction learning, the actual retrieval context acts as 'occasion setter' that gates reactivation of one of the two memory traces and determines the actual meaning of the CS. This is in line with the observation that ROF can be elicited when the extinguished CS is presented in a context other

[1] Fear conditioning is a form of classical conditioning which was first described by Pavlov (1927). While fear conditioning is often referred to as the process of conditioned fear acquisition, here, it is used as an umbrella term describing several processes that are linked to conditioned fear (see also Lonsdorf et al., 2017).
[2] Research also supports direct associative binding between the CS and the UR (see Michael, 2017).

than the original extinction context (i.e., [contextual] renewal; Bouton, 2004; Vervliet et al., 2013).

In general, all of these processes are considered vital for the individual (Michael, 2017). That is, fear acquisition is highly adaptive as it prepares the individual to detect and respond promptly and adequately to stimuli that formerly signaled danger (LeDoux, 2014). The phenomenon of extinction further shows that this implicit memory can be updated if fear responses are no longer appropriate while the original response pattern is still available and active in case of uncertainty, allowing the individual to flexibly interact with their environment (Bouton, 2004). However, it is assumed that experiencing trauma can alter associative memory processing towards overactive and inflexible fear responding in safe environments (Keane et al., 1985; Mineka & Oehlberg, 2008; Norrholm & Jovanovic, 2018; Pitman, 1989).

1.6 Fear Conditioning as Translational Model of Posttraumatic Stress Disorder

Fear acquisition is considered a key mechanism in explaining posttraumatic re-experiencing symptoms. In accordance with cognitive models of PTSD (Ehlers & Clark, 2000; Foa et al., 1992) and experimental findings (e.g., Franke et al., 2021; Ney et al., 2022), traumatic threat can be translated to the US, whereas the CS resembles a stimulus that was in a meaningful relationship with the traumatic experience. Subsequently emerging distress, physiological arousal or intruding memories of the trauma are considered CRs triggered by the reoccurring CS. One influential hypothesis in the context of PTSD is that the specific conditions of trauma promote strong fear acquisition (Ehlers & Clark, 2000; Zuj & Norrholm, 2019). This was previously also referred to as ‘superconditioning’ (Pitman, 1989), proposing that the extreme stress during trauma, mediated via stress-responsive neuromodulators, promotes an over-consolidation of conditioned fear. Albeit the acquisition and retrieval of conditioned fear is considered a good model for the development of re-experiencing symptoms initially after trauma, this construct alone is not sufficient to explain why the majority of trauma-exposed individuals do not develop PTSD (Keane et al., 1985; Pitman et al., 2000).

When translating the fear conditioning framework to PTSD, it is important to consider that fear of stimuli that previously signaled threat is adaptive overall and the development of pathological fear is not the prevailing outcome of aversive events (Beckers et al., 2013). What differentiates adaptive from maladaptive fear is whether a situation is dangerous or safe and what determines whether an individual develops pathological fear may be related to their tendency to detect and respond to signals of potential danger in safe environments (Michael, 2017). That is, individuals are assumed to make inferences about the world to predict future events and pathological fear can be understood as a shift of information processing that follows the ‘better safe than sorry’ principle (Van Den Bergh et al., 2021). This explains fear in response to stimuli that signal safety caused by increased threat sensitivity for the cost of

specificity, which is, from an evolutionary perspective, a vital strategy (Michael, 2017). Moreover, this hypothesis further accounts for several processes of fear conditioning that are assumed to underlie the expansion of conditioned fear to stimuli that were never directly associated with the US. For instance, conditioned fear can transfer to a stimulus that was paired with the CS after conditioning (i.e., second-order conditioning) or to a stimulus that resembles certain perceptual or conceptual features of the CS (i.e., fear generalization; Dunsmoor et al., 2022; Dymond et al., 2015). Fear expansion largely corresponds with the assumptions of models of PTSD that point out the wide range of stimuli that are capable of triggering re-experiencing (Ehlers & Clark, 2000) and that this could be explained by mechanisms like stimulus generalization (Foa et al., 1989; Keane et al., 1985).

Another mechanism that is assumed to underlie the persistence of PTSD symptoms is avoidance (Zuj & Norrholm, 2019). Based on Mowrer's two-factor theory (Mowrer, 1960), avoiding fear-related stimuli instantly reduces or prevents upcoming fear, thereby, reinforcing future avoidance behavior. In the long-term, avoidance is assumed to maintain conditioned fear responses, which is supposed to rely on the 'protection from extinction' (Lovibond et al., 2000; Rescorla, 2003). That is, the ability to avoid a potentially aversive outcome during exposure to a fear-related stimulus suppresses the reactivation of the conditioned fear memory and prevents the individual from experiencing a violation of their expectation, i.e., that the fear-related stimulus may not be followed by an aversive outcome. Accordingly, Ehlers and Clark (2000) outline that avoidance preserves PTSD symptoms by preventing change in memories and appraisals of the traumatic event. While avoidance is assumed to play a critical role in interfering with extinction learning during exposure, a deficit in extinction learning itself is proposed to be a key variable in explaining persistent PTSD (Zuj, Palmer, Lommen et al., 2016).

Fear extinction is considered central for explaining etiological processes of PTSD. Extinction is assumed to underlie natural recovery from initial fear and distress after trauma exposure and the persistence of these symptoms is linked to deficits in extinction learning and recall (Mineka & Oehlberg, 2008; Rothbaum & Davis, 2003; Zuj & Norrholm, 2019). Furthermore, it is widely assumed that exposure therapy underlies extinction and that the success of exposure therapy depends on the extinction capacity (Craske et al., 2018; Vervliet et al., 2013). While it is commonly assumed that PTSD is linked to impairments in extinction, it is still unclear which specific mechanisms are critical. Potential mechanisms that are discussed include the resistance to extinction due to increased conditioned fear, a general impairment in fear inhibition, as well as impaired retrieval of the extinction memory that may be related to altered processing of context information (Lissek & Van Meurs, 2015; Norrholm & Jovanovic, 2018; Zuj, Palmer, Lommen et al., 2016). The latter is of particular importance since, even after successful fear reduction during exposure therapy, relapse of symptoms can

occur (Zuj & Norrholm, 2019). Therefore, current attempts in augmenting exposure therapy and preventing relapse aim to target the consolidation of the inhibitory memory trace and its accessibility and generalizability during retrieval (Craske et al., 2018; Dunsmoor et al., 2015; Vervliet et al., 2013).

It is important to note that the fear conditioning framework is not specific to PTSD. In order to investigate elementary memory processes, fear conditioning has been studied for almost a century and long before a concept of PTSD existed (Bienvenu et al., 2021). Clinical research suggests that psychological disorders, in particular anxiety disorders, PTSD, obsessive-compulsive disorder and addiction, rely on maladaptive conditioning processes that lead to psychopathology (e.g., Mineka & Oehlberg, 2008; Pittig et al., 2018). Albeit the lack in specificity, the translation of the fear conditioning framework to PTSD has convincing face validity as its learning principles resemble the most basic assumptions of PTSD etiology. That is, a traumatic event (i.e., an aversive learning experience) is an obligatory precondition for the development of PTSD, and strong psychological, behavioral or physiological responses to trauma-related stimuli are a specific feature of PTSD (APA, 2013; WHO, 2019), which aligns with the concept of conditioned fear reactions (Bienvenu et al., 2021; Keane et al., 1985; Norrholm & Jovanovic, 2018).[3]

1.7 Experimental Evidence on the Role of Fear Conditioning in Posttraumatic Stress Disorder and Methodological Considerations

1.7.1 Modeling Peritraumatic Processing and Posttraumatic Re-Experiencing: Methods of Fear Conditioning Protocols and Analog Trauma Paradigms

In humans, fear conditioning is mainly investigated with cue conditioning protocols presenting discrete items (e.g., objects or human faces) as CS which are followed by unpleasant stimuli (e.g., electro-tactile shocks or loud tones) serving as US (Lonsdorf et al., 2017). A common practice is to contrast a CS that is paired with the US (i.e., CS+) with a second, unpaired CS (i.e., CS-), allowing the distinction of responses attributed to conditioned fear acquisition from general fear responsivity. More recently, examining CS- responses itself has become of interest in studies focusing on psychopathology since they are assumed to provide information about inhibitory conditioning processes (i.e., safety learning; Lissek et al., 2005; Lonsdorf et al., 2017). Extinction learning is induced by presenting the CS+ repeatedly, without the occurrence of the US, and the subsequent assessment of responses to the extinguished CS+ during retention test is assumed to mark whether the extinction memory trace is retrieved and actively inhibits the competing fear memory trace (Lonsdorf et al., 2017). An alternative protocol by Milad et al. (2007) extends this procedure by presenting two CS+ during acquisition

[3] As outlined by Bienvenu et al. (2021), the initial conceptualization of PTSD was strongly influenced by behaviorism which constitutes a bias in translating the fear conditioning model to characteristics of PTSD.

training but only one CS+ undergoes subsequent extinction training. When presented during retention test, the difference in responses between these CS+ is supposed to contrast fear and extinction recall, which is assumed to be a more sensitive approach to assess fear discrimination and inhibition during extinction recall (Fullana et al., 2018). Besides from using discrete cues, fear conditioning research further includes manipulations of the context (e.g., background stimuli on a computer screen) in which fear conditioning occurs (Lonsdorf et al., 2017). This is mainly established by combined cue-and-context conditioning protocols, which are of use to model context-dependent fear acquisition, extinction and ROF. As conditioned fear can be expressed on a variety of response levels, CRs are commonly observed on several outcome measures such as subjective ratings (e.g., fear or US expectancy), psychophysiological markers of fear and arousal (e.g., skin conductance response [SCR] or fear-potentiated startle [FPS]) and correlates of neuronal activity (e.g., blood oxygen level dependent [BOLD] activity; Lonsdorf et al., 2017).

A major limitation of classical fear conditioning protocols in the context of PTSD is that they do not allow investigating episodic memory, whereas the core symptom of PTSD is unintentional recall of (details of) the traumatic episodes (Dunsmoor & Kroes, 2019; Mertens et al., 2020). To address this gap, an experimental paradigm was invented that enables investigating fear conditioning processes and their role in the development of re-experiencing symptoms. The ‘conditioned-intrusion paradigm’ (Wegerer et al., 2013) draws on previous research using aversive (also termed as ‘traumatic’) film clips containing actual or threatened death or serious injuries. These highly aversive films were shown to reliably elicit intrusive memories and other typical trauma reactions and are therefore considered a valuable analog to trauma exposure (Holmes & Bourne, 2008; James et al., 2016). Wegerer et al. (2013) paired a CS with the occurrence of aversive film clips that served as USs and demonstrated successful acquisition of conditioned fear to the CS afterwards. Since then, a growing number of studies used aversive films as USs and a recent meta-analysis (Ney et al., 2022) provided evidence that this protocol yields effective fear acquisition similar to classical fear conditioning designs. Most importantly, Wegerer et al. (2013) reported that the exposure to the aversive films induced analog intrusions and that presentations of the CS+ (paired with the aversive films) triggered more intrusive memories than the (unpaired) CS- or a control condition. This finding was later replicated by Streb et al. (2017) and supports the assumption that the occurrence of intrusive re-experiencing can be explained by mechanisms of fear conditioning. Together, findings deriving from experimental studies investigating fear conditioning with aversive film clips provide important insights into the memory processes linked to PTSD under more ecologically valid conditions (Ney et al., 2022). For instance, studies have started to examine potential moderators of fear conditioning and its role in intrusion development. Such experiments indicated that variables like sex (Rattel, Wegerer, et al., 2019) or estradiol

(Wegerer et al., 2014) affect intrusive re-experiencing through alterations in fear conditioning. With that, fear conditioning protocols using aversive film clips are a promising tool to investigate the mechanisms that are assumed to influence PTSD development and recovery.

1.7.2 Experimental Evidence on Alterations in Fear Conditioning Processes in Individuals with Posttraumatic Stress Disorder

Several studies have investigated whether individuals with PTSD in contrast to healthy controls show alterations during fear conditioning protocols. A meta-analysis by Duits et al. (2015)[4] revealed that PTSD patients, compared to healthy controls, showed no differences in fear expressions to the CS+ or differential fear expressions (i.e., $CS_{\mathbf{diff}}$ = [CS+] – [CS-] responses) averaged over acquisition training. In the presence of the CS- during acquisition training, however, individuals with PTSD showed higher fear expression than healthy controls. During fear extinction training, PTSD patients responded more strongly to the CS+, while no difference was observed for CS- responses (Duits et al., 2015). These findings suggest that PTSD is characterized by fear overgeneralization indicated by increased fear responses to safety stimuli. This was also supported by a meta-analysis showing increased generalization indicated by less discrimination in fear responsivity to perceptual similarities between CS+ and CS- associated with PTSD (Cooper et al., 2022). Furthermore, the findings by Duits et al. (2015) provide evidence that PTSD is linked to impaired extinction learning. Although these meta-analyses did not investigate retention test performance, research suggests that PTSD patients also show impairments in extinction recall. For instance, Milad et al. (2008) investigated fear conditioning in monozygotic twins; one of which served as soldier in combat (half of them were diagnosed with PTSD), whereas the other twin was not combat-exposed. They found higher conditioned fear during retention test in twins with PTSD compared to the combat-unexposed co-twin as well as combat-exposed twins without PTSD. These findings suggest that PTSD is associated with deficits in extinction recall. Furthermore, the findings indicate that impaired extinction recall is acquired upon trauma rather than a biological vulnerability factor (but see Scheveneels et al., 2021, suggesting that pre-trauma extinction performance could predict subsequent PTSD development). Further studies found support for the assumption of deficient extinction recall in PTSD patients (Garfinkel et al., 2014; Milad et al., 2009), while some indicated that sex is an important moderator of this effect (Shvil et al., 2014), and others did not report significant differences in retention performance (Marin et al., 2016; Rougemont-Bücking et al., 2011).

[4] The meta-analysis by Duits et al. (2015) as well as Cooper et al. (2022) found similar effects in samples with anxiety disorders. Thus, the observed effects should be considered as transdiagnostic features associated with pathological fear and anxiety, rather than specific characteristics of PTSD.

1.8 Neurobiological Mechanisms of Fear Conditioning and their Link to Posttraumatic Stress Disorder

1.8.1 Neurobiological Circuitry of Fear Conditioning and Functional Abnormalities in Posttraumatic Stress Disorder

The link between fear conditioning processes and PTSD is strongly supported by neurobiological research. Specifically, it is proposed that the dysfunctions in memory observed in PTSD underlie altered functioning of predominantly the amygdala, dorsal anterior cingulate cortex (dACC), ventromedial prefrontal cortex (vmPFC), and hippocampus (Bryant, 2019; Elzinga & Bremner, 2002; Pitman et al., 2012). These areas are also considered critical for fear conditioning, which is outlined in the following (for extensive reviews, see e.g., Herry et al., 2010; Ledoux, 2000; Maren, 2001; Maren & Quirk, 2004; Milad & Quirk, 2012; Pape & Pare, 2010; Tovote et al., 2015).

The amygdala, a heterogeneous group of nuclei within the temporal lobe, plays a key role in fear acquisition and the expression of conditioned fear (Ledoux, 2000; Maren, 2001; Tovote et al., 2015; see also Fullana et al., 2016; Visser et al., 2021; Wen et al., 2022, for [contrasting] evidence and discussion of methodological pitfalls in research on humans). According to its functional organization in the context of fear conditioning, the amygdala is commonly divided into a basolateral and a central complex of nuclei (Maren, 2001; Tovote et al., 2015).[5] The basolateral amygdala (BLA) receives and conjunctively processes sensory input from cortical areas and the thalamus, which is assumed to enable associative binding (Fanselow & LeDoux, 1999; Maren, 2001). Activity-dependent neural plasticity of the BLA has been linked to building and maintaining CS-US associations (Maren & Quirk, 2004; Tovote et al., 2015). As a result of associative binding, fear is expressed in response to CS that is supposed to be mediated by the central complex of the amygdala (Ledoux, 2000; Maren, 2001). The central complex receives projections from the BLA and innervates several brain areas such as the hypothalamus and nuclei in the brainstem, which are involved in the generation of physiological and behavioral defensive responses (Ledoux, 2000; Maren, 2001). Activity-dependent neural plasticity of BLA nuclei has also been linked to inhibiting fear during extinction learning (Maren, 2011; Tovote et al., 2015). In line with the assumption that extinction involves the formation of a new inhibitory memory trace (Bouton, 2004), research suggests the existence of distinct ‘fear’ and ‘extinction neurons’ in the BLA after extinction learning (Herry et al., 2008). While it is still unclear which mechanisms underlie extinction, one hypothesis is that these extinction neurons directly inhibit fear expression within the amygdala (Tovote et al., 2015). Beyond the significant role of the amygdala, it is important to note that

[5] The definition of amygdala subdivisions differs depending on the functionality, cytoarchitecture and anatomical position and is not restricted to these nuclei (see e.g., Maren et al., 2001; Wen et al., 2022).

fear conditioning-related changes in neural plasticity have been also observed in several other brain structures (Tovote et al., 2015). Furthermore, research has demonstrated that the expression or inhibition of CRs depends on the activity of a widely distributed neural network (Fullana et al., 2016; 2018).

A brain area that has been consistently linked to fear conditioning processes is the dACC (prelimbic cortex in rodents; see Fullana et al., 2016; 2018; 2020) and is assumed to promote fear expression by gating and sustaining fear signals in the BLA (Milad & Quirk, 2012; Tovote et al., 2015). The inhibition of conditioned fear is associated with the vmPFC (infralimbic cortex in rodents; see Fullana et al., 2020). Specifically, the vmPFC is supposed to prevent fear expression indirectly through projections to the BLA and to inhibitory interneurons of the amygdala (Herry et al., 2010; Tovote et al., 2015). This suggests that fear expression and inhibition depend on functional connectivity between the amygdala, dACC and vmPFC. In line with the functional distinction of fear and extinction neurons (see Herry et al., 2008), defined cells in the BLA were shown to project either to the prelimbic cortex (dACC in humans) during fear recall, or to the infralimbic cortex (vmPFC in humans) during extinction recall (Senn et al., 2014). Whether a CS elicits retrieval of the acquisition memory or the inhibitory extinction memory is supposed to depend on the retrieval context (Bouton, 2004). The encoding of contextual information is strongly linked to the hippocampus (Rudy et al., 2004). Since the hippocampus directly projects to the BLA, the dACC, as well as the vmPFC, it is able to gate retrieval of both memory traces (Maren, 2011; Milad & Quirk, 2012). Specifically, research has shown that, similar to the amygdala, distinct fear and extinction cells also exist in the hippocampus that could govern fear responding (Lacagnina et al., 2019). This is further indicated by a recent study in humans, in which the activity of the amygdala and specific subregions of the hippocampus predicted activity of either dACC or vmPFC during fear and extinction retrieval (Hennings et al., 2022).

Functional abnormalities in the brain are assumed to underlie the pathological fear conditioning processes that are linked to PTSD. This is supported by a recent meta-analysis on neuronal activity during fear conditioning in PTSD patients compared to trauma-exposed healthy controls (Suarez-Jimenez et al., 2020). PTSD patients had increased amygdala activity in response to a CS during fear acquisition, extinction and later retrieval test. In the presence of a stimulus signaling safety during fear acquisition, PTSD patients showed decreased activity of the vmPFC. Finally, extinction recall[6] was associated with greater activation of the amygdala, anterior hippocampus, dACC and vmPFC in PTSD patients. The increased activity of the amygdala found across conditioning phases supports the assumption that PTSD is characterized by an overactive fear system (Pitman et al., 2012). The alterations in vmPFC

[6] Extinction recall was tested by comparing responses to an extinguished and an unextinguished CS+ during retention test.

activity in response to safety stimuli as well as during extinction learning and retrieval are in line with the hypothesis that PTSD patients show a general impairment in the regulatory inhibition of fear (Milad & Quirk, 2012). Moreover, the results indicate altered hippocampal activity that corresponds with the assumption of impaired contextual processing in PTSD, which might result in a failure to detect safe contexts and promoting fear overgeneralization (Besnard & Sahay, 2016; Maren et al., 2013). A question that is still unanswered is whether the functional neuroanatomic abnormalities observed in PTSD patients constitute pretraumatic risk factors or evolve along with PTSD (Bryant, 2019; Pitman et al., 2012). While evidence exists that some characteristics are rather vulnerability factors, others seem to emerge during or after trauma (e.g., Pitman, 2006). These acquired features are strongly linked to traumatic stress.

1.8.2 The Role of Traumatic Stress: a Neurobiological Account on Fear Conditioning Processes in the Context of Posttraumatic Stress Disorder

A prominent neurobiological account of PTSD by Pitman et al. (2012) hypothesizes that strong neurochemical stress responses emerging during trauma shift information processing from elaborated, context-dependent higher-order processing that strongly depends on prefrontal and hippocampal functionality to a more 'primitive' salience-based processing under control of the amygdala. With that, traumatic threat is supposed to enhance the amygdala-mediated excitation of monoaminergic neurons in the brainstem, in particular the locus coeruleus, raphe nuclei and ventral tegmental area. This should, in turn, facilitate the release of norepinephrine, serotonin and dopamine. In addition, the amygdala is supposed to initiate the activation of the hypothalamic-pituitary-adrenal (HPA) axis, which should result in a further increase in norepinephrine levels and, subsequently, the release of glucocorticoids. This is assumed to alter the functional dominance of prefrontal and cortical regions that exert inhibitory control over amygdala activity to a relative dominance of the amygdala during information processing. The activity of the prefrontal cortex is supposed to be modulated by monoamines in a U-shaped relationship. That is, while moderate levels of monoamines enhance the inhibitory control over the amygdala, high levels interfere with prefrontal functions. This should indirectly promote associative binding in the BLA. In addition, the release of norepinephrine and dopamine is supposed to strengthen CS-US binding and fear expression directly in the amygdala (Pitman et al., 2012). Increased levels of glucocorticoids, furthermore, are assumed to strengthen fear memory consolidation additionally by directly acting on the amygdala and the hippocampus (de Quervain et al., 2017).

In accordance with this account, higher levels of norepinephrine were consistently found to be associated with the development of intrusive re-experiencing in PTSD patients (Bryant, 2019). With regard to glucocorticoids, findings to date suggest a more complicated role in

PTSD etiology. That is, PTSD patients appear to have increased cortisol levels in the direct aftermath of trauma which attenuate on the long-term, resulting in hypocorticosolism (Sopp, Michael, et al., 2021; Steudte-Schmiedgen et al., 2016). This is of importance since high levels of cortisol are assumed to interfere with memory retrieval and the administration of glucocorticoids has a diminishing effect on posttraumatic re-experiencing (de Quervain et al., 2017). Together, research revealed alterations in neurobiological processes during fear conditioning linked to PTSD. It is strongly suggested that these rely, at least in part, on abnormal brain functions initiated by traumatic stress (Pitman et al., 2012). This corresponds with the cognitive model of PTSD (Ehlers & Clark, 2000) that emphasizes the role of traumatic stress-related impairments in information processing in the etiology of PTSD.

2. Sleep and its Relationship to Posttraumatic Stress Disorder

2.1 Phenomenological and Physiological Aspects of Sleep

Sleep can be defined as a natural, transient, periodically occurring state of reduced conscious awareness of the external world (Chokroverty, 2017). Whether an individual is in the state of sleep is determined by behavioral and electrophysiological criteria (Vassalli & Dijk, 2009). On the behavioral level, sleep characteristics include reduced mobility, (species-specific) sleep posture, quiescence, reduced response to stimulation, and elevated arousal threshold (Chokroverty, 2017; Vassalli & Dijk, 2009). Electrophysiological characteristics are based on findings from electroencephalography (EEG), electromyography (EMG), and electrooculography (EOG), which are jointly used to measure sleep, referred to as polysomnography (PSG; Chokroverty, 2017). The electrophysiological markers vary largely across sleep and are commonly used to distinguish four sleep stages of non-rapid eye movement (NREM) sleep (further divided into stages N1-3) and rapid eye movement (REM) sleep (Berry et al., 2012; Chokroverty, 2017). These sleep stages periodically alternate in sleep cycles lasting for approximately 90-120 minutes, whereas the relative amount of the sleep stages changes across time asleep (Chokroverty, 2017). Stage N1 is also termed as 'transitional sleep' as this stage usually occurs when individuals fall asleep, and between sleep cycles and accumulates to approximately 3-8% of total sleep (Chokroverty, 2017; Malhotra & Avidan, 2014). According to the current guidelines of the American Academy of Sleep Medicine (AASM; Berry et al., 2012)[7], stage N1 is defined by low-amplitude, mixed-frequency EEG activity which is dominated by theta rhythm (4-7 Hz). Stage N1 is usually followed by stage N2 sleep that cumulatively accounts for the majority of sleep time (up to 50%; Malhotra & Avidan, 2014). The characteristic features of N2 are K complexes and (sleep) spindles (Berry et al., 2012). K complexes are defined as waves with a sharp, high-amplitude negative deflection,

[7] The following description illustrates the characteristic features of each sleep stage. For further specifications, please see the manual for the scoring of sleep and associated events by the AASM (Berry et al., 2012).

followed by a slower positive deflection standing out from the background activity. Spindles are discrete trains of sinusoidal waves with a frequency varying typically within the sigma range (11-16 Hz) and last for approximately 0.75 seconds (Berry et al., 2012; Fernandez & Lüthi, 2020). The amplitude of spindle cycles rises and falls ('waxing and waning') symmetrically, leading to the characteristic spindle-like shape. The background activity of N2 is usually dominated by theta rhythm, while the activity changes gradually to slower frequencies during transition to SWS (Malhotra & Avidan, 2014). SWS (synonym to N3 or 'deep sleep') is defined by slow wave activity (SWA), which the AASM describes as the occurrence of high-amplitude waves of a (slow) frequency at 0.5-2 Hz and accounts for a minimum of 20% of the time epoch (Berry et al., 2012)[8]. Slow oscillations (<1 Hz) within SWA reflect global fluctuations in neuronal excitability with synchronously increased excitability in the up-phases of a slow wave and synchronous silencing of neurons in the down-phase (Steriade et al., 1993). Spindles also occur during SWS though less prevalent (Dijk, 2009). SWS accumulates to approximately 20% of sleep time, whereas the amount of SWS and SWA is highest during the first sleep cycles and gradually decreases over the consecutive NREM episodes (Dijk, 2009; Shrivastava et al., 2014). In the transition to stage REM, SWS is often briefly interrupted by N2, which is followed by REM sleep (Chokroverty, 2017). REM sleep is characterized by a low-amplitude, mixed-frequency EEG (mostly resembling that in stage N1), a relatively low EMG tone, and the occurrence of conjugate rapid eye movements (REMs; Berry et al., 2012). The amount of REM sleep accumulates to approximately 25% of total sleep and, opposed to SWS, progresses with sleep cycles (Malhotra & Avidan, 2014; Shrivastava et al., 2014).

The oscillation of sleep-wake cycles, as well as of sleep stages, are assumed to depend on the circadian rhythmicity (marked by changes of core body temperature and levels of melatonin and cortisol), and by homeostatic sleep pressure (marked by changes in electrophysiological brain activity; Borbely et al., 2016). Research strongly suggests that SWA is a marker of homeostatic sleep pressure as it increases gradually during wakefulness and decreases during sleep largely independent of circadian factors (Borbely et al., 2016; Dijk, 2009). Therefore, processes underlying SWS are considered essential for sleep-wake regulation and likely contribute to adaptive daytime functioning (Dijk, 2009). Specifically, it is assumed that sleep homeostatic processes, in particular SWA, play a role in processing waking experience-induced neuronal changes and support network stabilization and memory consolidation (Vassalli & Dijk, 2009). Before this is going to be outlined in Chapter I.3, an

[8] The defining range in frequency and the terminology of SWA and related events varies depending on methodology, analytical approach, and investigated species (Timofee et al., 2020). An alternative nomenclature of EEG activity during SWS, for instance, distinguishes between slow oscillations (>1 Hz) and delta waves (1-4 Hz) and their spectral power is termed as SWA (see e.g., Rasch & Born, 2013).

overview of findings of sleep, sleep disturbances, and sleep interventions in the context of PTSD is provided.

2.2 Sleep Disturbances and Posttraumatic Stress Disorder: a Bidirectional Relationship

Sleep disturbances and PTSD are interrelated. Disturbed sleep (as symptom of hyperarousal) and nightmares (as symptom of re-experiencing) are part of the symptom clusters defining PTSD (APA, 2013). Based on self-reports, approximately 70-90% of PTSD patients have sleep disturbances and about 50-70% have nightmares (Lancel et al., 2021; Maher et al., 2006). A recent meta-analysis on PSG-based studies (Zhang et al., 2019) showed that PTSD patients, in comparison with healthy controls, have less total sleep time (TST) and sleep efficiency (i.e., amount of sleep time sleep relative to time in bed). Furthermore, PTSD patients had less SWS percentage and less consolidated sleep, indicated by wake (time) after sleep onset (WASO). As these parameters are all considered markers of sleep quality (Ramlee et al., 2017), PTSD seems to be featured by a general decrement in sleep quality.

Research strongly suggests that sleep disturbances are not a mere symptom of PTSD (Spoormaker & Montgomery, 2008). This is based on evidence showing that sleep problems prior (Gehrman et al., 2013; Neylan et al., 2021) or immediately after trauma (Koren et al., 2002; McLay et al., 2010) predict PTSD development. Specifically, a prospective cohort study showed that individuals reporting poor sleep quality had a 60% increased risk for subsequently developing PTSD (DeViva et al., 2021). Furthermore, sleep disturbances frequently resist PTSD therapy (e.g., Pruiksma et al., 2016; Schnurr & Lunney, 2019; Zayfert & DeViva, 2004). Accordingly, a meta-analysis revealed that sleep-targeting interventions, in particular sleep-focused psychotherapy, were more efficient in enhancing sleep quality than treatments focusing on PTSD (Maher et al., 2021). These findings underline that sleep disturbances are not a mere result of hyperarousal in context of PTSD. Numerous studies, therefore, have investigated the association between sleep problems and PTSD, and it is commonly assumed that PTSD symptoms and sleep disturbances are reciprocally related (see e.g., Germain et al., 2017; Lancel et al., 2021, for reviews). For instance, a meta-analysis on ecological momentary assessment studies revealed a bidirectional association between poorer sleep quality during the night and PTSD symptoms during daytime (Slavish et al., 2022). A recent study, furthermore, showed that this bidirectional relationship was also evident when PTSD patients received psychotherapy, indicating that pre-treatment insomnia predicts PTSD therapy outcomes (Kartal et al., 2021). This aligns with research suggesting that sleep disturbances impede recovery from PTSD (López et al., 2017; Reist et al., 2017; Sullan et al., 2021). However, it is important to note that some findings indicate that this effect is moderated by depression (Lommen et al., 2016), and others did not find any effect (Sexton et al., 2017).

Together, previous research indicates that disturbed sleep plays a causal role in PTSD etiology and recovery (Lancel et al., 2021). Therefore, enhancing sleep quality constitutes an important aim for (early) interventions after trauma exposure to prevent PTSD development or chronification (Azza et al., 2020; Socci et al., 2020).

2.3 Sleep Interventions as Adjunctive Treatments for Posttraumatic Stress Disorder

Sleep interventions are considered promising adjunctive treatments in the context of PTSD therapy (Colvonen, Drummond et al., 2019). However, to date, little is known about whether sleep interventions effectively reduce PTSD symptom severity or augment response rates of trauma-focused psychotherapy. To date, cognitive-behavioral therapy for insomnia (CBT-I) is the most efficacious treatment for insomnia (Riemann & Perlis, 2009). Currently, there is only one randomized controlled study that investigated CBT-I effects in PTSD patients, showing CBT-I improved sleep quality and global functioning, but did not significantly altered non-sleep-related PTSD symptoms (Talbot et al., 2014).[9] A growing body of research further suggests hypnosis as a promising tool to treat sleep disturbances (Chamine et al., 2018). During hypnosis, a subject is guided by a hypnotist to respond to suggestions targeting perception, sensation, emotion, thought or behavior (Green et al., 2005). Indeed, current evidence shows that hypnotic suggestions addressing sleep can directly affect physiological markers of sleep (see Cordi et al., 2014; 2015; 2020; see Chapter I.4.3, for further details). Three studies have investigated the effect of sleep-directed hypnosis in PTSD patients: Abramowitz et al. (2008) compared adjunctive hypnotherapy with pharmacological treatment with zolpidem of sleep in PTSD patients while all patients were treated with supportive psychotherapy and antidepressant medication. In comparison with the adjunctive pharmacological treatment, hypnotherapy improved sleep quality and, most importantly, reduced PTSD symptoms. In contrast, two studies by Galovski et al. (2016) and Arditte Hall et al. (2021) evaluated the effect of sleep-directed hypnosis compared to a control condition (i.e., sleep and symptom monitoring) as adjunctive treatment to subsequent cognitive processing therapy in PTSD patients. While both studies indicated that sleep-directed hypnosis in comparison with the control condition initially was superior in improving sleep quality, no augmenting effect of sleep-directed hypnosis on PTSD symptoms emerged. In summary, strong support for an effect of sleep interventions on PTSD symptoms is currently lacking. It is argued that further research on the exact mechanisms could provide critical suggestions concerning which sleep-specific processes should be targeted by clinical interventions (Azza et al., 2020). Of specific interest

[9] Several studies have further investigated the effect of CBT-I in combination with Imagery Rehearsal Therapy (IRT) to treat nightmares in PTSD patients (see Maher et al., 2021, for an overview). Since IRT includes reprocessing of nightmare contents comprising also traumatic memories (Krakow & Zadra, 2010), it is difficult to disentangle IRT effects on sleep from effects on trauma memory.

to this research field is sleep's suggested role in memory processing (Lancel et al., 2021; Talamini & Juan, 2020; van der Heijden, van den Heuvel et al., 2022).

3. Sleep-Dependent Memory Processing: Theoretical Models and Current Evidence on the Role of Slow Wave Sleep in Encoding and Consolidation

3.1 The Role of Sleep in Memory Encoding: the Synaptic Homeostasis Theory

According to the synaptic homeostasis hypothesis (SHY; Cirelli & Tononi, 2022; Tononi & Cirelli, 2003; 2014), sleep is necessary to regulate synaptic plasticity, thereby promoting ideal conditions for information processing in the next period of wakefulness. Synaptic plasticity describes the activity-dependent change in synaptic strength and is considered to be a key component of learning and memory (Magee & Grienberger, 2020). The central hypothesis of the SHY is that the net synaptic strength (i.e., overall facilitation of neuronal excitation in the brain) varies systematically across a sleep-wake cycle. While ongoing wakefulness leads to an accumulation of synaptic strength, sleep selectively weakens synaptic strength.

The assumptions of the SHY build on neurobiological research on excitatory, glutamatergic synapses and their activity patterns during information processing. During wakefulness, neurons receive an extensive amount of inputs, but they only respond to a small subset of them with a release of burst firing (Balduzzi & Tononi, 2013). Whether a neuron initiates firing and to which extend is assumed to depend on whether inputs 'suspiciously coincide' (Barlow, 1987). That is, the neuron detects regularities between inputs and fires in response to them. With that, information about the external environment in interaction with internal states is communicated across neurons. Firing to input that is salient to the individual (by its novelty or by signaling threat or reward) is further strengthened through neuromodulators (like norepinephrine or dopamine) that gate long-term synaptic potentiation (Magee & Grienberger, 2020). While this mechanism enables storing of information (by sustaining activity) over a period in which this information (or input) is absent, this process is supposed to be limited by biological and informational constraints (Tononi & Cirelli, 2014). Regarding biological constraints, synaptic firing is assumed to require energy supplies, cellular space and to produce waste products. Regarding informational constraints, with accumulating information during wakefulness, neurons are assumed to increase their range of allocating high synaptic strength to several lines of input. With that, the signal-to-noise ratio in neuronal excitation is supposed to decrease as neurons fire less selectively. This saturation in the efficiency of synaptic plasticity together with cellular energy depletion is assumed to cause impairments in vigilance, cognition and learning that are linked to prolonged wakefulness/sleep deprivation (Krause et al., 2017; Lim & Dinges, 2010; Newbury et al., 2021).

The SHY posits that sleep regulates brain functioning by restoring cellular functions and synaptic down-selection. The former is linked to processes such as restoring glucose depots

and eliminating waste molecules in the brain that are assumed to rely on NREM-specific processes, though findings also suggest an additional role of REM sleep (Cirelli & Tononi, 2022). The latter, most emphasized, process of synaptic down-selection is linked to various mechanisms. The currently best investigated mechanism that offers an explanation for synaptic down-selection is synaptic depression (though other forms of synaptic homeostasis may also contribute to renormalizing synaptic plasticity; see Cirelli & Tononi, 2022; Fauth & Tetzlaff, 2016). Synaptic depression can be conceptualized as the opponent process to synaptic potentiation, that is, a long-term reduction in synaptic strength (Collingridge et al., 2010). While it is, to date, unclear which specific form of synaptic depression underlies sleep-dependent synaptic down-selection, the SHY strongly suggests a role of SWA during NREM sleep. In particular, the synchronous low-frequency bursts of activity characterizing SWA are supposed to put synapses in a labile state in which they could either be strengthened or depressed. Neuromodulators linked to synaptic potentiation, like acetylcholine and norepinephrine, are reduced during NREM sleep, which is assumed to support shifting synaptic plasticity towards depression. However, as the lowest noradrenergic tone (combined with a high cholinergic tone) is found during REM sleep, both NREM and REM sleep may play a role in synaptic homeostasis and the exact interplay with neuromodulators are yet considered elusive (Cirelli & Tononi, 2022). According to the SHY, synaptic depression during sleep is a selective process, emphasizing that not all synapses are weakened. In fact, synapses that were activated strongly and consistently during sleep might even become relatively stronger. This proportional difference between synapses could facilitate memory retrieval after sleep through an increased signal-to-noise ratio (Tononi & Cirelli, 2014), whereas this is partly challenged by other accounts on sleep-dependent memory consolidation (e.g., Beck et al., 2021; further outlined in Chapter I.3.3).

Evidence for the SHY is manifold and has been extensively reviewed and integrated into the framework since it was first proposed in 2003 (e.g., Cirelli & Tononi, 2022; Tononi & Cirelli, 2014; see also Frank, 2011; Puentes-Mestril & Aton, 2017, for reviews challenging the SHY). For instance, markers of increased synaptic strength during wakefulness and reduced synaptic strength after sleep were found in animal models (e.g., de Vivo et al., 2019; Liu et al., 2010; Miyamoto et al., 2021; Vyazovskiy et al., 2008), as well as in humans (e.g., Huber et al., 2013; Kuhn et al., 2016). Furthermore, the assumption that synaptic potentiation during wakefulness increases SWA during subsequent sleep has been supported by correlative findings (Vyazovskiy et al., 2008) as well as by experimental studies, which manipulated cortical potentiation directly (Huber et al., 2007) or indirectly through learning tasks (Huber et al., 2004; Mascetti et al., 2013). Moreover, boosting or interfering with SWA during sleep was found to impact subsequent memory encoding during wakefulness (Antonenko et al., 2013; Ong et al., 2018; Van Der Werf et al., 2009). There are, however, also contradicting findings, for instance,

by showing a potentiation rather than a de-potentiation of cortical excitability after SWS (Chauvette et al., 2012). Furthermore, several findings suggest a more essential role of REM sleep in synaptic pruning (Grosmark et al., 2012; Watson et al., 2016) and promoting memory encoding (Cousins et al., 2018). Current accounts (including the latest version of the SHY; see Cirelli & Tononi, 2022) suggest that both NREM and REM could contribute to sleep-dependent synaptic renormalization (Navarro-Lobato & Genzel, 2019; Niethard & Born, 2019).

While, currently, little is known about the exact functions of sleep, it is well acknowledged that sleep is necessary for memory formation (Frank & Heller, 2018). For instance, two recent studies have shown that post-learning fatigue (i.e., reduced capacity for new information encoding after intense learning) could be compensated by a daytime nap, but not by a period of restful wakefulness (Nelson et al., 2021; Nissen et al., 2021). Notably, these beneficial effects on performance after the nap were positively related to SWA in both studies. Furthermore, a recent meta-analysis has synthesized evidence from 55 studies contrasting sleep with sleep deprivation before learning and showed that sleep deprivation leads to detrimental memory retrieval (Newbury et al., 2021). However, only few studies investigated learning with emotional stimuli. These studies reported negative effects of sleep deprivation on learning neutral as well as on emotional stimuli (Kaida et al., 2015; Tempesta et al., 2016; Walker & Stickgold, 2006) and one specifically suggested that the effects are linked to NREM sleep rather than REM sleep (Kaida et al., 2015). Critically, some of these studies indicated that the encoding of negative stimuli may be less affected by sleep deprivation than the encoding of neutral or positive stimuli (Tempesta et al., 2016; Walker & Stickgold, 2006). This further underlines the importance of investigating whether sleep is beneficial for fear extinction learning.

3.2 Sleep Effects on Subsequent Extinction Learning

Fear extinction is considered as a form of associative, non-declarative learning that, like other forms of memory, has to be encoded, consolidated and retrieved to be expressed at a subsequent time point (Pace-Schott, Germain, et al., 2015). Albeit differing brain circuitry linked to fear extinction in contrast to, for instance, declarative memories, memory is in general assumed to build on synaptic plasticity (Magee & Grienberger, 2020; Pace-Schott, Germain, et al., 2015). In particular, there is strong evidence that synaptic plasticity of glutamatergic cells in the basolateral complex of the amygdala drive fear, as well as extinction learning (Maren, 2011; Tovote et al., 2015), and that these can undergo synaptic depression similar to cells in the hippocampus (Collingridge et al., 2010). Therefore, the assumptions of the SHY could similarly apply to extinction learning. That is, sleep promotes encoding of extinction memories during the subsequent period of wakefulness.

To date, little research exists on the role of sleep on subsequent extinction learning in humans and even less studies have investigated sleep effects in contrast to wakefulness. Two studies (Pace-Schott, Rubin, et al., 2015; Pace-Schott et al., 2013) examined time-of-day effects on fear acquisition and immediate extinction in either the morning or the evening. They found a stronger reduction in differential fear expressions during extinction training in participants who underwent fear conditioning sessions in the morning. These findings could indicate that extinction learning might have been affected by differences in sleep pressure. It is important to note that these effects are confounded by potential circadian influences such as high cortisol levels in the morning, which have been linked to benefits in extinction-related processes in previous studies (e.g., Lass-Hennemann & Michael, 2014; Merz et al., 2018). Another important caveat of these studies is that the potential sleep effects on extinction learning are hardly dissociable from potential effects on prior fear acquisition. Straus et al. (2017) contrasted sleep with sleep deprivation in the night between acquisition and extinction training. The pre-extinction sleep manipulation had no effect on fear expressions during extinction training. After a recovery night, however, the pre-extinction deprivation group showed impaired extinction recall in comparison with the pre-extinction sleep group, indicated by FPS. This finding aligns with the assumption that sleep is beneficial for subsequent extinction learning and that these effects persist up to later retrieval, whereas the fact that no direct effects were found during extinction training requires further investigation. In contrast to this hypothesis, a recent study (Pavlov et al., 2022) did not find evidence for altered fear extinction or subsequent fear reacquisition after a nap compared to a period of wakefulness. Notably, in both investigations, sleep manipulations were carried out immediately after acquisition training. Thus, future studies need to disentangle potential effects of sleep in extinction learning from effects on the consolidation of the conditioned fear memory trace since research suggests a role of sleep in the consolidation of newly acquired fear associations (e.g., Davidson et al., 2018; Menz et al., 2013). If future research provides evidence for a beneficial role of sleep in extinction learning, it still remains unclear which specific processes may be responsible for this hypothesized effect. A recent meta-analysis did not report any significant correlations between the amount of single sleep stages and the success of subsequent fear extinction (Schenker et al., 2021). In summary, the few current findings point towards a beneficial role of sleep on subsequent extinction learning, but to date, no strong evidence exists. Further research is needed to prove whether sleep causally affects extinction learning and, if so, by which mechanisms.

3.3 The Role of Sleep on Memory Consolidation: the Active Systems Consolidation Framework

Not all memories initially encoded are stored in long-term memory and memory consolidation takes time, during which the risk of eliminating new memories is high (Dudai, 2004; Dudai et al., 2015). While this, at first glance, seems to be a serious flaw in information processing, it is rather considered to prosper adaptive behavior. Based on the two-stage model of memory consolidation (Marr, 1971), it is assumed that information is simultaneously encoded in a fast learning, short-term storage and in a slow learning, long-term storage, but their interplay is needed to form a lasting memory representation. While short-term storage is able to learn information efficiently, its capacity to hold these memories is limited in time and space. Long-term storage learns slowly and should protect preexisting memories from interference. Therefore, it is assumed that short-term storage repeatedly reactivates memory representations, which initiates co-activation of their representation in the long-term storage. Over time, memory retrieval no longer depends on short-term storage as the representation is now consolidated in long-term storage. By that, short-term storage regains capacity for new encoding, while new information can be slowly integrated into the network of long-term memories without causing interference. The latter (termed as 'interleaved learning'; McClelland et al., 1995), is assumed to support the extraction of causal relationships underlying previous experiences, guiding responses to related experiences in the future (Cowan et al., 2021). Evidence for this account derives from studies on declarative memories that require the hippocampus during encoding and initial retrieval, whereas, across time, their dependency shifts from the hippocampus to neocortical structures (termed as 'corticalization'; Takashima et al., 2009).[10] This strongly suggests a reorganization of memory representations across brain structures and is referred to as 'systems consolidation' (Dudai et al., 2015). While research indicates that systems consolidation occurs during both wakefulness and sleep, it is hypothesized that sleep is the favorable state of this process (Dudai et al., 2015; Rasch & Born, 2013).

According to the active systems consolidation theory (ASCT; first proposed by Buzsáki, 1998, and extensively elaborated by Born and colleagues, e.g., Born & Wilhelm, 2012; Diekelmann & Born, 2010; Klinzing et al., 2019), sleep facilitates systems consolidation by supporting neuronal reactivation and communication between distributed networks in the brain. Neuronal reactivation attributes to the re-emergence of activity in neuronal ensembles that were previously active during memory encoding, occurring in the hippocampus (as well as in other brain structures) preferably during SWS (O'Neill et al., 2010). These reactivations are

[10] As noted by Klinzing et al. (2019), the assumptions of the two-stage model have been refined and are currently assumed as less simplistic in terms of the role of the hippocampus as well as the neocortex (see e.g., Kumaran et al., 2016; Squire et al., 2015).

supposed to strengthen the memory representations and promote their redistribution through coupling with rhythmic neuronal activity. It is assumed that during SWS a triple-coupling of rhythmic activity from the neocortex, thalamus and hippocampus migrates local neuronal activity from hippocampal towards neocortical areas. From a functional perspective, this process is analog to the reorganization of memory representations from short-term to long-term storage. Based on empirical findings, this interplay is supposed to be hierarchically ordered, that is distributed low-frequency oscillations nest local high-frequency oscillations in their troughs: During SWS, the up-phase of slow oscillations generated in the neocortex drive spindle generation in the thalamus, whereas the spindles, themselves, group hippocampal ripples in their troughs (Staresina et al., 2015). Ripple activity (high-frequency activity, >80 Hz; often accompanied by sharp waves) coincides with neuronal reactivation in the hippocampus (Diba & Buzsáki, 2007) and is supposed to coordinate the local reactivation pattern with the emerging spindle oscillations. These spindles are assumed to transmit the information from the hippocampus and re-arrive in cortical regions. As the spindles tend to nest in the up-states of slow oscillations (Staresina et al., 2015), the input accompanying the spindles reaches cortical cells in a state of increased susceptibility to synaptic plasticity (Niethard et al., 2018). With that, memory consolidation during sleep is considered to be driven by neuronal reactivations of memory engrams in the hippocampus, which propagate through the brain by oscillatory coupling. This information transfer is likely to be regulated by spontaneous slow oscillations, which could reflect a top-down mechanism for selective memory consolidation (Ngo et al., 2020), whereas current findings also emphasize hippocampal ripples (Oyanedel et al., 2020) and thalamic spindles in coordinating the neocortex-hippocampus dialogue (Durkin et al., 2017; Schreiner et al., 2022).

In accordance with the ASCT, systems consolidation favors specifically SWS. This is based on several findings such as that neuronal reactivations mostly occur during SWS in comparison with wakefulness and REM sleep (Klinzing et al., 2019; Kudrimoti et al., 1999). This is linked to the fact that SWS is characterized by low acetylcholine levels, which are considered to regulate neuronal reactivation and expression of hippocampal cells, thereby potentially shifting information processing from the mode of encoding to consolidation (Rasch et al., 2006). Furthermore, as outlined beforehand, ripples, spindles and slow oscillations feature SWS and their coupling, as a hallmark event occurring specifically during SWS (and to a lower extent during N2), are assumed to be the central mechanism enabling the reorganization of memory representations. In line with these assumptions, a recent meta-analysis demonstrated that cueing neuronal reactivations during SWS, but not during REM sleep, significantly improved memory retrieval (Hu et al., 2020). Nevertheless, REM sleep is also assumed to support memory consolidation, while its specific contribution is currently

debated (see e.g., Ackermann & Rasch, 2014; Almeida-Filho et al., 2018; Goldstein & Walker, 2014; Lewis et al., 2018; Navarro-Lobato & Genzel, 2019).

3.4 Findings on the Role of Sleep after Extinction Learning

Research suggests that fear extinction memory undergoes circuit reorganization in terms of systems consolidation. In particular, findings from animal studies indicate that while initial extinction learning does not require the vmPFC, recall of extinction memory depends on the vmPFC (Milad & Quirk, 2012; Pape & Pare, 2010; Sotres-Bayon et al., 2008). Furthermore, a first study on humans support the assumption of consolidation-based neuronal reactivation of extinction memory, showing that post-extinction vmPFC activity predicted extinction recall 24 hours later (Gerlicher et al., 2018).

To date, existing research on the effect of sleep on fear extinction consolidation in humans has brought rather mixed evidence. A first study (Pace-Schott et al., 2009) compared a 12-hour period of nighttime sleep with daytime wakefulness after extinction training and reported no group differences in fear expressions to the extinguished CS+ ($CS+_{E}$) during retention test. Notably, the sleep group showed similarly low SCRs to the unextinguished CS+ ($CS+_{U}$) in comparison to participants of the wake group who responded more strongly to the $CS+_{U}$ during retention test. As the $CS+_{U}$ is assumed to resemble retrieval of the conditioned fear memory that should have been unaffected by extinction training (see Milad et al., 2007), the authors suggested that sleep might have promoted generalization of the extinction memory. However, it is important to note that the extinction training and subsequent recall were carried out in a morning-to-evening or evening-to-morning period respectively, which may have influenced the effects (see also Pace-Schott et al., 2013, indicating time-of-day effects on extinction learning and generalization). Another study contrasting sleep with sleep deprivation, also found no effect of sleep on extinction recall (Menz et al., 2013). Notably, in contrast to the previous findings of Pace-Schott et al. (2009), Menz et al. (2013) reported higher differential fear in response to the $CS+_{U}$ after sleep than after sleep deprivation. This indicates that sleep had rather consolidated fear memory than supported extinction generalization. Notably, the amount of fear recall in the sleep group was positively related to the amount of post-learning REM sleep. Further studies similarly reported no differences in extinction recall after nighttime sleep in contrast to sleep deprivation (Straus et al., 2017)[11] or in contrast to daytime wakefulness (Kuriyama et al., 2013)[12]. Another study (Menz et al., 2016) has investigated whether extinction retention might be affected differentially by early, SWS-rich sleep in comparison to late, REM-rich sleep in a split-night design (Yaroush et al., 1971). While

[11] Straus et al. (2017) manipulated sleep prior and after extinction training in three experimental groups. The finding mentioned here relies on the findings from the normal sleep and post-extinction deprivation groups.
[12] Kuriyama et al. (2013) investigated the impact of valproid acid and D-cycloserine on fear conditioning processes and sleep. The finding mentioned here is based on the results from the sleep and wake placebo control groups.

no differences were observed after sleep during the early night half compared to total sleep deprivation, sleep in contrast to wakefulness during the late night half resulted in significant differences in extinction recall. That is, the group that stayed awake during the late night half, but not the group that had late night sleep, showed differential fear in response to the $CS+_{E}$ during retention test. This could suggest that partial sleep deprivation in the wake group during the late night half has interfered with extinction consolidation, resulting in a ROF. However, it is important to note that no comparisons between the early and late night sleep and wake groups were reported. This is critical since within-group analyses suggested successful extinction retrieval similarly in the early night sleep group as well as in the total sleep deprivation group (indicated by non-differential fear expressions during retention test). Hence, whether deprivation from late night sleep was causally involved in the ROF in the late wake group cannot be established by the findings from Menz et al. (2016). Notably, the authors further examined responding to an $CS+_{U}$ and found a general decline in differential fear expressions in all experimental groups, whereas this effect was less pronounced in the late sleep group relative to the late wake group. In line with Menz et al. (2013), this finding might reflect a strengthening of conditioned fear memories by (REM-rich) sleep while, again, interpretation of these effects is limited as no comparisons between early and late night sleep and wake groups were reported.

4. Interim Summary and Research Objectives

4.1 Study 1

Study 1 aimed at investigating fear acquisition and analog intrusive re-experiencing with a particular interest in stress-induced changes in both processes. Experimental fear conditioning protocols model implicit associative learning, which is assumed to occur during trauma (Zuj & Norrholm, 2019). The conditioned-intrusion paradigm (Wegerer et al., 2013) combines fear conditioning protocols with the presentation of aversive film clips, enabling the investigation of the link between conditioned fear expressions and analog intrusions. Moreover, this paradigm allows investigation of whether fear conditioning processes serve as mediators in the relationship between certain pre-traumatic risk factors and posttraumatic intrusion development as indicated by previous research (see Rattel, Wegerer, et al., 2019; Wegerer et al., 2014). An important third variable that has been shown to influence both fear conditioning (Merz et al., 2016; Peyrot et al., 2020) and analog intrusions (Hilberdink et al., 2022; Schultebraucks et al., 2019) is stress. In accordance with neurobiological accounts (de Quervain et al., 2017; Giustino & Maren, 2018; Pitman et al., 2012), neurochemical stress responses promote the acquisition and consolidation of conditioned fear, and, thereby, may increase the risk for intrusion development. However, no study, to date, has examined whether stress prior to analog trauma affects analog intrusions via stress-induced alterations in fear

acquisition. In early 2020, when Study 3 was scheduled to start, the coronavirus disease 2019 (COVID-19) outbreak reached Germany and led to an immediate increase in psychological distress in the general population (Robinson et al., 2022; Schäfer et al., 2020). While these exceptional circumstances, on the one hand, slowed down any experimental work in the laboratory, they, on the other hand, offered the opportunity to explore fear conditioning processes and analog intrusion development in the context of a naturally occurring psychosocial stressor. Therefore, an online version of the fear conditioning experiment, originally designed for Study 3, was launched in March 2020, including additional rating inventories to assess distress and rumination in response to the COVID-19 outbreak. 122 participants filled out the questionnaires and underwent fear acquisition training, during which they were presented with neutral everyday objects (CS) of which some were followed by an aversive film clip (US). Conditioned fear responses were quantified based on the participant's ratings of their fear, valence, arousal, and US expectancy in the presence of the CS at the end of acquisition training. On the subsequent day, participants documented intrusive memories and ruminative thoughts about the film clip. It was hypothesized that the associative strength of conditioned fear was positively related to analog intrusions. In addition, Study 1 explored for the first time if ruminative thoughts after exposure to a trauma-analog event were also linked to fear conditioning processes. By assessing COVID-19-related distress and rumination, Study 1 examined whether the psychosocial stress due to the pandemic was associated with differences in conditioned fear responding and analog intrusions and rumination. Moreover, this study is the first to explore if stress-related variability in analog PTSD symptoms could be mediated by interindividual differences in fear acquisition. Finally, Study 1 was intended as a proof-of-concept to demonstrate a causal link between fear conditioning and analog intrusion development and, thereby, support the construct validity of the paradigm used in the present dissertation to examine fear conditioning processes in the context of PTSD.

4.2 Study 2

The major aim of Study 2 was to investigate whether a 3-hour period of sleep in contrast to wakefulness during the early night half enhances subsequent extinction learning and recall. Fear extinction is considered a key mechanisms underlying exposure therapy (Craske et al., 2018). Importantly, fear extinction is assumed to rely on the formation of a new inhibitory memory trace (Bouton, 2004). Therefore, extinction learning should follow basic principles of memory formation similar to other forms of learning, such as that it is based on synaptic plasticity (Magee & Grienberger, 2020; Pace-Schott, Germain, et al., 2015). The SHY (Cirelli & Tononi, 2022; Tononi & Cirelli, 2003) proposes that sleep promotes encoding during the subsequent period of wakefulness by renormalizing synaptic plasticity and restoring cellular functions. While current evidence suggests both NREM and REM sleep contribute to synaptic

renormalization (Cirelli & Tononi, 2022; Niethard & Born, 2019), several lines of research emphasize the role of SWA during NREM sleep (e.g., Antonenko et al., 2013; Nelson et al., 2021; Nissen et al., 2021; Van Der Werf et al., 2009; Vyazovskiy et al., 2008). With regard to fear extinction, only few studies have investigated whether extinction learning benefits from prior sleep. Two studies have tested extinction learning and recall after nighttime sleep in contrast to sleep deprivation (Straus et al., 2017) or after a daytime nap in contrast to wakefulness (Pavlov et al., 2022). While in both studies, the sleep manipulation had no direct effect on performance during extinction training, Straus et al. (2017) reported impaired extinction recall associated with sleep deprivation before extinction training. Pavlov et al. (2022), however, found no significant differences between the two conditions at subsequent fear reacquisition training. Considering this mixed evidence, further research was needed to investigate if sleep facilitates subsequent extinction learning and later recall. Moreover, it remained unclear if such an effect could be attributed to specific sleep stages. In contrast to the studies that manipulated sleep directly after acquisition training (see Straus et al., 2017; Pavlov et al., 2022), research should further test this assumption distinctly from potential effects of sleep on the consolidation of fear acquisition. 63 participants underwent a 3-day fear conditioning experiment with two neutral faces (CS) that were paired with aversive film clips (US) or neutral film clips (CC) during the acquisition training. This design was chosen in order to examine also analog intrusive memories of the US to transfer findings to specific features of PTSD. Ratings of fear, US expectancy and US-associated thoughts as well as SCR and FPS were assessed as conditioned fear expressions during all conditioning phases. After acquisition training on Day 1, participant had a normal night of sleep at home. On the evening of Day 2, participants of the sleep group had a 3-hour sleep opportunity until the middle of the night; participants of the wake group stayed awake during the early night half. The rationale for this sleep manipulation origins from experimental split-night designs (Yaroush et al., 1971), which make use of the uneven distribution of SWS and REM sleep across sleep cycles. During the early sleep cycles, SWS is typically more dominant (Dijk, 2009). In the middle of the night, both groups took part at extinction training and ROF test and were allowed to sleep for another 3-hour period during the late night half. In the morning of Day 3, they underwent retention test and an intrusion provocation task (IPT) to assess intrusions. At the beginning of all experimental sessions, psychomotor vigilance and subjective sleepiness were assessed. It was hypothesized that the sleep group shows improved extinction learning, which further results in better extinction recall and fewer analog intrusive memories, as compared to the wake group. Moreover, it was hypothesized that increased extinction learning and fewer intrusions, in the sleep group, are associated with more SWS and slow waves during the early night half.

4.3 Study 3

The major aim of Study 3 was to investigate if a hypnotic suggestion to sleep deeper after extinction training leads to enhanced extinction recall. Research suggests that, after extinction learning, two memory traces (i.e., acquisition and extinction memory) exist and compete for being recalled in the presence of the next CS (Bouton, 2004; Vervliet et al., 2013). Therefore, it is critical that the extinction memory trace is sufficiently consolidated. The ASCT (Born & Wilhelm, 2012; Diekelmann & Born, 2010; Klinzing et al., 2019) proposes that sleep facilitates consolidation by reactivating newly encoded hippocampal memory representations and promote their redistribution into cortical long-term storage through coupling with rhythmic neuronal activity during SWS. In line with this theoretical account, empirical evidence has shown a causal role of sleep, and in particular SWS, in memory consolidation (Hu et al., 2020; Rasch & Born, 2013). With regard to fear extinction, however, research is more mixed and only few studies have tested the effect of sleep in contrast with wakefulness on consolidation of extinction memories. Most of the studies reported no differences in extinction recall after nighttime sleep in comparison with sleep deprivation (Menz et al., 2013; Straus et al., 2017) or in comparison with daytime wakefulness (Kuriyama et al., 2013; Pace-Schott et al., 2009). Notably, sleep after extinction training has been shown to facilitate the generalization of extinction (Pace-Schott et al., 2009; but see Menz et al., 2013). Evidence for a role of sleep in extinction consolidation arises from research targeting specific sleep stages (e.g., Menz et al., 2016; Spoormaker et al., 2012) or carrying out correlation analyses (e.g., Pace-Schott et al., 2014). These studies rather suggest a role of REM sleep than SWS in subsequent extinction recall. However, it should be noted that only a minority of studies attempted to specifically investigate SWS processes. From a theoretical perspective, it can be assumed that extinction memory undergoes systems consolidation during SWS. In particular, there is evidence suggesting that neuronal representations of extinction memories are reorganized in the brain across time (Gerlicher et al., 2018; Milad & Quirk, 2012). Furthermore, a first study has shown coordinated amygdala-hippocampal ripple activity during NREM sleep in humans, which might resemble the potential key mechanism by which sleep could promote consolidation of emotional memories (Cox et al., 2020). First studies have investigated the assumptions of the ASCT in the context of fear conditioning. Two of these studies suggested that stimulating reprocessing of fear acquisition during SWS promoted fear extinction (Ai et al., 2015; Hauner et al., 2013; He et al., 2015), whereas another study (Ai et al., 2015; Hauner et al., 2013; He et al., 2015) indicated that stimulating reprocessing of fear extinction during SWS rather interfered with extinction consolidation. Considering this mixed evidence, further research was needed to investigate if SWS is involved in extinction consolidation. In particular, no study had investigated whether an intervention to boost SWS after extinction learning could impact extinction retention. In Study 3, at total of 211 participants underwent acquisition training during

which three neutral objects (CS) were presented in a box (conditioning context) either followed by an aversive film clip (US) or not (noUS) and had a normal night of sleep afterwards. On Day 2, participants documented intrusive memories and ruminative thoughts about the film clip. During subsequent extinction training, only one of the two CS+, which were paired with the US during acquisition training, was presented together with the CS-, which was never paired with the US. This design was adapted from Milad et al. (2007) and Pace-Schott et al. (2009) in order to test the effect of sleep manipulation on extinction recall (by examining the extinguished CS, $CS+_{E}$) as well as on extinction generalization (by examining the unextinguished CS, $CS+_{U}$). After extinction training, a whole night sleep period was manipulated by means of sleep-directed hypnosis, invented by Cordi et al. (2014) in order to increase SWS. One group of participants listened to an audio tape with a hypnotic suggestion to sleep deeper, whereas the other group listened to a neutral control text before sleep. This intervention has been shown to reliably increase the amount of SWS and relative SWA power (Cordi et al., 2014; 2015; 2020). Furthermore, sleep-directed hypnosis was shown to enhance subjective sleep quality (Cordi et al., 2020). On Day 3, all subjects were re-exposed with all CS in the original extinction context and in a new context. This was done since extinction recall is assumed to depend on the extinction context (Vervliet et al., 2013) and effects of sleep-directed hypnosis could also emerge during contextual renewal. As mentioned above (see Chapter I.4.1), Study 3 was scheduled to start in early 2020 and interrupted by the COVID-19 outbreak. Therefore, we decided to carry out an online version of the experiment, first, and a laboratory version, afterwards. It was hypothesized that sleep-directed hypnosis, in comparison with the control condition, increases SWS parameters and subjective sleep quality. With that, sleep-directed hypnosis was expected to strengthen extinction consolidation, which should manifest in enhanced extinction recall and extinction generalization in the hypnosis group compared to the control group. Finally, it was hypothesized that these effects would transfer to analog PTSD symptoms, such as that the hypnosis condition was associated with fewer intrusions and rumination related to the aversive film clip from the acquisition training.

II Study 1. COVID-19-Related Distress is Associated with Analog PTSD Symptoms after Exposure to an Analog Stressor

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Abstract
Background: The coronavirus disease 2019 (COVID-19) outbreak in early 2020 was associated with an immediate increase in mental health problems in a significant percentage of the general population. Therefore, it is crucial to investigate how the COVID-19 pandemic – as a psychosocial stressor – affected the etiological processes of mental disorders. Previous research has shown that stress potentiates associative (fear) learning and analog symptoms of posttraumatic stress disorder (PTSD) and that analog PTSD symptoms can emerge in response to associative learning. *Objective:* We investigated whether distress in response to the COVID-19 outbreak support the development of intrusions and rumination after exposure to a non-COVID-19-related analog trauma. Moreover, we examined if these effects are mediated by the strength of associative learning during analog trauma. *Method:* 122 undergraduate university students participated in an online experiment between March and July 2020. They completed questionnaires measuring distress and rumination related to the COVID-19 outbreak. On a subsequent day, they went through an associative learning task, in which neutral stimuli were paired with the appearance of a highly aversive film clip. Subjective ratings were assessed as indicators of associative learning. On the next day, participants documented film-related intrusions and rumination. *Results:* COVID-19-related distress but not rumination was associated with post-film intrusion and rumination load. These effects were mediated by associative learning. *Conclusions:* The current findings are in line with the assumptions that stress enhanced both associative learning and PTSD symptoms. Specifically, they indicate that prolonged psychosocial stress – like during the COVID-19 outbreak – is linked to individual differences in memory processing of aversive events. Further confirmatory research is needed to replicate these results.

1. Introduction

The coronavirus disease 2019 (COVID-19) outbreak was associated with an immediate increase in mental health problems in the general population (Lotzin et al., 2021; Robinson et al., 2022; Schäfer et al., 2020) such as heightened distress, anxiety, and depression (Javakhishvili et al., 2022). These findings underline that the COVID-19 outbreak constituted a large-scale psychosocial stressor[13], involving – amongst other things – social isolation, societal uncertainty, and financial insecurity. As such, it may have affected psychopathological processes, predisposing individuals towards the development of mental disorders. Specifically, learning processes involved in anxiety and stressor-related disorders – such as posttraumatic stress disorder (PTSD) – may have been affected by COVID-19-related distress.

This assumption is supported by research identifying previous adversities as one of the most consistent distal predictor of PTSD symptoms (Rattel, Miedl, et al., 2019). That is, experiencing a period of prolonged stress prior to trauma might predispose individuals towards maladaptive processing during and after trauma, resulting in the development of PTSD symptoms. PTSD is hallmarked by recurring, unwanted (intrusive) memories of the trauma, avoidance of trauma-related stimuli, negative alterations in cognitions and mood, and increased arousal and reactivity (APA, 2013). Amongst these core symptoms, intrusive re-experiencing of the trauma is considered to drive PTSD development. This assumption is supported by research showing that early intrusion characteristics (i.e., distress, 'nowness', and lack of context) are specific features of PTSD (Kleim et al., 2013) and are predictors of PTSD symptom severity 6 months later (Michael, Ehlers, Halligan, et al., 2005). Accordingly, it is assumed that these characteristics promote an ongoing sense of current threat and lead to other symptoms like avoidance and rumination that themselves perpetuate PTSD symptomatology (Ehlers & Clark, 2000; Holz et al., 2017).

Associative (fear) learning (or 'fear conditioning') is assumed to be one of the key processes underlying the development of PTSD symptoms (Ehlers & Clark, 2000; Zuj & Norrholm, 2019). During trauma, individuals are assumed to acquire associations between neutral stimuli (conditioned stimuli [CS]; e.g., approaching headlights) and the traumatic stressor (unconditioned stimulus [US]; e.g., fear of dying during car crash). After trauma, these CS that are associated with trauma are assumed to trigger intrusive memories in response to similar stimuli. Correspondingly, studies have demonstrated a link between the strength of associative learning and analog intrusion development (Franke et al., 2021; Streb et al., 2017; Wegerer et al., 2013). PTSD maintenance is further assumed to be supported by increased generalization and impaired extinction of traumatic associations (Cooper et al., 2022; Duits et

[13] While the outbreak likely constituted a psychosocial stressor for the general population, it is important to note that it may additionally qualify as a traumatic stressor in individuals who experienced a severe course of illness or the sudden loss of a loved one or worked as healthcare professionals.

al., 2015). Critically, the strength of associative learning varies systematically between individuals (Lonsdorf & Merz, 2017), which may result in interindividual differences in intrusion frequency and distress. Trauma-associated rumination occurs frequently in response to intrusions and is, in turn, assumed to perpetuate intrusive re-experiencing (Holz et al., 2017; Laposa & Rector, 2012; Michael, Ehlers, Halligan, et al., 2005). Though phenomenologically different (Ehlers, 2006), it has been suggested that rumination can also be initiated by memory processes (Watkins & Roberts, 2020) and, thus, could also be affected by differences in associative learning (Hoffman et al., 2019).

A potential mechanism by which the COVID-19 outbreak may have affected mental health is the modulation of memory processes. Stress has been shown to promote associative learning (Merz et al., 2016; Peyrot et al., 2020) and analog intrusions (Hilberdink et al., 2022; Schultebraucks et al., 2019) by altering neurochemical processes during memory formation. To our knowledge, no study to date has investigated whether the stress brought about by the COVID-19 outbreak might have affected analog PTSD symptoms and associative learning. Considering that high stress levels are assumed to strengthen associative learning, distress and rumination related to the COVID-19 outbreak may have enhanced associative learning during analog trauma, resulting in more frequent, prolonged, and distressing intrusive trauma memories, also referred to as 'intrusion load' (Rattel, Miedl, et al., 2019). Since intrusions are assumed to have a particularly negative impact on posttraumatic symptom development if they co-occur with rumination about the trauma (Holz et al., 2017), we expected to find similar associations of rumination load.

We tested these assumptions based on data from an analog study that we conducted online from March to July 2020, i.e., during the first months of the COVID-19 pandemic. During this period, psychological distress was generally increased (Robinson et al., 2022) and the restrictions imposed by the German government to contain infections affected almost all aspects of public life (see Supplementary File 1[14] for further information). As part of a larger study investigating the effect of a sleep intervention on fear extinction, healthy participants completed questionnaires measuring distress and rumination related to the COVID-19 outbreak (see Chapter II.2.2 and Figure II-1.A for the general procedure). On a subsequent day, they went through an associative learning task during which they were exposed to an aversive film clip (see Chapter II.2.3). Approximately 28 hours later, participants were asked to document film-related intrusive memories and ruminative thoughts (see Chapter II.2.4). We hypothesized that higher COVID-19-related distress and rumination would be positively correlated with associative learning and with analog PTSD symptoms. Moreover, we hypothesized that the relationship between COVID-19-related distress/rumination and analog

[14] Supplementary material for this manuscript is available online (https://www.tandfonline.com/doi/suppl/10.1080/20008066.2022.2127185?scroll=top).

symptoms would be mediated by the strength of associative learning. To account for potential effects of dispositional anxiety, we conducted all mediation analyses including trait anxiety as covariate.

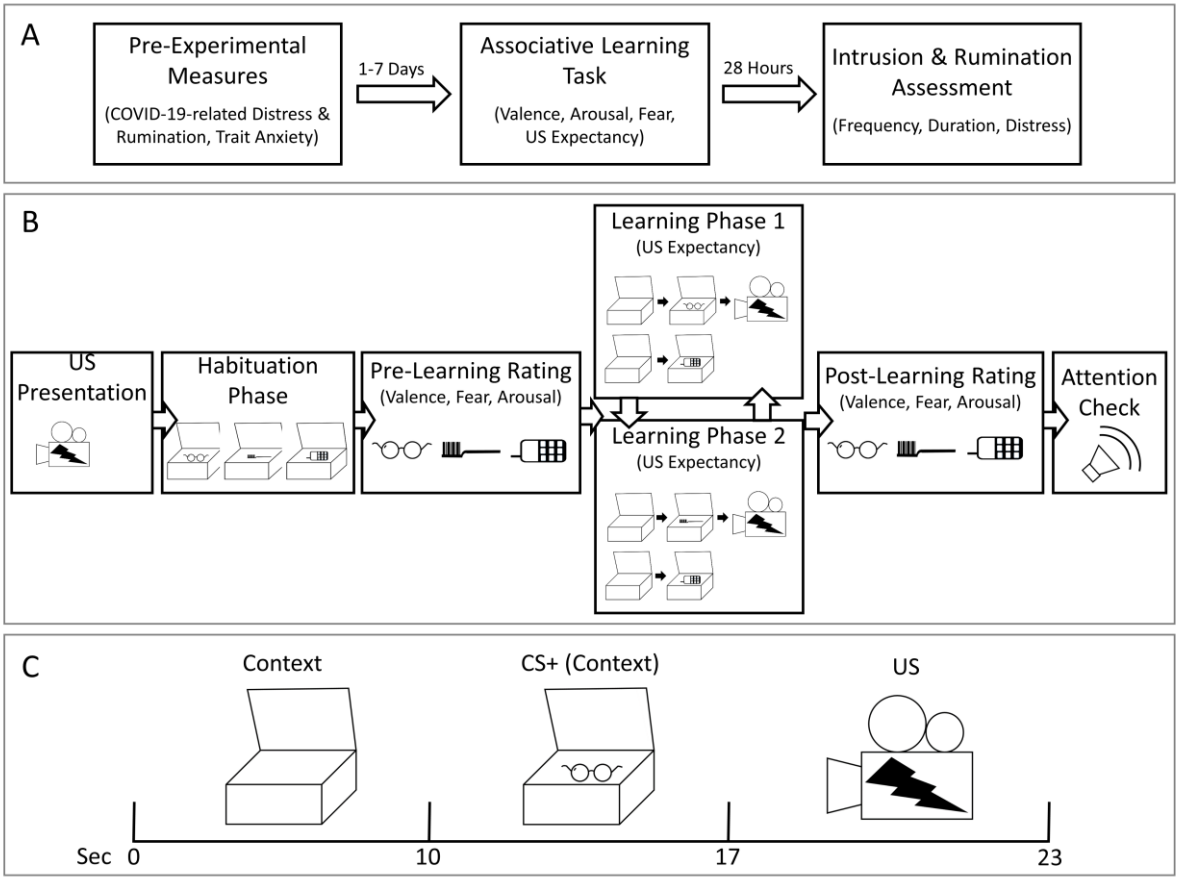

Figure II-1. Illustration of the study procedure.

Note. **A:** General study procedure. **B:** Procedure of the differential associative learning task. **C:** Stimulus presentation in a reinforced CS+ trial during the differential associative learning task. CS+ = conditioned stimulus; US = unconditioned stimulus.

2. Methods

2.1 Participants

One hundred twenty-two undergraduate university students took part in the study. Participants were recruited via online advertisements and their student status was verified by asking them to use their institutional email address. Due to technical errors, responses of ten participants were not recorded. Moreover, four participants did not show successful contingency learning (see Chapter II.2.3) and were discarded from further analyses. Thus, our final sample comprised 108 participants (87 females, 21 males). Of these 108, seven participants reported a history of COVID-19 and four reported that either a relative or close friend had been infected (further details are provided in Supplementary File 1). Study eligibility was restricted to individuals meeting the following criteria: normal or corrected-to-normal vision, sufficient

German language skills, no current or chronic neurological or psychological disorders, and no lifetime interpersonal trauma exposure. Participants gave written informed consent for participation. All methods were carried out in accordance with the Declaration of Helsinki. The study protocol (A 15-3) was approved by the local ethics committee of the Faculty of Human and Business Sciences at Saarland University.

2.2 Pre-Experimental Measures

Rumination about and distress caused by the COVID-19 pandemic were assessed using modified versions of the Perseverative Thinking Questionnaire (Ehring et al., 2011) and the Peritraumatic Distress Inventory (Bunnell et al., 2018). Both questionnaires were adapted for a previous publication (Schäfer et al., 2020). Internal consistency of both measures was excellent (α = 0.91 - 0.96) in the sample of Schäfer et al. and good-to-excellent in the current sample (α = 0.80 – 0.95). We further assessed trait anxiety using the State-Trait Anxiety Inventory (STAI; German version by Laux et al., 1981) which revealed excellent internal consistency in the current sample (α = 0.92). Sum scores were calculated and used for all further analyses. Data was collected using the online platform *SoSci Survey* (Leiner, 2014). Descriptive data and items of the COVID-19-related questionnaires are provided in Supplementary File 1.

2.3 Differential Associative Learning Task

Participants were subjected to a differential associative learning task (Figure II-1.B; for details, see Supplementary File 1) adapted from Pace-Schott et al. (2009) using an aversive film clip of a kitchen accident as US (Landkroon et al., 2020). To further increase ecological validity, we used naturalistic stimuli (i.e., everyday objects) as CS. By using a partial reinforcement schedule (75%), we aimed to limit the reliability with which participants were able to predict the appearance of the US. Such ‘weak situations’ are assumed to increase interindividual variance, which is critical for the differentiation between adaptive and pathological associative learning (Lissek et al., 2006).

Task presentation as well as the assessment of analog PTSD symptoms (see Chapter II.2.3 and II.2.4) were conducted via *Labvanced* (Finger et al., 2017). Following Landkroon et al. (2020), we first presented a full length version of the aversive film clip (10 seconds) and provided participants with information about the protagonist. Participants were instructed that a short version of the film clip would follow some (but not all) everyday objects that were to be presented on the screen and to pay attention which objects were associated with the clip. After a short habituation phase, participants saw all three objects (brush, cellphone, and glasses) that would be presented in the upcoming learning task and were asked to provide valence, arousal and fear ratings (all rates on a scale ranging from 0 to 100). During the learning phase,

one of these objects was presented as the CS- whereas the other two objects were presented as CS+$_1$ and CS+$_2$. The two different CS+ were used to implement two separate learning procedures, which was necessary for further manipulations that took place after the assessment of analog symptoms (see Chapter II.2.4)**.** Hence, the learning procedure was divided in two halves. In one half of the procedure, participants saw eight CS- trials and eight CS+$_1$ trials, six of which were followed by the US. In the other half of the procedure, participants saw eight CS- trials and eight CS+$_2$ trials, six of which were followed by the US. Both halves were presented without interruption and the order of presentation was balanced across participants.

During each trial, participants first saw an empty wooden box, serving as the learning context (10 seconds; see Figure II-1.C, for trial procedure). Subsequently, the CS (brush, cellphone, or glasses) appeared in the wooden box (7 seconds) and participants were asked to provide their US expectancy rating (0 – 100). During reinforced trials, the US (6 seconds) was presented immediately after CS offset. During unreinforced trials, the trial ended after CS offset. At the end of the learning procedure, participants were again asked to provide valence, arousal, and fear ratings for each CS. Since distinguishing between CS+$_1$ and CS+$_2$ is not relevant for the current research questions, ratings were averaged across both CS+ for further analyses. Successful contingency learning was defined as a non-negative difference between US expectancy during the final CS+ and CS- trial. Post-learning ratings (arousal, valence, and fear) and US expectancy during the final CS+ trial were subjected to correlation and mediation analyses. Additional analyses on post-learning CS difference scores [CS- subtracted from CS+] and CS- are provided in Supplementary File 1. Finally, attention to the experimental stimuli (and whether participants still wore their headphones) was tested by presenting three short tones without prior instruction and subsequently asking the participants how many tones they had heard.

2.4 Assessment of Film-Related Intrusions and Rumination

Intrusive memories of the aversive film clip were assessed using the Intrusive Memory Questionnaire (IMQ; Michael & Ehlers, 2007). The IMQ was adapted to assess frequency and duration (in seconds) of intrusions as well as distress (0 – 100) associated with intrusions since watching the aversive film clip (see also Wegerer et al., 2013). Intrusions were defined as sudden, spontaneous, and non-initiated memories of the film clip. Subsequently, participants completed an adapted version of the IMQ that assessed film-related rumination frequency, duration, and related distress. For further analyses, we calculated intrusion and rumination load by standardizing (*z*-transformation) and summing the frequency, duration, and distress items. Descriptive statistics are provided in Supplementary File 1.

2.5 Data Analyses

Data analyses were conducted using *SPSS 25* (IBM Corp., U.S.) and the *PROCESS* macro (Hayes, 2017). Univariate mixed analyses of variance (ANOVAs) were conducted to test differential CS responding during the associative learning task. Bivariate Pearson's correlation coefficients (*r*) were used to quantify the relationship between COVID-19-related measures, post-learning CS+ ratings, and analog PTSD symptoms. Whenever COVID-19-related measures were significantly correlated with analog PTSD symptoms, we conducted mediation analyses to examine whether the effect of COVID-19-related distress and rumination on analog symptoms was mediated by the strength of associative learning. Trait anxiety and attention-check scores (dummy-coded) were included as covariates in all mediation analyses. To this end, we employed Hayes's *PROCESS* macro using 5.000 bootstrap resampling for calculation of confidence intervals (Hayes, 2017). Incomplete cases were assessed and excluded separately for each subanalysis. The alpha level was set to .05 for all analyses.

3. Results

3.1 Manipulation Checks

ANOVAs including the within-subject factors CS (CS+, CS-) and Time (pre-, post-learning) and valence, arousal or fear ratings as outcome revealed significant CS*Time interaction effects (all $p < .001$). Likewise, an ANOVA including the within-subjects factors CS and Trial (1-8) and US expectancy as dependent variable revealed a significant CS*Trial interaction effect ($p < .001$). In all analyses, the effects supported successful differential associative learning as indicated by an increase in arousal, fear and US expectancy and a decline in valence for the CS+ but not for the CS- across the learning task (see Supplementary File 1, for further details). The attention check was successful in 87 participants (81%).

3.2 Correlations between COVID-19-Related Measures and Analog PTSD Symptoms

Analyses revealed significant positive correlations between COVID-19-related distress and film-related intrusion ($r = .23$, $p = .016$) and rumination load ($r = .25$, $p = .009$). COVID-19-related rumination was not correlated with either measure (all $p > .05$; see Table II-1).

Table II-1. Bivariate associations between COVID-19 related measures, strength of associative learning, and analog PTSD symptom

Measures	1	2	3	4	5	6	7	8	9
1. COVID-19 distress	-								
2. COVID-19 rumination	r = .75*	-							
3. Post-ACQ CS+ Valence	r = -.17	r = -.06	-						
4. Post-ACQ CS+ Arousal	r = .28*	r = .19*	r = -.64*	-					
5. Post-ACQ CS+ Fear	r = .28*	r = .13	r = -.63*	r = .84*	-				
6. Post-ACQ CS+ US EXP	r = .01	r = .13	r = -.26*	r = .24*	r = .20*	-			
7. Intrusion Load	r = .23*	r = .08	r = -.44*	r = .37*	r = .44*	r = .14	-		
8. Rumination Load	r = .25*	r = .09	r = -.37*	r = .31*	r = .31*	r = .14	r = .72*	-	
9. Trait Anxiety	r = .33*	r = .34*	r = .11	r = -.03	r = -.05	r = -.04	r = -.10	r = .07	-

Note. ACQ = Acquisition; US EXP = US expectancy; CS+ = conditioned stimulus (reinforced); US = unconditioned stimulus; * p < .05.

3.3 Correlations between COVID-19-Related Measures and Post-Learning Ratings

Analyses revealed significant positive correlations between COVID-19-related distress and post-learning CS+ arousal (r = .28, p = .003) and fear ratings (r = .28, p = .004). These associations were neither evident for pre-learning ratings nor for CS difference scores or CS-ratings (all p > .05; see Supplementary File 1). COVID-19-related rumination was only correlated with post-learning CS+ arousal ratings (r = .19, p = .047). No significant correlations were evident for valence or US expectancy ratings (all p > .05; see Table II-1).

3.4 Mediation Models

Mediation analyses with COVID-19-related distress as independent variable, film-related intrusion load as dependent variable and trait anxiety and the attention-check score as covariates showed that the association was fully mediated by the strength of associative learning, as indicated by post-learning CS+ fear and arousal ratings (see Figure II-2). That is, participants with greater COVID-19-related distress experienced higher arousal and fear after learning in presence of the CS+, which was in turn associated with a higher intrusion load. The same pattern emerged for film-related rumination load as dependent variable. Analyses of valence ratings revealed that CS+ responses partially mediated the effect of COVID-19-related distress on intrusion load, whereas no mediation effect was found when predicting rumination

load. All mediation analyses controlled for potential effects of trait anxiety and attention-check scores. While trait anxiety was not associated with any CS+-related measure, the attention-check score was positively correlated with post-learning valence for CS+.

Additional mediation analyses on CS difference scores revealed similar effects for intrusion load as outcome, i.e., differential scores for valence and fear mediated the relationship between COVID-19-related distress and intrusion load. Importantly, both COVID-19-related distress as well as intrusion load were associated with higher (not lower) differential CS ratings. Analyses including rumination load as outcome did not reveal significant mediation effects (details provided in Supplementary File 1).

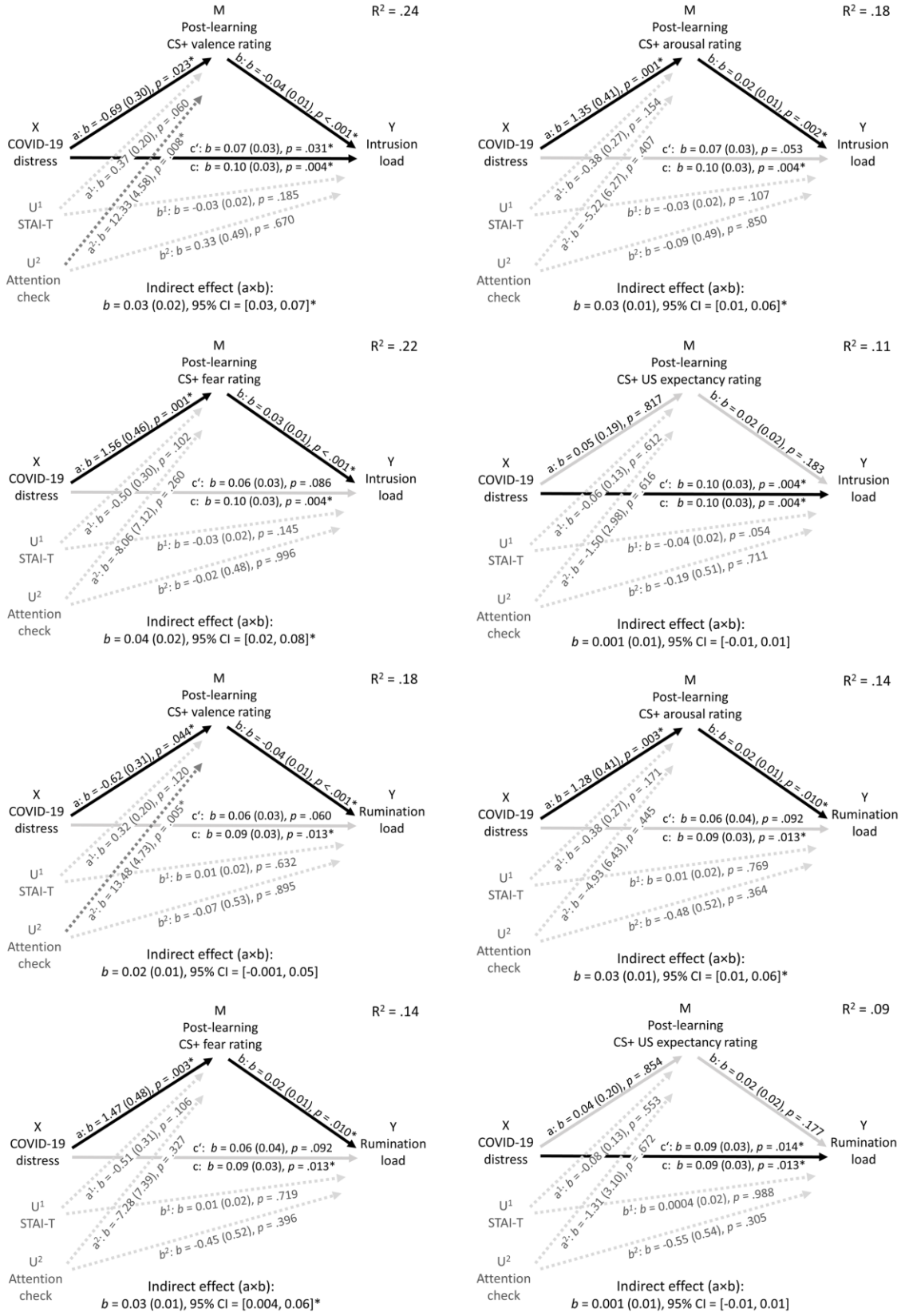

Figure II-2. Mediation models.

Note. Mediation models examining the effect of COVID-19-related distress (X) on analog symptoms (Y) mediated by the strength of associative learning (M). All models included the covariates (U) trait anxiety and attention-check scores. Path c shows the total effect of X on Y, and path c′ shows the effect after controlling for M. Standard errors are given in parentheses. CI = confidence interval (bias-corrected); CS+ = conditioned stimulus; STAI-T = trait anxiety. *p < .05

4. Discussion

The current study investigated whether distress and rumination related to the COVID-19 outbreak was related to more analog PTSD symptom development in healthy individuals after exposure to a non-COVID-19-related analog traumatic stressor. Moreover, we tested whether this relationship could be explained by strengthened associative learning.

Our first finding was that COVID-19-related distress was associated with increased intrusion load, which is in line with previous studies showing that a psychosocial stressor before analog trauma exposure results in higher intrusion load (Hilberdink et al., 2022) and supports the idea that biological stress responses predict subsequent intrusions (Schultebraucks et al., 2019). Moreover, our findings align with the assumption that the COVID-19 outbreak had the potential to increase allostatic load (Fofana et al., 2020). That is, during the time of assessment, the pandemic acted as a prolonged psychosocial stressor that may have surpassed individual recources for adaptive coping. Hence, the current findings indicate that prolonged stress – as evident during the COVID-19 outbreak – may result in an earlier 'tipping point' at which trauma exposure results in PTSD development (Rattel, Miedl, et al., 2019).

We further found that increased distress related to the COVID-19 pandemic was associated with stronger associative learning as indicated by increased post-learning valence, arousal and fear ratings to the CS+. This corresponds with previous findings of stress-induced strengthening of associative learning (Merz et al., 2016; Peyrot et al., 2020). Several experimental investigations have found a positive relationship between differential associative learning and intrusions (e.g., Franke et al., 2021; Streb et al., 2017; Wegerer et al., 2013). In line with these studies, our analyses revealed that associative learning predicts intrusion load, thus, providing further support for the hypothesis that associative learning is a key process underlying intrusion development.

Finally, and most importantly, we found that the relationship between COVID-19-related distress and intrusion load was partly (for valence) and fully (for arousal and fear) mediated by associative learning. As such, the current findings support the assumption that allostatic load enhances maladaptive memory processing which facilitates intrusive memory formation (Schultebraucks et al., 2019). Moreover, our results indicate that associative learning may play a role in the development of posttraumatic rumination, presumably by indirectly affecting the occurrence of intrusions (Holz et al., 2017). However, these results were less consistent since differential CS ratings did not correlate with rumination load. Hence, caution is warranted in interpreting these findings.

In 2020, pandemic-related stressors had a devastating impact on a significant percentage of the general population (i.e., 18%; Lotzin et al., 2021). However, recent research indicates that most of the mental health problems declined over the course of the pandemic (Robinson et al., 2022). Moreover, in some areas, the pandemic had positive side-effects on

mental health (e.g., digital health care, flexible and remote working options; Javakhishvili et al., 2022). Thus, early warnings of a 'second pandemic' of mental illness (Choi et al., 2020) are, fortunately, not supported by the current data. Our findings might, therefore, reflect a temporary increase of psychosocial stress in the general population elicited by the COVID-19 outbreak in early 2020. Nevertheless, a subgroup of individuals may be at risk for a further increase in mental health problems (Javakhishvili et al., 2022). The current findings, hence, may suggest that chronically heighted distress during the early phase of the COVID-19 outbreak resulted in pathological processing of aversive events in a subgroup of the general population.

Despite remarkably consistent associations between COVID-19-related distress and analog PTSD symptoms, no correlations were evident between COVID-19-related rumination and analog intrusion and rumination load. Although it may appear counterintuitive that rumination related to the COVID-19 pandemic was not related to film-related rumination, it is important to differentiate between rumination as a pathogenic process and rumination as a symptom of PTSD. Rumination as a pathogenic process has been shown to enhance depressive affect, whereas worry enhances anxious affect, which in turn is known to strengthen fear associations (Gazendam & Kindt, 2012; McLaughlin et al., 2007). Hence, COVID-19-related rumination may be more relevant for explaining depressive symptoms, whereas only COVID-19-related anxiety may be involved in modulating the strength of associative learning. Correspondingly, previous research has shown that rumination related to analog trauma – but not trait-rumination – was correlated with analog intrusive memories (Holz et al., 2017; Laposa & Rector, 2012; Sopp, Streb, et al., 2021). Our measure of COVID-19-related distress may thus have assessed anxious responses to COVID-19, whereas COVID-19-related rumination may have measured responses relating to depression.

Another inconsistency of the current findings is that US expectancy did not mediate the association between COVID-19-related distress and analog PTSD symptoms. This lack of significant association could be related to restricted variance, i.e., variance (*SD* = 12.09) was markedly lower for US expectancy than for the other indicators of associative learning (*SD* = 19.78-30.60). This could have prevented finding significant associations. Alternatively, this pattern of results could suggest that the subjective, emotional responses to the CS+ – rather than the expectation of the US – may be relevant for analog symptom development. Relatedly, it has been proposed that subjective fear – as compared to indirect or (neuro-)physiological measures of fear - may be the most important indicator of clinical anxiety and its successful treatment (LeDoux & Hofmann, 2018). Future research should thus investigate associations between different indicators of associative learning and analog symptoms in greater depth.

Although providing interesting indications, our study has several limitations that need to be considered. First, we investigated analog symptoms in a sample of healthy participants of

which we did not assess pandemic-related trauma exposure. Thus, interpretation of distress levels and generalization to processes during real-life trauma is restricted and conclusions on psychopathology must be drawn cautiously. For instance, research to date has found mixed evidence whether a general disposition towards stronger associative learning predicts PTSD development, whereas other processes like the capacity to extinguish these associations have been more consistent predictors of PTSD (Scheveneels et al., 2021; but see Lommen & Boddez, 2022). Future research should investigate whether robust markers of PTSD development may be found if associative learning is examined in the context of stress manipulations since the memory processes that are assumed to underlie PTSD development occur during extreme/traumatic stress (Dunsmoor et al., 2022). Furthermore, though experimental analog studies consistently show a causal link between associative learning and intrusions (e.g., Franke et al., 2021; Streb et al., 2017), recent findings indicate that stronger associative learning may also support the success of extinction learning in some cases (Franke et al., 2021). Such findings emphasize the need for further research examining which mechanisms determine (mal-)adaptive processing of aversive events. Nevertheless, it is promising to see that findings from analog studies have been shown to replicate also in clinical populations (e.g., Kessler et al., 2018). Another limitation which needs to be considered is that, while causality is established in the relationship between associative learning (including film exposure) and analog symptoms, this cannot be said for the relationship between COVID-19 distress and associative learning. That is, whether individuals showed enhanced fear learning in response to COVID-19-related distress or whether a disposition towards heightened associative learning caused higher COVID-19-related distress (see Funkhouser et al., 2022; Hunt et al., 2022), cannot be established based on our mediation analyses. Further research is needed to support our hypothesized model, for instance, by examining interindividual differences in associative learning and responses to psychosocial stressors in a cross-lagged panel design. Furthermore, though we controlled for effects of trait anxiety, we cannot rule out the possibility that a third variable influenced our outcomes.

Another limitation of our study is that we conducted all assessments online. Although necessary in light of the public restrictions that were in place during the assessment period, remote testing reduces the possibility to monitor attention and compliance. Although we controlled for potential effects using attention-check scores, we did not assess attention using a standardized tool. Moreover, we cannot rule out that the unstandardized setting increased error variance. Furthermore, it is important to note that, while we assume that biological stress responses to the COVID-19 outbreak promoted associative learning and intrusion (and rumination) development, we did not investigate these mechanisms. Additionally, we consider the COVID-19 outbreak as a prolonged psychosocial stressor without explicitly assessing the timing, intensity, and duration of stress. This is critical since research suggests a complex

interaction between memory processes and stress depending on its intensity, timing, and duration (Merz et al., 2016). Therefore, further research is required to better characterize the impact of prolonged stressors – such as the COVID-19 pandemic – on the individual stress levels as well as their interaction with the memory processes investigated here. Notwithstanding, as one of the first studies to investigate the effects of a large-scale stressor in this context, our results provide important first insights. These findings may also transfer to other large-scale stressors (e.g., the upcoming consequences of the climate change). At the same time, it is important to note that associative learning is not the only process driving PTSD and anxiety symptoms and further research should examine how large-scale stressors affect these processes.

The current findings indicate that psychosocial stress related to the pandemic is related to associative learning and analog PTSD symptom development. This underlines the importance of investigating stress effects on memory processes that are assumed to underlie PTSD. Further research should study and compare the effects of both experimentally induced and naturalistic stressors - such as the one investigated here. Our findings are in line with the assumption that ongoing psychosocial stress (as evident during the COVID-19 outbreak) puts individuals at risk for maladaptive processing of aversive events, which may subsequently result in symptom development. However, confirmatory research is needed to replicate these results in the context of real-life trauma.

III Study 2. Investigation of Early Night Sleep Effects on Subsequent Fear Extinction Learning and Recall

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Abstract
Extinction learning is considered an important underlying process of successful treatment of posttraumatic stress disorder (PTSD). However, sleep disturbances may impede this learning process: Current accounts postulate that sleep facilitates encoding by promoting neural plasticity during slow wave sleep (SWS). Based on this hypothesis, we tested whether early night sleep, with high amounts of SWS, facilitates subsequent extinction learning and recall. Sixty-three participants took part in a trauma-adapted fear conditioning experiment. One group received a three-hour sleep opportunity in the early night half, whereas the other group stayed awake. Thereafter, both groups underwent extinction training and a return-of-fear test. Retention was assessed after another sleep opportunity in both groups. Linear mixed-effects models and Bayesian inference did not support the hypothesis of strengthened fear extinction by prior early night sleep. Subsequent exploratory analyses, in contrast, point to a role of rapid eye movement (REM) sleep in promoting successful fear extinction learning. Further confirmatory research should re-investigate these effects and their implications for the treatment of PTSD.

1. Introduction

Clinical practice guidelines for the treatment of posttraumatic stress disorder (PTSD) strongly recommend trauma-focused cognitive behavioral therapy (TF-CBT), comprising exposure therapy as its core element (Hamblen et al., 2019). Despite TF-CBT's effectiveness, rates of non-responders and dropouts are high (Schottenbauer et al., 2008), indicating the need for further improvements of treatment (Michael et al., 2019). Since PTSD and sleep disturbances are highly interrelated, it has been suggested that adjunctive treatments addressing sleep may enhance the efficacy of TF-CBT (Difede et al., 2014). Therefore, the current study investigates if learning processes, which underlie successful TF-CBT, are strengthened by preceding sleep. Sleep disturbances are assumed to be a risk factor for chronic PTSD and treatment resistance (for reviews see e.g., Azza et al., 2020; Colvonen, Straus et al., 2019; Germain et al., 2017). This assumption is based on studies reporting a negative association between sleep disturbances and the likelihood of remission (Marcks et al., 2010) as well as PTSD symptom decline during prolonged exposure therapy (López et al., 2017; Reist et al., 2017; but see Sexton et al., 2017). Consequently, it has been suggested that sleep problems impede critical recovery processes. Specifically, it is hypothesized that disturbances of sleep-related processes may impair learning, thereby compromising processes that support the dissipation of pathological fear during exposure therapy while direct evidence of this hypothesis is still missing (Colvonen, Straus et al., 2019; Davidson & Pace-Schott, 2020).

Previous research indicates that successful exposure therapy relies on processes of fear conditioning (Craske et al., 2018; but see Scheveneels et al., 2021). According to translational models of fear conditioning (Michael, 2017), traumatized individuals acquire conditioned fear to neutral stimuli that appear in contingency with threatening stimulus during trauma (i.e., unconditioned stimulus; US). As a result of conditioning, the formerly neutral stimulus (now conditioned stimulus, CS), elicits a conditioned reaction (i.e., fear and avoidance to the CS). During repeated exposure to the CS in absence of the US, conditioned reactions may decline, which is attributed to fear extinction processes. Fear extinction is assumed to rely on the formation of a new memory trace that inhibits the former CS-US trace (Bouton, 2004). The fear conditioning framework has been used to explain PTSD symptom development, especially the development of intrusive memories (Ehlers et al., 2002). Correspondingly, experimental analog studies have shown that fear acquisition of traumatic associations is related to intrusion development (Franke et al., 2021; Streb et al., 2017). Moreover, fear extinction is suggested to be the process underlying the remission of intrusive memories and thus of successful TF-CBT (Craske et al., 2018). In line with this assumption, it has been shown that successful extinction learning of fear associations reduces the probability and severity of intrusions (Franke et al., 2021). Hence, investigating effects of sleep on extinction learning could provide critical insights on how to facilitate exposure therapy during TF-CBT.

Sleep is critical for subsequent learning. That is, sleep restriction or deprivation prior to encoding negatively impacts encoding (Cousins et al., 2018) and later recall (e.g., Drummond et al., 2000; Kaida et al., 2015; Yoo et al., 2007). Moreover, findings indicate that specific processes during non-rapid eye movement (NREM) sleep, and slow wave sleep (SWS) specifically, may be critical for optimal learning during subsequent wakefulness (Kaida et al., 2015; Mander et al., 2011). SWS is characterized by slow wave activity (SWA), defined as high amplitude (> 75 µV), low frequency (0.5 – 2 Hz) EEG activity (Berry et al., 2012). The manipulation of SWA during sleep has been shown to impact subsequent learning (Antonenko et al., 2013; Van Der Werf et al., 2009), suggesting that SWA is critical for restoring learning capabilities (but see Cousins et al., 2018, for contrasting findings). Relatedly, a prominent account hypothesizes that SWA actively functions as a homeostatic regulator of neuronal plasticity (Tononi & Cirelli, 2014). However, this assumption is debated and competing theoretical accounts propose that rapid eye movement (REM) sleep or the succession of NREM and REM sleep are more essential for restoring neuronal plasticity (Navarro-Lobato & Genzel, 2019; Poe, 2017).

Since sleep is assumed to promote subsequent learning, it may also affect learning processes involved in TF-CBT, especially extinction learning. Accordingly, a recent study showed that sleep deprivation in contrast to rested sleep was associated with alterations in brain activity during fear extinction (Seo et al., 2021). However, the interpretation of these results is limited as no psychophysiological or subjective fear conditioning indices were reported. Moreover, sleep manipulation did not directly target fear extinction since the acquisition training was performed preceding the extinction training at the same day. To the best of our knowledge, only one study to date investigated the direct impact of preceding sleep on fear extinction learning: Straus et al. (2017) examined effects of sleep on subsequent fear extinction by manipulating sleep prior to extinction training. Results show that sleep deprivation in contrast to undisturbed sleep did not lead to differences in fear expressions during subsequent extinction training. After a recovery night, however, the pre-extinction deprivation group showed enhanced fear recall during a retention test compared to the undisturbed sleep group. This was reflected in increased startle reactions – but not US expectancy or anxiety ratings - towards the aversive conditioned stimulus (CS+). These results indicate that sleep deprivation prior to fear extinction learning affects fear extinction by interfering with memory encoding and preventing successful recall. However, interpretation of these findings is limited since sleep was manipulated immediately after acquisition training (i.e., within the fear acquisition consolidation window). Thus, it is difficult to disentangle effects of sleep on the consolidation of fear acquisition and on extinction learning in this study design. Moreover, it remains unclear whether the effects are related to SWS specifically or to other sleep stages.

Therefore, we conducted a study to examine effects of early night sleep on subsequent fear extinction learning. Moreover, by using a trauma-adapted fear conditioning experiment, we sought to investigate the relationship between sleep and processes implicated in TF-CBT. Two experimental groups underwent fear acquisition training and a full night of sleep. Neutral faces served as CS and aversive film clips as USs. On the next day, one group slept during the first three hours of the night while a second group remained awake. The amount of SWS and REM sleep are known to be unevenly distributed throughout night sleep. Since SWS is most prominent during early sleep cycles (Yaroush et al., 1971), this design was chosen to contrast effects of SWS-rich sleep in the early night half with wakefulness. At approximately 3 AM, both groups were subjected to fear extinction training and a return-of-fear (ROF) test. During the late night half, both groups were allowed to sleep until morning. Afterwards, extinction recall was assessed during a retention test and intrusions were measured using an intrusion provocation task (IPT). We hypothesized that early night sleep, in contrast to wakefulness, enhances extinction learning and leads to a stronger decline in differential fear expressions during extinction training. Moreover, we expected lower conditioned fear expression in the ROF test and in the retention test in the sleep group compared to the wake group. We further explored whether these effects transfer to intrusion frequency. Finally, we sought to investigate whether interindividual differences in outcome measures could be predicted by preceding sleep physiology. Specifically, we hypothesized that higher amounts of SWS and numbers of slow waves are associated with strengthened fear extinction learning and recall as well as fewer intrusions in the sleep group.

2. Methods

2.1 Sample

Sixty-three participants took part in the experiment. Criteria for study eligibility were: age between 18 and 30 years; secondary school certificate or higher; no interpersonal trauma exposure; no clinically relevant depressive symptoms ([PHQ-9] < 10; Löwe et al., 2004) or insomnia ([RIS] < 13; Crönlein et al., 2013); no other acute mental or physical illness; no medication aside from hormonal contraceptives; no pregnancy; no heavy smoking or other drug abuse; no frequent consumption of horror or splatter movies. While participating in the experiment, subjects were instructed to go to sleep at 11 PM and to rise at 7 AM. Furthermore, they were requested to refrain from consuming alcohol and caffeine, and from napping.

Four participants were excluded from further analyses as they withdrew their participation (n = 2) or due to technical errors during the experiment (n = 2). Another eight participants did not meet the criterion for successful differential contingency learning and were therefore excluded from further analyses. Contingency learning was defined as a non-negative difference of US expectancy ratings between CS+ and CS- on the final trial of acquisition

training or providing accurate responses on the contingency memory test (see Chapter III.2.3.2, for more details).[15] The final sample thus comprised 51 participants: wake group: n = 25, 15 females, M_{age} = 23.48 (SD = 3.29); sleep group: n = 26, 13 females, M_{age} = 24.12 (SD = 2.92). Groups did not differ in age, $t_W(47.77) = 0.73$, p = .470, gender, $X^2(1) = 0.19$, p = .663, nor in subjective sleep quality (PSQI; Buysse et al., 1989), $t_W(45.73) = 1.25$, p = .217. However, the sleep group showed higher scores than the wake group for trait anxiety (STAI-T; Laux et al., 1981), $t_W(45.5) = 2.61$, p = .012, depressive symptoms, $t_W(46.45) = 2.45$, p = .018, and insomnia symptoms, $t_W(44.63) = 2.66$, p = .011. Secondary analyses revealed significant positive relationships between these characteristics in our sample (r_s = .31 – .48; all p's < .027). To account for these unexpected pre-experimental differences in further analyses, the scales were z-standardized and summed up into an index of subclinical psychopathology. This index was introduced as a covariate in all subsequent analyses. Further information about pre-experimental group characteristics are provided in Supplementary Material B[16].

2.2 Study Procedure

The study procedure is shown in Figure III-1.A. Approximately one week before they participated in the fear conditioning experiment, subjects filled out trait questionnaires and pre-rated a pool of potential CS stimuli (for details, see Chapter III.2.3.1). The fear conditioning experiment took place in a sound-proof booth on a 27" LCD monitor while participants wore headphones. At the beginning of each experimental phase (Day 1 – 3), psychomotor vigilance and subjective sleepiness were assessed by means of a short version of the Psychomotor Vigilance Task (PVT; Roach et al., 2006) and the Stanford Sleepiness Scale (SSS; Hoddes et al., 1973). On Day 1, acquisition training took place at approximately 7 PM. Afterwards, subjects went home and had a full night sleep period. On Day 2, they returned to the laboratory at 9.30 PM and were prepared for polysomnographic recordings. Thereafter, participants were pseudorandomly divided into two experimental groups. The sleep group received a sleep opportunity from 11 PM. The time of awakening was determined by the time of the first NREM2 epoch plus three hours. If participants had not fallen asleep after 30 minutes, the sleep opportunity was set to 3.5 hours in total. After awakening, participants had time to recover from sleep inertia for 30 minutes. The wake group remained awake during the first night half and was continuously monitored by an experimenter. Drinks without caffeine and snacks were provided, and the subjects spent their time reading, crafting, and walking through the corridors. At approximately 2.30 AM, both groups went through the second experimental session including extinction training and the ROF test. Thereafter, both groups had a sleep opportunity

[15] Although we pre-registered the exclusion of non-learners, the contingency awareness criterion was not specified. We chose the most conservative by excluding participants only when they provided signs of non-awareness in both measures.
[16] Supplementary material for this manuscript is available online (https://journals.sagepub.com/doi/full/10.1177/20438087221090350).

during the second night half. As in the early night half, the sleep period was set to three hours from the first NREM2 epoch while the maximum time in bed lasted 3.5 hours. After another period of 30 minutes to compensate for sleep inertia, the retention test and the intrusion provocation task (IPT) were performed during the third experimental session at approximately 6.30 AM. Subjects gave written consent according to the Declaration of Helsinki and received € 83 for their participation. The study protocol (A 15-3) was approved by the local ethics committee of the Faculty of Human and Business Sciences at Saarland University and was pre-registered (https://osf.io/fjqcm).

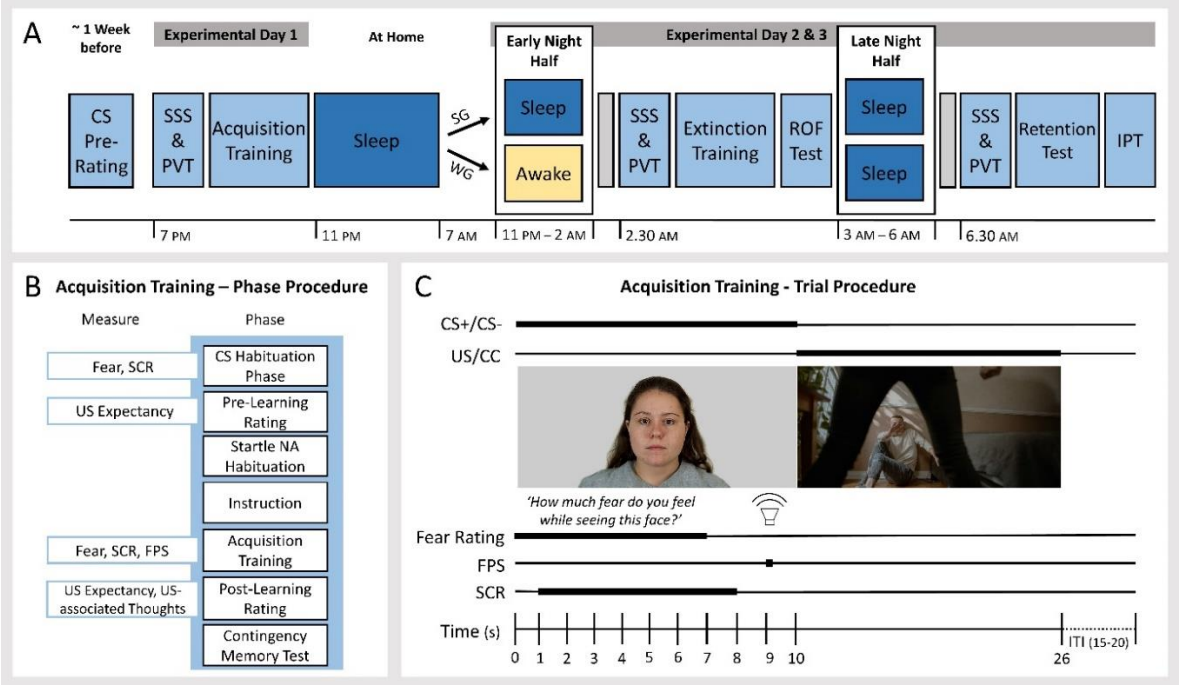

Figure III-1. Schematic illustration of the experimental procedure and fear acquisition procedure.

Note. Figure 1A: Experimental procedure. Approximately one week prior to the fear conditioning experiment, participants pre-rated a pool of potential conditioned stimuli (CS). At Experimental Day 1, participants filled out the Stanford Sleepiness Scale (SSS) and underwent Psychomotor Vigilance Task (PVT) and fear acquisition training. Thereafter, they went home and had a full night sleep opportunity from 11 PM to 7 AM. At Experimental Day 2, participants returned to the laboratory in the evening and were then divided into two groups. The sleep group (SG) had a sleep opportunity from 11 PM to 2 AM while the wake group (WG) remained awake during this period. After the sleep period, the SG had time to recover from sleep inertia for 30 minutes (indicated by the grey box). Both groups performed the next experimental session at approximately 2.30 AM including SSS ratings, PVT, extinction training, and return-of-fear (ROF) test. Afterwards, both groups had a 3-hour sleep opportunity from 3 to 6 AM. After another 30-minute resting period, participants underwent SSS ratings, PVT, retention test and intrusion provocation task (IPT). Figure 1B: Phase procedure during acquisition training. Participants were habituated to the CS while subjective fear and skin conductance responses (SCRs) were recorded. Then, CS were presented again to assess their expectation of being presented with an aversive film clip (unconditioned stimulus, US) afterwards. Thereafter, ten auditory startle probes (noise alone, NA) were presented. Prior to acquisition training participants were instructed to pay attention to the following stimulus contingencies. Fear ratings, SCR and fear-potentiated startle (FPS) were recorded during acquisition training. Thereafter, US expectancy and thoughts associated with the US as well as participants' explicit memory of the CS-US contingency were assessed. Figure 1C: Reinforced CS+ (aversive conditioned stimulus) trial from fear acquisition training. Neutral faces, serving as CS, were presented for ten seconds. In a CS+ trial, the CS presentation was followed by 16-second aversive film clips (US). After a CS- (safety stimulus) trial, neutral film clips (control condition, CC) were presented. During the first seven seconds of CS presentation, participants were asked to rate their fear on a visual analog scale Nine seconds after CS onset, the auditory startle probe was presented and FPS was measured afterwards. SCRs were analyzed from the first to the eighth second after CS onset. After each trial, an inter-trial interval (ITI) varied between 15 and 20 seconds. Images were taken from the Chicago Face Database (Ma et al., 2015) and https://www.pexels.com.

2.3 Fear Conditioning Procedure

2.3.1 *Stimuli*

Stimuli were adapted from a previous study (Brueckner et al., 2019). Pictures of White male and female persons serving as CS were taken from the Chicago Face Database (Ma et al., 2015). Based on the individual pre-rating valence scores of each participant, two equally neutral rated faces were chosen as conditioned stimuli. This procedure was applied to account for interindividual differences in face perception (Vriends et al., 2011). Nine aversive (USs) and nine neutral (control conditions, CCs) 16-second film clips were taken from commercial movies and contained scenes of interpersonal violence (i.e., physical or sexual assault) or daily activities (e.g., man brushing his teeth, people sitting in a bus) respectively. Details on film clips are provided in Supplementary Material D.

2.3.2 *Conditioning Phases*

Prior to acquisition training, a habituation phase took place, in which two neutral faces (CS) were randomly presented for ten seconds six times each. Meanwhile, subjective fear towards the CS was assessed. At the end of habituation, both CS were presented again, and participants were asked to rate their expectation of an eventually upcoming aversive film clip after the CS. Afterwards, participants were habituated to the startle probe by presenting 10 bursts (50 ms) of white noise at 105 dB. During acquisition training (Figure III-1.B and III-1.C), CS were each presented 12 times for ten seconds. The CS+, i.e., aversive conditioned stimulus, was followed by aversive film clips (US) in nine of 12 trials (reinforcement ratio = 75%), whereas the CS-, i.e., safety stimulus, was followed by neutral film clips (CC) with the same reinforcement ratio. Participants were instructed to pay close attention to the different stimuli and whether these were followed by aversive film scenes. The trial order was pseudorandomized in two blocks, assuring that each CS type was not displayed more than twice in a row. During the first seven seconds of each trial, subjective fear was recorded. Nine seconds after CS onset, a startle probe was presented. The intertrial-interval was jittered between 15 and 20 seconds. After acquisition training, the CS were presented again to re-assess US expectancy as well as US-associated thoughts (Zenses et al., 2021). Finally, explicit memory of the contingency between the CS+ and the USs was measured by asking participants which of the three faces (CS and a distractor picture) was repeatedly followed by aversive film clips during the task.

The same parameters used during acquisition training were also used during the following experimental sessions. Prior to extinction training and the retention test, a startle habituation phase took place. During extinction training, 12 CS+ and 12 CS- were presented without US or CC. Thereafter, the last two aversive film clips from acquisition training were re-presented to the participants without preceding CS presentation. Fear reinstatement was

tested during the subsequent ROF fear test that contained six trials per CS, again without US or CC presentation. The retention test was similar to the ROF test. US expectancy and US-associated thoughts were assessed before and after extinction training, the ROF test (post-assessment only), and the retention test.

2.3.3 *Subjective Indices of Fear*

Subjective fear was assessed on a visual analog scale ranging from 0 to 100 (‘*no fear at all’* – ‘*extremely fearful’*), which disappeared after responding (seven seconds maximum presentation time). Prior to each conditioning phase, participants received the following instructions to anchor the individual level of fear: ‘*Imagine the greatest fear that could occur during this experiment. Consider this your maximum on the scale ranging from no fear at all to extremely fearful’.* Pre-post ratings were similarly collected on a visual analog scale ranging from 0 to 100 (US expectancy: ‘*no expectation at all’* – ‘*very high expectation’*; US-associated thoughts: ‘*not thinking about the aversive film clips*’ – ‘*very strongly thinking about the aversive film clip’*). Analyses of US-associated thoughts during the conditioning phases are provided in Supplementary Material A.

2.3.4 *Psychophysiological Indices of Fear*

We assessed fear-potentiated startle and skin conductance responses during each conditioning phase. Analyses of acquisition training did not reveal differential fear learning in fear-potentiated startle. Regarding skin conductance, successful acquisition of conditioned responses was only found in the sleep group. Therefore, no further analyses were conducted. A detailed account of analyses can be found in Supplementary Material A.

2.4 Polysomnographic Recording and Analyses

Nighttime sleep and wakefulness were recorded in accordance with the AASM guidelines (Berry et al., 2012), which included six EEG locations (Fz, Cz, F3, F4, C3, C4), submental EMG, and EOG on the lower right and upper left canthi. Signals were sampled at a rate of 256 Hz using the *SOMNOscreen* system (SOMNOmedics GmbH, Germany). Pre-processing and sleep stage scoring was conducted using the programs *EEGlab* (Delorme & Makeig, 2004) and *FASST.2* (Leclercq et al., 2011). Prior to sleep stage scoring, EEG signals were re-referenced to the contralateral mastoid. For wave detection, Fz and Cz were re-referenced to the average mastoid. In accordance with the AASM (Berry et al., 2012), 20-second epochs were visually scored by two independent raters as NREM1, NREM2, SWS, REM, or wakefulness. Slow waves during SWS in the early night half were automatically detected using the built-in algorithm provided by *FASST.2* (Leclercq et al., 2011). Each potential slow wave was reviewed manually by a trained research assistant.

2.5 Intrusion Provocation Task

The procedure of the IPT was adapted from Michael, Ehlers, Halligan, et al. (2005) and James et al. (2015). Participants saw for two-second blurred pictures taken from the scenes of the nine aversive film clips presented during acquisition training. After viewing all nine pictures, they were instructed to close their eyes for two minutes, allowing their mind to wander freely. In addition, they were asked to press the spacebar every time they experienced an intrusive memory triggered by the pictures. Intrusive memories were defined as '*vivid images or sounds from the film scenes*'.

2.6 Data Analyses

Statistical tests were conducted in *R* (R Core Team, 2020) and *JASP* (JASP Team, 2020). Continuous changes in fear expressions over the learning periods were analyzed by means of linear mixed-effects modeling (LMM) and analysis of variance (ANOVA). LMM analyses were conducted using the R packages *nlme* (Pinheiro et al., 2022) and *reghelper* (Hughes, 2021). Plots were built with *ggplot2* (Wickham, 2016).

All LMMs were built using the same sequential procedure: For each dependent variable and trials of interest, intercept-only models including a by-subject random intercept were evaluated. Subsequently, the fixed effects (CS type, Trial, Group) and their interactions were introduced. All predictors were centered, that is, dichotomous predictors were dummy coded (0.5 = sleep group/CS+; -0.5 = wake group/CS-) and the continuous predictor Trial was mean-centered. Thereafter, by-subject random slopes of CS type and Trial were sequentially introduced to the full model if they significantly increased model fit. Grand-mean centered covariates (sleep characteristics during the early night half, subclinical psychopathology index and SSS ratings) were added to examine their impact on model parameters.[17] Analyses of fear ratings during ROF test and retention test were confined to the first trial of the respective phase to avoid potential re-extinction confounds. Effects were considered significant at $p < .05$. Degrees of freedom vary across analyses due to missing data. Model parameters and coefficient tables are provided in Supplementary Material C.

The hypothesized effects of the sleep/wake manipulation on fear extinction processes were additionally tested using Bayesian inference. Reported Bayes factor BF_{0+} quantifies likelihood of the null hypothesis over the alternative hypothesis given the observed data and prior, i.e., expected, distribution (Wagenmakers et al., 2016). Tests were performed one-sided using the default JZS prior ($r = 1/\sqrt{2}$; van Doorn et al., 2020). This was done in addition to the pre-registered analyses, to quantify evidence for the null hypotheses. In deviance to our pre-registered - and also performed - procedure of evaluating three-way interactions, setting up

[17] Please note that testing of sleep characteristics as predictors of fear extinction and retention was done on an exploratory basis, i.e., not specified in our pre-registration.

directional hypotheses required reductions in model complexity. The influence of Group on differential fear expressions (CS_{diff} = [CS+] – [CS-]) was analyzed during each conditioning phase after acquisition training (i.e., $Extinction_{change}$ = [first extinction trial] – [last extinction trial], and ROF_{change} = [last extinction trial] – [first ROF trial]).

3. Results

3.1 Sleep and Vigilance

3.1.1 *Objective Sleep Parameters*

Sleep data and test statistics are shown in Table III-1. As expected, analyses of polysomnographic recordings revealed significant differences in sleep stage proportions between groups. During the late night half, the sleep group showed less SWS and more REM sleep (both in minutes and proportional; $p < .001$) compared to the wake group. Furthermore, the amount of SWS did not differ significantly between the sleep group during the early night half and the wake group during the late night half (in minutes and proportional; all p's > .881). These results confirm successful manipulation of sleep by showing high amounts of SWS during the earliest sleep opportunity in both groups and fading sleep pressure in the sleep group throughout the night. Across both night halves, the sleep group exhibited relatively high amounts of NREM1 (9.59 %) and NREM2 (56.49 %) and relatively low amounts of SWS (12.42 %) and REM (21.51 %) compared with previous studies, i.e., approximately 5 % NREM1, 50 % NREM2, 20 % SWS, and 25 % REM (Shrivastava et al., 2014).

Table III-1. Sleep parameters in the experimental groups

Measure	Sleep stage	Sleep group		Wake group		Test statistics		
		M	*SD*	*M*	*SD*	t_W	df	*p*
Early night half								
Minutes	NREM1	19.62	7.89	-	-	-	-	-
	NREM2	97.92	20.58	-	-	-	-	-
	SWS	39.41	23.58	-	-	-	-	-
	REM	19.29	9.45	-	-	-	-	-
	TST	176.24	22.14	-	-	-	-	-
% TST	NREM1	11.68	6.14	-	-	-	-	-
	NREM2	55.42	9.10	-	-	-	-	-
	SWS	22.21	12.74	-	-	-	-	-
	REM	10.68	5.18	-	-	-	-	-
Late night half								
Minutes	NREM1	14.32	4.29	13.65	6.50	-0.43	39.39	.673
	NREM2	102.08	16.63	96.10	16.86	-1.26	47.57	.231
	SWS	4.56	5.48	40.39	22.92	7.46	25.43	< .001
	REM	56.86	17.52	35.67	15.60	-4.52	47.94	< .001
	TST	177.82	22.20	185.81	7.81	1.72	31.53	.095
% TST	NREM1	8.08	2.24	7.41	3.89	-0.74	36.14	.462
	NREM2	57.52	7.00	51.82	9.53	-2.39	42.02	.021
	SWS	2.84	4.01	21.68	12.23	7.44	27.53	< .001
	REM	31.56	7.90	19.09	8.29	-5.44	47.22	< .001

Note. NREM = non-rapid eye movement sleep; SWS = slow wave sleep; REM = rapid eye movement sleep; TST = total sleep time.

3.1.2 *Subjective Sleepiness and Vigilance Task Performance*

A mixed ANOVA including the factors Time point, Group, and SSS ratings as dependent variable revealed a significant Group*Time point interaction effect, $F(1,98) = 5.67$, $p = .005$, and main effects of Group, $F(1,49) = 9.94$, $p = .003$, and Time point, $F(1,98) = 70.49$, $p < .001$. The wake group reported significantly higher sleepiness levels during the second and third experimental session compared to the sleep group, T2: $t_W(47.87) = -3.60$, $p < .001$; T3: $t_W(42.89) = -2.58$, $p = .013$. A mixed ANOVA of PVT reaction times and the factors Time point and Group revealed a global increase of reaction times over time, $F(1.48,63.85) = 7.00$, $p = .004$. No other effects were found. Descriptive data and Group comparisons are reported in Supplementary Material B.

3.2 Fear Conditioning

Introducing the subclinical psychopathology index and SSS ratings as predictors did not significantly improve model fit and had no effect on the direction of effects that are described in the following sections. Means and standard errors of subjective fear and US expectancy ratings during the conditioning phases are shown in Figure III-2. Model comparisons and coefficient tables for each conditioning phase are provided in Supplementary Material C.

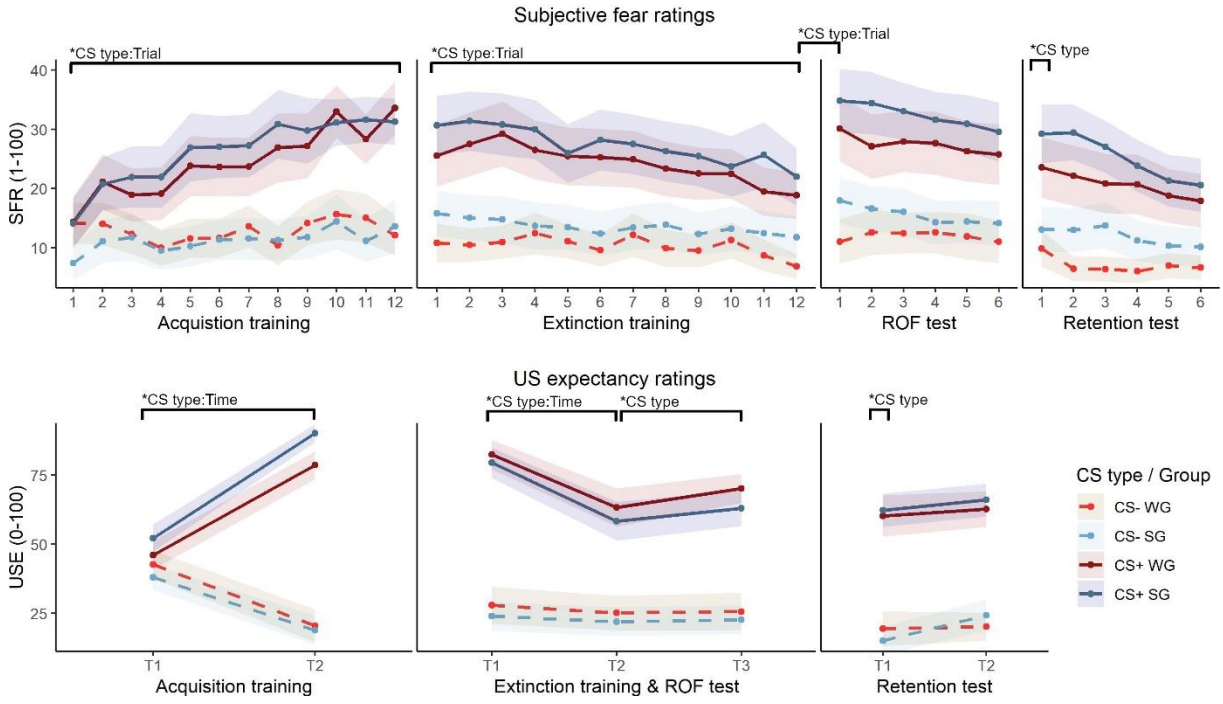

Figure III-2: Fear expressions during the conditioning phases.

Note. Means and standard errors of subjective fear ratings (SFR, top) and US expectancy ratings (USE, bottom) for CS+ (aversive conditioned stimulus) and CS- (safety stimulus) in the sleep (SG) and wake group (WG). Note that means and standard errors do not represent all components of the linear mixed-effects models that were built by the data; plots are shown for illustration. Brackets indicate analyses of conditioning phases and main outcomes. * < .05.

3.2.1 *Subjective Fear Ratings*

3.2.1.1 Habituation and Acquisition Training

No CS type or Group effects were found during the last habituation trial (all *p*'s > .592), indicating no baseline differences in subjective fear after familiarization. For acquisition training, analyses revealed a significant interaction between CS type and the slope of Trial, *b* = 1.21, *se* = 0.42, 95% CI [0.91, 1.51], *t*(1128) = 7.84, *p* < .001, as well as main effects of Trial, *b* = 0.84, *se* = 0.21, 95% CI [0.43, 1.25], *t*(1128) = 4, *p* < .001, and CS type, *b* = 13.57, *se* = 2.86, 95% CI [7.97, 19.16], *t*(1128) = 4.74, *p* < .001. Post-hoc contrast revealed a significant rise in subjective fear across trials for the CS+, *b* = 1.44, *se* = 0.22, *t*(1128) = 6.45, *p* < .001, but not for the CS- (*p* = .292). Higher fear ratings were evident for the CS+ compared to the CS- on the first, *b* = 6.92, *se* = 2.99, *t*(1128) = 2.32, *p* = .021, and on the final trial of acquisition training, *b* = 20.21, *se* = 2.98, *t*(1128) = 6.78, *p* < .001. As CS type effects were not found prior to the acquisition training, these results indicate successful fear acquisition. Moreover, groups did not differ in response patterns during acquisition training (all *p*'s > .659).

3.2.1.2 Extinction Training

Analyses revealed a significant CS type*Trial interaction effect, *b* = -0.6, *se* = 0.09, 95 % CI [-0.78, -0.43], *t*(1142) = -6.67, *p* < .001, a main effect of CS type, *b* = 14.03, *se* = 2.97, 95 % CI [8.23, 19.83], *t*(1142) = 4.73, *p* < .001, and of Trial, *b* = -0.58, *se* = 0.18, 95 % CI [-0.93, -0.22], *t*(1142) = -3.19, *p* = .002. Post-hoc contrasts showed a significant decline in subjective fear over extinction training for the CS+, *b* = -0.88, *se* = 0.19, *t*(1142) = -4.71, *p* < .001, while the CS- remained stable (*p* > .138), indicating successful fear extinction. Significant differences between CS types persist from the first, *b* = 17.35, *se* = 3.01, *t*(1142) = 5.77, *p* < .001, to the final trial of the extinction training, *b* = 10.71, *se* = 3.01, *t*(1142) = 3.56, *p* < .001, reflecting incomplete extinction. In contrast to our hypothesis, no main effect or interactions with Group were found (all *p*'s > .493). A Bayesian analysis was conducted to examine if the sleep group showed a stronger decline in differential fear ratings compared to the wake group (alternative hypothesis). In correspondence with the LMM results, the analysis indicated that the data were almost three times (BF_{0+} = 2.915) more likely under the null hypothesis while evidence for this hypothesis lies between anecdotal and moderate.

3.2.1.3 Return-of-fear Test

LMM analyses of the last response during extinction training and the first ROF test trial, revealed a significant interaction between CS type and the linear slope of Trial, *b* = 6.2, *se* = 2.42, 95 % CI [1.50, 10.89], *t*(144) = 2.56, *p* = .012. Main effects of CS type, *b* = 14.16, *se* = 3.01, 95 % CI [8.34, 19.99], *t*(144) = 4.71, *p* < .001, and of Trial, *b* = 8.57, *se* = 1.98, 95 % CI [4.74, 12.39], *t*(144) = 4.34, *p* < .001, were also significant. Post-hoc analyses revealed a

significant rise in subjective fear towards the CS+, *b* = 11.66, *se* = 2.31, *t*(144) = 5.05, *p* < .001, and the CS-, *b* = 5.47, *se* = 2.32, *t*(144) = 2.35, *p* = .020, reflecting successful fear reinstatement. Differential fear expression responses towards the CS+ compared to the CS- were found across all trials (last extinction training trial: *b* = 11.07, *se* = 3.24, *t*(144) = 3.42, *p* < .001; first ROF test trial: *b* = 17.26, *se* = 3.25, *t*(144) = 5.31, *p* = .001. No significant effects of Group were found (all *p*'s > .285), not supporting our hypothesis. Bayesian analyses revealed that differential change between extinction and ROF test is over three times more likely under the null hypothesis (BF0+ = 3.557), i.e., there is moderate evidence for the hypothesis of same or more elevation in fear ratings in the sleep group compared to the wake group.

3.2.1.4 Retention Test

A significant main effect of CS type was found for the first trial of the retention test, *b* = 14.92, *se* = 3.35, 95 % CI [8.32, 21.43], *t*(48) = 4.45, *p* < .001, reflecting higher fear ratings for the CS+ compared to the CS-. Contrary to our hypothesis, there were no effects of Group (all *p*'s > .386). Bayesian analyses of Group differences on the first trial of the retention test showed that the data are almost five times more likely under the null hypothesis (BF0+ = 4.995, i.e., there is moderate evidence for H0), stating same or higher differential subjective fear in the sleep group compared to the wake group.

3.2.2 *US Expectancy Ratings*

3.2.2.1 Acquisition Training

A mixed ANOVA of pre- and post-acquisition US expectancy ratings revealed a significant CS type*Time point interaction effect, *F*(1,49) = 44.38, *p* < .001, a main effect of CS type, *F*(1,49) = 112.49, *p* < .001, and Time point, *F*(1,49) = 6.11, *p* = .017. All other effects were non-significant (all *p*'s > .087). Post-hoc comparisons showed that CS types did not differ significantly prior to acquisition training (*p* = .377). After acquisition training, however, US expectancy was higher for the CS+ compared to the CS-, *b* = 64. 72, *se* = 5.44, *t*(94.6) = 11.89, *p* < .001. These results reflect successful fear acquisition.

3.2.2.2 Extinction Training

A mixed ANOVA of pre- and post-extinction US expectancy ratings revealed a significant CS type*Time point interaction effect, *F*(1,48) = 9.37, *p* = .004, and main effects of CS type, *F*(1, 48) = 52.90, *p* < .001, and Time point, *F*(1,48) = 16.29, *p* < .001. Post-hoc analyses showed that US expectancy for the CS+ significantly declined from pre- to post-extinction training, *b* = -18.57, *se* = 3.71, *t*(95.8) = -4.99, *p* < .001, but not for the CS- (*p* = .943). However, ratings for the CS+ were significantly higher compared to the CS- at both levels of time (*p*'s < .001),

indicating a successful though incomplete extinction. In contrast to our hypothesis, the analysis did not show effects of Group (all *p*'s > .365). Bayesian analyses were conducted to examine if the sleep group showed a stronger decline in differential US expectancy ratings compared to the wake group (alternative hypothesis). In line with the ANOVA, results indicated moderate evidence against our hypothesis since these findings are three times (BF_{0+} = 3.596) more likely under the null than under the alternative hypothesis.

3.2.2.3 Return-of-fear Test

A mixed ANOVA of post-extinction to post-ROF test ratings of US expectancy ratings revealed a main effect of CS type, $F(1,49) = 40.97$, $p < .001$, with higher US expectancy for the CS+ compared to the CS-. No other effects were significant, indicating no reinstatement-induced ROF and no effects of sleep manipulation as was hypothesized (all *p*'s > .061). Correspondingly, Bayesian analyses revealed that differential change between extinction and ROF test is almost five times more likely under the null hypothesis (BF_{0+} = 4.816), thus providing moderate evidence for the hypothesis of same or more elevation in fear ratings in the sleep group compared to the wake group.

3.2.2.4 Retention Test

A mixed ANOVA revealed a significant main effect of CS type, $F(1,48) = 50.82$, $p < .001$, with higher US expectancy ratings prior to retention test towards the CS+ compared to the CS- across both groups. Against our hypothesis, no other effects were evident (all *p*'s > .075). In addition, Bayesian analyses of Group differences prior to the retention test indicated that data is more than five times more likely under the null hypothesis (BF_{0+} = 5.448, i.e., there is moderate evidence for H_0), stating same or higher differential US expectancy in the sleep group compared to the wake group.

3.2.3 *Intrusion Frequency*

During the IPT, the groups (sleep group: M = 7.62, SD = 6.66; wake group: M = 6.04, SD = 4.87) did not, against our hypothesis, significantly differ in their reported intrusion frequency, $t_W(45.84) = 0.97$, $p = .339$. Bayesian analyses were conducted to examine if the sleep group showed fewer intrusions during the IPT compared to the wake group (alternative hypothesis). The results indicated moderate evidence against this hypothesis since data is more than six times more likely under the null hypothesis (BF_{0+} = 6.282). Examining effects of different sleep stages during the early night half on intrusion frequency in the sleep group revealed no significant effects (all *p*'s > .087).

3.2.4 *Exploratory Analyses on Associations between Early Night Sleep Characteristics and Subsequent Fear Extinction Learning*

To examine differences in subjective fear ratings during extinction training associated with preceding sleep during the early night half (minutes of NREM1, NREM2, SWS, REM, number of slow waves), exploratory subgroup analyses were conducted in the sleep group.[18] Goodness-of-fit tests revealed significant improvements in model fit by including pre-extinction NREM2 (X^2 = 13.49, p = .009), SWS (X^2 = 16.18, p = .003), and REM (X^2 = 38.50, p < .001) as centered predictors. Introducing NREM1 or number of slow waves did not significantly improve model prediction (p's > .820). To examine which of the sleep stages accounted for unique variance in trajectories of fear extinction learning, stepwise model comparisons including Trial, CS type, and different sleep parameters were conducted (all comparisons are listed in Supplementary Material C). Goodness-of-fit tests revealed that REM accounted for incremental variance in models including NREM2 or SWS respectively (all p's < .001). NREM2 and SWS, however, did not significantly improve model fit when REM was included in the model (all p's > .087). Our final model thus included the factors Trial, CS type and REM. The analysis revealed a significant CS type*Trial*REM interaction, b = -0.02, se = 0.004, 95 % CI [-0.03, -0.02], t(579) = -5.75, p < .001, Trial*REM interaction, b = -0.02, se = 0.01, 95 % CI [-0.02, -0.01], t(579) = -2.47, p = .014, Trial*CS type interaction, b = -0.66, se = 0.12, 95 % CI [-0.96, -0.38], t(579) = -5.52, p < .001, and main effects of CS type, b = 14.13, se = 4.62, 95 % CI [5.14, 23.08], t(579) = 3.06, p = .002, and Trial, b = -0.64, se = 0.23, 95 % CI [-0.78, -0.49], t(579) = -2.82, p = .005. All other effects were non-significant (all p's > .613). Post-hoc contrasts showed that, after high amounts of REM (i.e., M + 1 SD), subjective fear decreased for the CS+, b = -1.88, se = 0.33, t(579) = -5.63, p < .001, but not for the CS- (p = .107; see Figure III-3). By contrast, after low amounts of REM (i.e., M - 1 SD), no significant decline in fear ratings was found for the CS+ (p = .844) or for the CS- (p = .780). These results suggest that high amounts of REM sleep during the early night half are associated with improved fear extinction learning, indicated by differential decline in fear ratings across extinction training. We further examined whether early night REM sleep may have influenced fear responses from last acquisition trial to first extinction trial. Analysis did not support the assumption of REM amount being a significant predictor for the change in fear across sleep (p = .269). Moreover, examining effects of early night sleep on other conditioning phases or on US expectancy ratings did not reveal any significant effects.

[18] To test the robustness of these results, we repeated the analyses including the wake group (sleep variables set to zero). Model comparisons showed that NREM2 and SWS no longer improved the prediction, whereas analysis indicated REM sleep is still a significant predictor. LMM analysis including REM sleep-related interactions revealed comparable results as described in the main text.

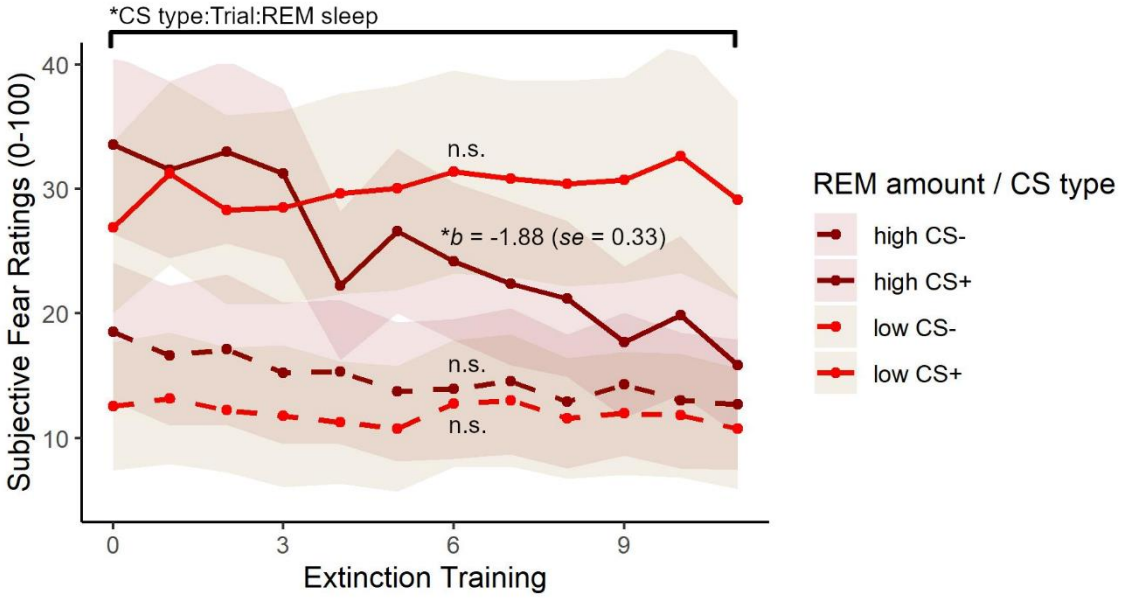

Figure III-3: Subjective fear ratings during extinction training divided according to amounts of REM sleep during the early night half.

Note. Means and standard errors of subjective fear ratings in the sleep group during extinction training divided through median splits in high and low subgroups of REM sleep (mean-centered rapid eye movement sleep in minutes). Note that subgroups and parameters do not represent all components of the linear mixed-effects models that were built by the data; plots are shown for illustration. Linear-mixed model analysis revealed a significant three-way interaction between CS type, Trial and REM sleep amount (indicated by brackets) in the sleep group. Post-hoc tests showed that fear ratings to the CS+ (aversive conditioned stimulus) decreased only after high amounts of early night REM (significant slope indicated by asterisk). * < .05, n.s. >= .05.

4. Discussion

The current study aimed to investigate whether early night sleep compared to wakefulness facilitates subsequent fear extinction learning and recall. By using a trauma-adapted fear conditioning experiment, we further sought to explore if effects on fear extinction result in fewer intrusions on the next day. In addition, we conducted exploratory regression analyses in the sleep group with the aim of linking specific sleep stages to successful extinction learning and recall. Our analyses did not reveal a stronger decline in fear expressions during extinction training after early night sleep compared to wakefulness. Furthermore, no differences emerged between experimental groups in the subsequent ROF test and the retention test on the next day. The absence of expected group differences was confirmed by Bayesian inference. In contrast to the hypothesis that SWS is critical for learning, successful fear extinction learning was associated with early night REM sleep.

4.1 Effects of Early Night Sleep on Subsequent Extinction Learning

Research has frequently shown that sleep is beneficial for encoding (e.g., Cousins et al., 2018; Kaida et al., 2015). Therefore, it has been suggested that the effect of sleep is also evident in

extinction learning (Davidson & Pace-Schott, 2020). Contrary to this assumption, the present study did not reveal effects of sleep on subjective ratings during extinction training, the ROF test, or the retention test. Hence, the attempt to enhance fear extinction by means of early night sleep was not successful. The absence of expected group differences was confirmed by Bayesian inference that revealed moderate evidence in favor of the null hypotheses in all analyses except for fear ratings during extinction training, where evidence was between anecdotal and moderate (van Doorn et al., 2020). Furthermore, no effect of sleep on intrusion frequency was observed. It is important to note that only one previous study investigated effects of sleep directly preceding extinction learning, yielding similar results: In line with our findings, Straus et al. (2017) did not find an effect of sleep on extinction training. With regard to extinction recall, both studies showed no differences between experimental groups in US expectancy and fear/anxiety ratings. However, Straus and colleagues did find increased startle reactions towards the CS+ in the pre-extinction sleep deprivation group during fear recall. Since we were not able to conduct analyses of psychophysiological responses during extinction training and recall, future studies are required to further address these findings. Prospective studies should investigate the robustness of extinction memory by, for instance, including a ROF test.

4.2 Effects of Specific Sleep Stages on Extinction Learning

Although we did not find direct evidence for sleep-dependent fear extinction learning and recall, our results indicate that fear extinction training was affected by interindividual differences in early night sleep physiology: NREM2, SWS, and REM during early night sleep predicted trajectories of subjective fear during extinction training. Further analyses, however, suggested that only REM sleep accounted for incremental variance in predicting fear extinction performance. Slow waves during early night SWS failed to predict fear expressions during extinction training. Therefore, our results do not support an effect of preceding SWS on extinction learning. These findings are in line with results from a recent meta-analysis that show no correlation between conditioned responses during extinction training and preceding NREM sleep, including SWS, in healthy individuals (Schenker et al., 2021). Note, however, that pre-extinction SWS percentage was associated with less psychophysiological reactivity to both CS+ and CS- during extinction in patients with insomnia and PTSD.

In contrast to our hypothesis, our exploratory findings suggest a role of REM sleep on subsequent fear extinction. A significant three-way interaction revealed higher fear towards the CS+ compared to the CS- diminished across extinction training after high but not after low amounts of REM sleep. This finding indicates that REM sleep prior to extinction learning may predict successful fear extinction. Please note that these effects were also evident when including the wake group’s extinction performance. Previous investigations on the relationship

between REM sleep and subsequent fear extinction have reported mixed findings (Lerner et al., 2017; Spoormaker et al., 2014) and no overall effect was found in a meta-analysis (Schenker et al., 2021). Furthermore, caution is warranted in interpreting these findings: First, although we found a robust effect of early night REM sleep on extinction training, group effects were not evident. Thus, it has yet to be proven that REM sleep contributes substantially to subsequent fear extinction. Second, early night sleep did not affect fear expressions in the ROF test and the retention test. Moreover, REM sleep amounts did not predict intrusion frequency. This lack of consistent effects might be related to the experimental design: Since we manipulated the early night half, the amount of REM sleep in the sleep group was reduced compared to full night sleep. Thus, future studies should examine whether effects of REM sleep on fear extinction may emerge in the ROF test and the retention test after a full night of sleep. Even if effects are not found to persist from extinction training to long-term fear retention, they may have implications for the improvement of TF-CBT: Diminishing the level of distress that patients experience during exposure sessions may be an important target to improve patient's treatment adherence. As a result, patients may be less reluctant to continue treatment, which could reduce the substantial dropout rate of TF-CBT (i.e., 18%; Lewis, Roberts, Gibson, et al., 2020).

4.3 Potential Mechanisms underlying REM Sleep-Dependent Fear Extinction Learning

While the assumption that sleep plays a role in promoting optimal neuronal plasticity is widely accepted, the proposed mechanisms are still debated (e.g., Puentes-Mestril & Aton, 2017; Seibt & Frank, 2019): Previous research provided evidence for the assumption that SWA acts as a homeostatic regulator of synaptic plasticity (Huber et al., 2007; Vyazovskiy et al., 2008). However, there are likewise contradicting findings (Chauvette et al., 2012), some of which indicate a more important role of REM sleep in promoting plasticity (Grosmark et al., 2012; Watson et al., 2016). The proposed mechanism by which REM sleep is assumed to promote synaptic plasticity involves the locus coeruleus-norepinephrine (LC-NE) system, which blocks de-potentiation but is nearly inactive during REM sleep (Poe, 2017). Several authors aim to reconcile these contradicting accounts and propose that both NREM and REM sleep contribute to neuronal plasticity, albeit in different ways (Navarro-Lobato & Genzel, 2019; Niethard & Born, 2019). Our finding that fear extinction learning was affected by early night REM sleep might therefore reflect a more dominant role of REM sleep in promoting optimal learning conditions. On the other hand, since both SWS and REM sleep are proposed to contribute to synaptic down-selection, the succession of NREM and REM sleep could have led to additive effects in synaptic homeostasis. That is, the effect of SWS may only emerge if followed by a sufficient amount of REM sleep. This could explain why we were able to find associations

between REM sleep and extinction learning despite the overall small amount of REM sleep during the early night half. Moreover, this account could explain the fact that we found higher extinction rates in the high REM sleep group than the wake group (as indicated by our follow-up analyses; see footnote 18), yet no significant extinction in the low REM sleep group. This finding may suggest that the disruption of processing during successive SWS and REM sleep may negatively impact extinction learning and that beneficial effects of sleep only surface after a sufficient length of REM sleep. This hypothesis should be investigated by future research.

Beyond the framework of sleep-dependent synaptic homeostasis, REM sleep is further proposed to act as a modulator of emotional memory and reactivity (Goldstein & Walker, 2014; Tempesta et al., 2018). Similar to the proposed mechanisms of REM-dependent synaptic renormalization, the assumed modulation of emotional processing involves the LC-NE system that innervates critical brain regions associated with fear acquisition and extinction (Giustino & Maren, 2018). Based on this framework, REM sleep has been proposed to weaken affective components of memories (Goldstein & Walker, 2014). Whereas some studies have provided evidence in favour of this assumption (e.g., van der Helm et al., 2011; Wassing et al., 2019) others have not (e.g., Baran et al., 2012; Lara-Carrasco et al., 2009). Another important assumption arising from this framework is that REM sleep regulates emotion processing during wakefulness. In the context of fear processing, it is suggested that silencing of the LC-NE system during sound REM sleep is critical for preserving balance in fear expression and inhibition since high levels of NE disturb prefrontal control of fear expression in the amygdala (Giustino & Maren, 2018; Goldstein & Walker, 2014). However, evidence for this hypothesis is mixed so far (e.g., Franzen et al., 2009; Wagner et al., 2002). Based on these considerations, our finding that REM sleep predicted fear extinction may correspond to successful inhibition of fear associated with more REM sleep. To address this possibility, we examined whether changes in fear expressions in the sleep group from acquisition to extinction training were affected by REM sleep. These analyses did not yield any significant results, thus not providing any direct evidence of REM sleep effects on emotional reactivity.

4.4 Limitations

Our interpretation is limited by several drawbacks of the current study design. First of all, our design does not allow drawing causal inferences about the underlying mechanism by which sleep affects fear extinction. This specifically concerns REM sleep, which our study was not designed to examine, and analyses were made on an exploratory basis. Furthermore, due to the complex design, the number of analyses was relatively large, which increases the risk of false positives. Another limitation is that several confounding influences cannot be disentangled from our sleep manipulation. These include alterations in attention and working memory due to potential sleep deprivation in the wake group (Krause et al., 2017), which were

reflected in increased SSS ratings. Although secondary analyses did not reveal any effect of sleepiness on subjective ratings, such effects cannot be ruled out entirely and may have influenced fear extinction learning. Furthermore, the sleep group exhibited a relatively high amount of NREM1 and NREM2 while time spent in SWS and REM was relatively low thorough the course of night. This may have influenced our effects and is likely due to the unfamiliar setting during sleeping as participants were not adapted to the sleep laboratory, i.e., first night effect (Agnew et al., 1966). Another potential confound concerns the group differences in sleep physiology prior to the retention test, which also complicates measuring effects on intrusions. Deprivation of SWS induces sleep pressure, resulting in rebound effects during recovery sleep (Borbely et al., 2016). As described in Table III-1, these effects were also evident in the wake group compared to the rested sleep group during the second night half. Research suggests that sleep, in particular REM sleep, promotes the consolidation of fear extinction memory while strong evidence in favor of this assumption is currently missing (Davidson & Pace-Schott, 2020). Hence, it is likely that different sleep patterns between groups may have influenced fear expressions during the retention test, obscuring effects of our initial sleep manipulation. This reduces the comparability of our study and the study by Straus et al. (2017) that tested retention after a whole recovery night. In addition, comparability with their findings is restricted as we did not find any indication of successful fear acquisition across both groups in the psychophysiological data and thus refrained from conducting further analyses. The failure of successful fear acquisition in psychophysiological measures may have resulted from gradual habituation. Moreover, non-differential skin conductance responses during acquisition training may be related to the presentation of startle probes since these have been shown to impact fear learning (de Haan et al., 2018; Sjouwerman et al., 2016). On the other hand, analyses of skin conductance revealed differences between groups in fear acquisition, which may be related to baseline differences in indices of subclinical psychopathology. Although introducing this covariate into analyses did not change the direction of effects, we cannot fully rule out potential pre-manipulation effects.

4.5 Conclusion

The current study investigated whether early night sleep compared to wakefulness facilitates subsequent fear extinction learning and recall. Our results did not confirm that preceding sleep promotes fear extinction. Moreover, sleep did not affect intrusions of the US. Not supporting our hypothesis, exploratory analyses suggest that early night REM sleep – rather than SWS - predicts successful fear extinction learning. This finding may indicate that REM sleep promotes optimal conditions for subsequent fear extinction learning. Future studies are required to confirm these findings. Moreover, clinical trials should evaluate the usefulness of boosting REM sleep and preserving the cycling alteration of SWS and REM sleep by preventing

awakenings during the nighttime. Promising approaches could be, for instance, applying cognitive behavioral therapy for insomnia prior to exposure session to improve TF-CBT efficacy.

IV Study 3. Sleep-Directed Hypnosis improves Subjective Sleep Quality but not Extinction Memory after Exposure to Analog Trauma

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Abstract
Background: Evidence-based treatments of posttraumatic stress disorder (PTSD) aim to promote fear extinction learning. Post-learning sleep, particularly slow wave sleep (SWS), promotes memory consolidation and recall. Thus, boosting SWS might strengthen extinction recall. The current study investigated whether sleep-directed hypnosis designed to increase SWS and sleep quality improves extinction recall and reduces analog PTSD symptoms. *Method*: In two subsamples (remote/laboratory), 211 healthy individuals underwent fear conditioning with a traumatic film clip. On the next evening, they underwent extinction training. Thereafter, the experimental group received sleep-directed hypnosis, whereas the control group listened to a control text. Extinction recall and generalization and film-related intrusions and rumination were assessed on the following morning. *Results*: Subjective sleep quality declined following exposure to an aversive film. No group differences were found in SWS though exploratory analyses indicated less rapid eye movement sleep after hypnosis. After hypnosis, the experimental group reported improved sleep quality, whereas the control group showed a further deterioration. Hypnosis had no effects on extinction retention and generalization nor on analog intrusions and rumination. *Conclusions*: The current results indicate that sleep-directed hypnosis may be beneficial for improving subjective sleep quality after trauma but not for enhancing extinction memory and reducing analog PTSD symptoms.

1. Introduction

The psychological therapies for posttraumatic stress disorder (PTSD) with the strongest evidence of effect are those in which the memories of the traumatic event are actively processed like in trauma-focused cognitive behavioral therapies or in eye movement desensitization and reprocessing (Hamblen et al., 2019). These therapies are commonly referred to as trauma-focused psychotherapy (TF-PT). While TF-PT works for many patients, unfortunately, a significant number continues to have residual symptoms following therapy (Schnurr & Lunney, 2019; Schottenbauer et al., 2008). Thus, it has been argued that research investigating interventions with the potential to boost the effectiveness of TF-PT is crucial (Michael et al., 2019). PTSD is characterized by disturbed emotional learning and memory resulting in re-experiencing of the traumatic event in the present, avoidance of trauma reminders associated with re-experiencing of the traumatic event, and a persistent sense of current threat (Ehlers et al., 2004; WHO, 2019). It is assumed that a central mechanism in the pathogenesis of PTSD is associative learning that leads to the formation of strong aversive memories (Craske et al., 2018). During the traumatic event, individuals are assumed to acquire fear associations between neutral stimuli that are present in the environment (conditioned stimuli, CS) and the existential threat of trauma (unconditioned stimulus, US). Whenever individuals are subsequently faced with stimuli that resemble the CS, they experience a complex conditioned reaction in the form of unwanted, distressing (intrusive) trauma memories and perceptions of ongoing threat. The occurrence of intrusive memories is strengthened by abstract, repetitive thinking about the trauma (i.e., rumination), which often arises in an effort to control intrusions (Laposa & Rector, 2012). During TF-PT, fear associations are reactivated via various methods, thereby exposing patients to the trauma memory. Since this reactivation takes place in a safe setting (i.e., in the absence of the US), it is assumed to initiate fear extinction, resulting in a dissipation of the conditioned fear response. The memory trace acquired during extinction competes against, but does not erase, the original traumatic memory (de Quervain et al., 2017). Thus, it is of particular importance that the extinction memory is well consolidated so that later the extinction memory and not the traumatic memory will be recalled.

Recent accounts propose that the consolidation of extinction memory can be enhanced by manipulating post-extinction sleep. Research of the past two decades has firmly documented a strengthening effect of post-encoding sleep on subsequent memory performance (Rasch & Born, 2013). These effects are assumed to emerge due to offline consolidation processes occurring during slow wave sleep (SWS). Specifically, models propose that slow oscillations during SWS drive reactivation and subsequent redistribution of hippocampal memory traces (Diekelmann & Born, 2010). Correspondingly, first studies indicate that SWS may play a crucial role for reactivation and reprocessing of fear memory

traces (Hauner et al., 2013; He et al., 2015) though this assumption is challenged by research suggesting rapid eye movement (REM) sleep to be critical for the consolidation of extinction memory (e.g., Menz et al., 2016; Spoormaker et al., 2012). Moreover, preliminary findings suggest that sleep facilitates the generalization of extinction to unextinguished stimuli (Pace-Schott et al., 2009).

Although manipulating post-extinction sleep appears to be a promising approach to enhance extinction – thereby potentially boosting treatment effects of TF-PT – no study to date has investigated the impact of sleep-enhancing interventions on the retention and generalization of extinction. An intervention that is easily administered and has been shown to directly affect objective and subjective sleep quality is sleep-directed hypnosis. Across several experiments, Cordi and colleagues investigated the impact of a hypnotic suggestion that aims to increase sleep depth on daytime and nighttime sleep (Cordi et al., 2014; 2015; 2020). They found that the suggestion increased subjective sleep quality (Cordi et al., 2020) and SWS duration (Cordi et al., 2014; 2015; 2020). The latter finding is particularly interesting since SWS has been implicated in memory consolidation (Hu et al., 2020) and facilitation of fear extinction (Hauner et al., 2013; He et al., 2015; but see Ai et al., 2015, for contrasting evidence).

Based on these findings, the current study sought out to investigate the impact of sleep-directed hypnosis on subsequent sleep quality as well as retention and generalization of extinction. Healthy participants were subjected to a trauma-adapted fear conditioning paradigm, resulting in the acquisition of a conditioned fear response to neutral stimuli that predicted the occurrence of a traumatic film clip. After extinction training, participants were either subjected to sleep-directed hypnosis or a control condition prior to a full night of sleep. On the following day, participants completed an extinction retention and fear renewal test for previously extinguished and unextinguished conditioned stimuli. Sleep quality, intrusive memories, and rumination were assessed repeatedly throughout the experiment. We predicted to find higher SWS duration and sleep quality following sleep-directed hypnosis as compared to the control condition. Moreover, we expected that participants receiving sleep-directed hypnosis would show stronger retention and generalization of extinction. Finally, we expected that these effects would transfer to intrusive memories and ruminative thoughts such that participants would report fewer intrusive memories and ruminative thoughts about the traumatic clip after sleep-directed hypnosis.

2. Methods

2.1 Sample

The sample consists of two subsamples: The first subsample completed the experiment under remote conditions (using online stimulus presentation) without psychophysiological assessment, whereas the second subsample completed the experiment at the laboratory and

underwent the hypnosis intervention at home. Psychophysiological assessment was carried out for the second subsample during the experiment and during sleep. Criteria for study eligibility were: age between 18 and 35 years; normal or corrected-to-normal vision; sufficient German language skills; no current or chronic mental disorder; no acute physical illness; no lifetime trauma exposure. Participants were requested to refrain from alcohol and drug consumption during the experimental days. In the laboratory subsample, participants were additionally required to be highly hypnotizable since previous research has shown that sleep-directed hypnosis is not effective in low hypnotizable individuals (Cordi et al., 2014; 2015; 2020). Participants received financial compensation or student credits for participation (Online Experiment: € 20; Lab Experiment: € 75).

2.1.1 *Remote Subsample (1)*

One hundred twenty-two undergraduate university students took part remotely. Eleven participants were excluded due to technical problems. Four additional participants were removed from analyses based on their performance during acquisition training.[19] The resulting sample comprised 107 participants: hypnosis group: n = 55, 46 females, 9 males; control group: n = 52, 41 females, 11 males. Please note that non-related analyses based on this subsample are reported in another publication (Friesen et al., 2022).

2.1.2 *Laboratory Subsample (2)*

Eighty-nine undergraduate university students took part at the laboratory. Nine datasets had to be excluded due to drop-out (n = 5) or technical problems (n = 4). Additional four datasets were removed from analyses due to failed contingency learning during acquisition training.[1] Two participants were excluded due to an insufficient amount of sleep (i.e., 2:55 h:m, more than five *SD*s below the group mean) or high levels of distress during study participation due to a breakup in between study sessions. The final sample comprised 74 participants: hypnosis group: n = 38, 23 females, 15 males, M_{age} = 23.32 (SD = 3.09); control group: n = 36, 27 females, 9 males, M_{age} = 23.11 (SD = 3.12).

Descriptive statistics of hypnotizablity (HGSHS-A; Shor & Orne, 1963), baseline sleep quality (SQS; Snyder et al., 2018) and trait anxiety (STAI-T; Laux et al., 1981) are provided in Table IV-1. Groups did not differ in baseline characteristics (p's >= .280). However, the laboratory subsample was more hypnotizable, $t_w(165.83) = 5.18$, $p < .001$ (due to deviations in inclusion criteria; see also below), and reported higher sleep quality, $t_w(169.73) = 2.18$, $p = .030$, than the remote subsample.

[19] Participants showing no indication for differential contingency learning, i.e., negative US expectancy difference scores for mean CS+ and CS- at the final acquisition trial, were excluded from analyses.

Table IV-1 Sample characteristics according to Group and Subsample

Subsample	Variable	Hypnosis group (n = 93)			Control group (n = 88)			Test statistics		
		M	*SD*	%	*M*	*SD*	%	X^2/t_w	df	*p*
Remote (n = 107)	HGSH-A	7.33	2.42	-	7.20	2.09	-	-0.28	98.85	.777
	% HGSH-A ≥ 7	-	-	61.82	-	-	61.54	< 0.01	1	> .999
	% Females	-	-	83.64	-	-	78.85	0.15	1	.699
	SQS	7.06	1.29	-	7.04	1.41	-	-0.06	100.87	.951
	STAI-T	38.55	9.75	-	37.67	9.74	-	-0.46	104.68	.644
Laboratory (n = 74)	HGSH-A	8.58	1.40	-	8.81	1.26	-	0.71	65.99	.480
	% HGSH-A ≥ 7	-	-	100	-	-	100	-	-	-
	% Females	-	-	60.53	-	-	75.00	1.17	1	.280
	SQS	7.51	1.06	-	7.40	1.28	-	-0.40	67.94	.688
	STAI-T	36.89	6.90	-	36.33	9.81	-	-0.28	62.71	.780
Total (n = 181)	HGSH-A[a]	7.84	2.15	-	7.83	1.97	-	-0.04	167.95	.971
	% HGSH-A ≥ 7[a]	-	-	77.42	-	-	77.27	< 0.01	1	> .999
	% Female[b]	-	-	74.19	-	-	77.27	0.10	1	.757
	SQS[c]	7.24	1.22	-	7.19	1.36	-	-0.28	172.04	.777
	STAI-T[b]	37.88	8.71	-	37.13	9.73	-	-0.55	173.85	.585

Note. HGSH-A = hypnotizability; SQS = baseline sleep quality, STAI-T = trait anxiety. [a] Difference between subsamples significant (Remote < Laboratory; p < .001). [b] No differences between subsamples (p's > .05). [c] Difference between subsamples significant (Remote < Laboratory; p = .030).

2.2 Experimental Procedure

2.2.1 *Screening*

Participant recruitment and screening was conducted online via *SoSci Survey* (Leiner, 2014) and telephone. Hypnotizability was determined by means of the HGSHS-A (Shor & Orne, 1963; German version by Bongartz, 1985; details are provided in the Supplementary Material[20]). Based on their scores, participants were divided into low-to-medium hypnotizability (HGSHS-A <= 6) and medium-to-high hypnotizability (HGSHS-A >= 7; Bongartz, 1985; Cordi et al., 2014). Group assignment was conducted pseudo-randomly to control for effects of baseline sleep quality and hypnotizability (see Supplementary Material).

2.2.2 *General Procedure*

The experiment was carried out on three consecutive days (see Figure IV-1.A). During this period, participants were instructed to keep a regular sleep schedule at home and to restrict their sleep time to eight hours. The remote subsample completed all experimental sessions web-based via *Labvanced* (Finger et al., 2017); the laboratory subsample completed all

[20] Supplementary material for this manuscript is available online (https://link.springer.com/article/10.1007/s10608-022-10345-6).

experimental sessions using *E-Prime 2.0* (Psychology Software Tools Inc., USA). On Day 1 (between 2 and 6 PM for the remote subsample and at 10 AM for the laboratory subsample), participants went through the first experimental session including assessment of sleep quality of the preceding night and fear acquisition training. On Day 2 (between 6 and 10 PM for the remote subsample and at 8.30 PM for the laboratory subsample), participants rated their sleep quality again and then, filled out a questionnaire assessing intrusions and rumination related to the aversive film clip from acquisition training (Intrusive Memories Questionnaire, IMQ). Thereafter, they underwent fear extinction training. The laboratory subsample was subsequently prepared for polysomnography (PSG) in accordance with the AASM guidelines (Berry et al., 2012) and went home (for details, see Supplementary Material). Participants received an audio file comprising either a hypnotic trance induction and a suggestion to sleep deeper (hypnosis group) or a control text (control group; see Cordi et al., 2014). They were instructed to listen to the audio file after preparing to go to sleep. On Day 3 (between 8 AM and midday for the remote subsample and at 8.30 AM for the laboratory subsample), sleep quality and film-related intrusions and rumination were re-assessed as described above. Afterwards, participants completed retention and renewal tests, and, finally, an intrusion provocation task (IPT).

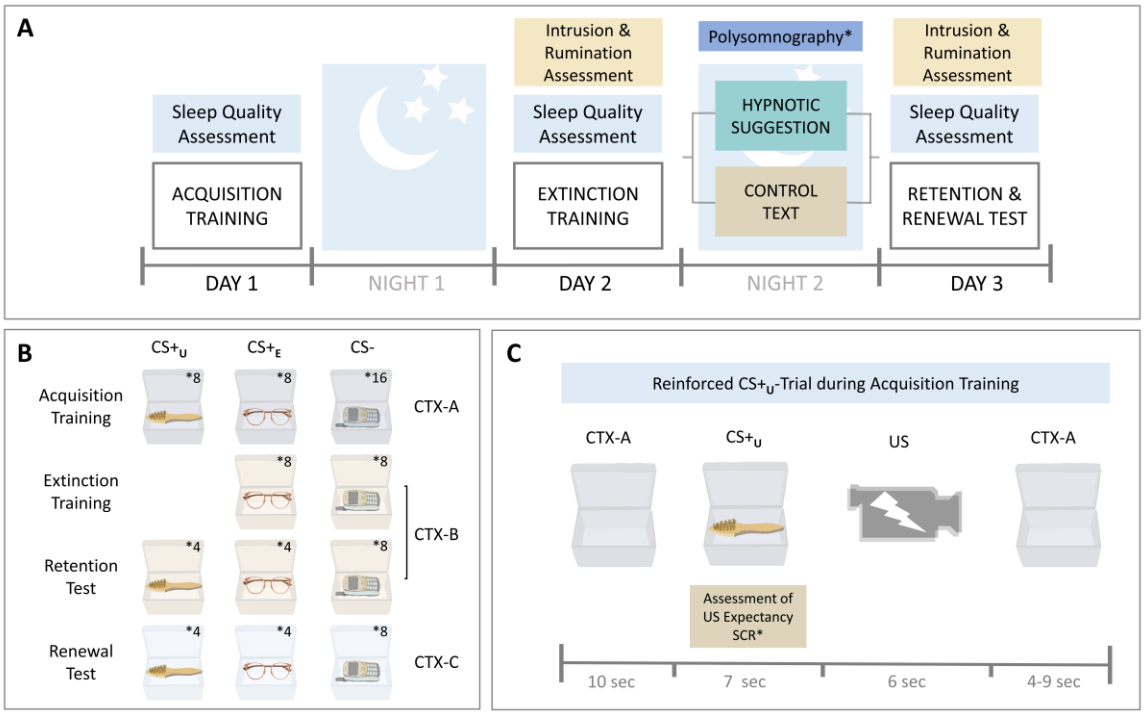

Figure IV-1. Experimental procedure.

Note. **1A:** Task procedure across experimental days. In both subsamples, participants filled out a sleep quality questionnaire at the beginning of each experimental day. After acquisition and extinction training, participants slept at home during night-time while the experimental groups received either a hypnotic suggestion or a control text before sleep in night 2. (*) Polysomnographic assessment was carried out only in the laboratory subsample. After sleep manipulation, participants underwent retention and renewal test on Day 3. Film-related intrusions and rumination from the acquisition training were assessed by questionnaires (Day 2 & 3) and an intrusion provocation task (Day 3). [*continued at the following page*]

[*Figure IV-1. continuation*] **1B:** Conditioned stimuli and contexts across the conditioning phases. During the conditioning phases (except for extinction training), three objects were presented in one of three boxes. (*) The number of trials for each conditioned stimulus are indicated by asterisks. One of the two aversive conditioned stimuli (CS+) was presented during extinction training ($CS+_E$) while the other was not ($CS+_U$). The boxes differed in type and color as well as different flooring in the background, serving as conditioning contexts specific to the phases. Retention was tested in the same context in which extinction training was carried out and thereafter in a new (renewal) context. **1C:** Stimulus presentation in a reinforced $CS+_U$ trial during acquisition training. An empty box (context) was presented for 10 seconds. Then, the conditioned stimulus appeared in the box for 7 seconds together with the US expectancy scale. (*) SCR assessment was carried out only in the laboratory subsample. The traumatic film clip (US) was presented immediately after stimulus offset. During the inter-trial interval, the context was presented for 4 to 9 seconds. CTX = Conditioning context, $CS+_U$ = aversive conditioned stimulus – unextinguished, $CS+_E$ = aversive conditioned stimulus – extinguished, CS- = safety stimulus, US = unconditioned stimulus, SCR = skin conductance response.

2.2.3 *Fear Conditioning Phases*

Prior to acquisition training, participants viewed an aversive film clip (US) about a female chef, who sustains severe burns during a kitchen accident accompanied by a piercing scream. The film clip was taken from a social marketing campaign by Ontario's Workplace Safety and Insurance Board (https://www.youtube.com/watch?v=tN2qpRcFKAQ) and was successfully used in previous fear conditioning experiments (Landkroon et al., 2020). Subsequently, participants were informed that they would see different objects of which some would be followed by an excerpt of the film clip. Three everyday objects (i.e., a brush, a cellphone and glasses), serving as to-be conditioned stimuli (CS), were presented in a box (acquisition context; see Figure IV-1.B). During CS presentation, participants were asked to rate their expectation to see the aversive film clip afterwards (*very low expectancy* [0] – *very high expectancy* [100]). In the laboratory subsample, skin conductance was recorded simultaneously (for details, see Supplementary Material). The presentation of the two CS+ was followed by a short version of the clip. The CS- was never followed by the clip. Acquisition training was divided into two sequential blocks, each consisting of eight CS+ (one of the two CS+) and eight CS- trials (see Figure IV-1.C, for trial procedure) in randomized order. US presentations followed the CS+ with a reinforcement ratio of 75%.

During extinction training, one of the two CS+ (extinguished CS+ [$CS+_E$]) and the CS- were presented eight times each in random order in a new box (extinction context). None of the CS presentations was followed by the US. As in acquisition training, retention test and renewal test were divided into two sequential blocks, during which one of the two CS+ ($CS+_E$ or the unextinguished CS+ [$CS+_U$]) and CS- were presented four times each. The US was not presented in any of the trials. During the retention test, CS were shown in the extinction context. During renewal test, CS were presented in a new box (renewal context). The order of CS+ blocks during acquisition training and retention and renewal test as well as the contexts were balanced across subjects. This design was adapted from Milad et al. (2007) to assess generalization of extinction (to the $CS+_U$) during sleep (for further information, see Supplementary Material). Secondary subjective fear indices (i.e., arousal, fear and valence

ratings) were measured in the remote subsample but will not be reported in the context of the current analyses.

2.2.4 *Measurement of Film-Related Intrusions and Rumination*

Intrusions and ruminative thoughts associated with the aversive film scene from acquisition training were assessed using a variant of the Intrusive Memory Questionnaire (IMQ; Michael & Ehlers, 2007). The questionnaire was adapted to assess frequency, duration (in seconds) and distress (*not at all* [0] – *extremely* [100]) of intrusions and rumination. Intrusion frequency was additionally assessed using an IPT (James et al., 2015; Michael, Ehlers, Halligan, et al., 2005). During the task, participants were re-exposed to the first four seconds of the film clip from acquisition training. After viewing the clip, they were instructed to close their eyes for two minutes. Finally, they were asked to rate intrusion frequency, duration and distress using the IMQ rating scales. Intrusion and rumination indices (sum scores of *z*-standardized frequency, duration, and distress items) were calculated for further analyses.

2.3 Data Preparation and Analyses

Based on sleep stage scoring and reports on time in bed during Night 2 in the laboratory subsample, the amount of time spent in sleep stages (minutes and % of total sleep time [TST]), sleep efficiency, sleep onset latency (SOL), wake after sleep onset (WASO), and sleep stage latencies were calculated (for details, see Supplementary Materials). In accordance with Cordi et al. (2020), spectral power of slow wave activity (SWA; 0.5-4 Hz) relative to total power (0.5-50 Hz) during non-rapid eye movement sleep stages 2 and 3 (N2 and N3 [i.e., SWS]) was extracted and calculated for the entire sleep phase and the first hour of sleep (for details, see Supplementary Materials). Two datasets were additionally excluded for all whole night analyses due to missing data in PSG recordings at the end of the sleep period.

In terms of manipulation checks, we first tested whether both CS+ induced comparable fear responses at the end of acquisition training. Moreover, we tested whether acquisition and extinction were successful. For analyses of the retention and renewal test, differential fear indices for $CS+_{E}$ and $CS+_{U}$ were calculated by subtracting CS- from CS+ responses from sequentially corresponding trials (see Pace-Schott, Rubin, et al., 2015). Afterwards, differential scores were averaged across trials.

Skin conductance responses (SCRs) were quantified as peak amplitudes by means of (non-model-based) trough-to-peak scoring (further details on SCR quantification are provided in the Supplementary Materials). SCR outlier detection ($Z >= \pm 3$) was based on raw magnitudes within-subjects. Statistical outliers were winsorized to the lowest/highest score within $Z =< \pm 3$ of individual scores. Afterwards, SCRs were square-root transformed. For all other measures, outlier detection was performed across subjects for each dependent variable

and univariate outliers were removed from analyses. Any deviations of results due to outlier exclusion are reported in corresponding footnotes.

Statistical analyses were conducted in *R* (R Core Team, 2020). Data of both subsamples were analyzed using linear mixed-effects models (LMMs) with individuals (level 1) being nested in subsamples (level 2). For repeated measures, measurements (level 1) were nested in individuals (level 2) which were nested in subsamples (level 3). All LMMs included (nested) random intercepts. (Nested) random slopes were included whenever they significantly improved model fit. In addition to LMM analyses with subsample as level, the main analyses were repeated including subsample and its interactions as fixed effects (results provided in the Supplementary Materials). In all linear models, fixed effects were centered within subsamples. Dichotomous predictors were dummy-coded (e.g., Group: control group [-0.5], hypnosis group [0.5]). LMM analyses were performed using the packages *nlme* (Pinheiro et al., 2022) and *reghelper* (Hughes, 2021). Robust linear regression analyses were conducted with *robustbase* (Maechler et al., 2022). Plots were built with *ggplot2* (Wickham, 2016). All other hypotheses were tested using X^2-tests or Welch's *t*-tests. Effects were considered significant at $p < .05$. Degrees of freedom varied due to missing data. Model parameters and coefficient tables are provided in the Supplementary Material.

3. Results

3.1 Effect of Sleep-Directed Hypnosis on Sleep Characteristics

3.1.1 *Subjective Sleep Quality*

3.1.1.1 Manipulation check

To investigate whether presentation of the aversive film clip affected sleep quality, we investigated changes in sleep quality from Day 1 to Day 2 across both subsamples. Both groups showed a decline in sleep quality from Day 1 to Day 2. That is, separate LMM analysis in each group including the fixed effect Day (1, 2) revealed significant negative slopes: hypnosis group: b = -0.21, 95% CI [-0.38, -0.05], se = 0.08, $t(90)$ = -2.60, p = .011; control group: b = -0.18, 95% CI [-0.34, -0.02], se = 0.08, $t(87)$ = -2.20, p = .031.

3.1.1.2 Intervention effects

To examine the effect of sleep-directed hypnosis on sleep quality, we ran a LMM analysis including the fixed effects Day (2, 3) and Group (hypnosis, control) across both subsamples. Sleep Quality on Day 1 was included as covariate to control for potential baseline effects. The analysis revealed a Day*Group interaction effect: b = 0.52, 95% CI [0.26, 0.79], se = 0.14, $t(172)$ = 3.86, $p < .001$. On Day 2, sleep quality did not differ by Group (p = .160). From Day 2 to Day 3, sleep quality changed inversely depending on the experimental group: While the

hypnosis group showed an increase in sleep quality, $t(172) = 2.42$, $p = .017$, sleep quality in the control group declined, $t(172) = -3.04$, $p = .003$. Sleep quality on Day 3 differed significantly between groups with higher scores in the hypnosis group compared to the control group, $t(177) = 3.47$, $p < .001$ (see Figure IV-2). These findings are in line with the hypothesis that sleep-directed hypnosis influenced subjective sleep quality. The LMM analysis further revealed a positive relationship between Sleep Quality at Day 1 and sleep quality at later time points, $b = 0.38$, 95% CI [0.27, 0.49], $se = 0.06$, $t(177) = 6.79$, $p < .001$.

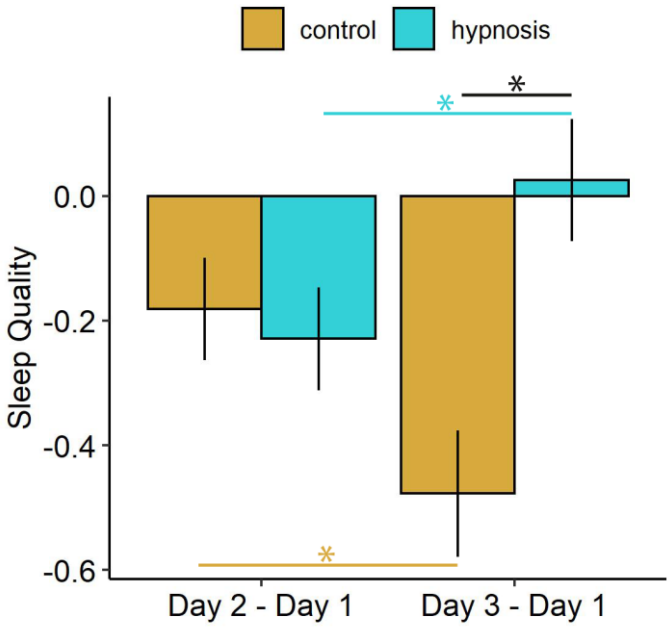

Figure IV-2. Change in sleep quality across experimental days.

Note. Means and standard errors of sleep quality change (Day [x] – Day 1). From Day 1 to Day 2, both groups showed decreased sleep quality. From Day 2 to Day 3, experimental groups showed inverse changes: sleep quality significantly improved in the hypnosis group to baseline (Day 1) level (turquoise asterisk), whereas sleep quality in the control group decreased further (yellow asterisk), leading to significantly different sleep quality scores at Day 3 by Group (black asterisk). Note that results are based on a linear-mixed effects model (LMM) analysis including Day 1 as covariate. The graph does not represent all components of the LMM that was built by the data; plot is shown for illustration.

3.1.2 *Sleep Architecture and Slow Wave Activity*

Sleep characteristics and group comparisons in the laboratory subsample are presented in Table IV-2. Analyses of N3 duration (minutes and % of TST) during the whole night and during the first hour of sleep revealed no significant differences between groups (p's >= .931). Furthermore, group comparisons on relative SWA power during N2 and N3 did not reveal any significant differences between the hypnosis and control condition across the whole night and the first hour of sleep (p's >= .593). Exploratory analyses of other sleep stage amounts across the whole night revealed significantly lower REM sleep duration (minutes and % of TST) in the hypnosis group compared to the control group (p's <= .034). Further exploratory analyses on

objective indices of sleep quality, i.e., sleep efficiency, SOL and WASO, or on N3 and REM sleep latency did not reveal any group effects (*p*'s >= .225). These findings do not support our hypothesis of increased amounts of N3 and SWA as a result of sleep-directed hypnosis.

Table IV-2. Sleep parameters of the whole night and first hour of sleep (laboratory subsample)

Measure	Sleep Stage	Hypnosis Group		Control Group		Test Statistics		
		M	*SD*	*M*	*SD*	t_W	df	*p*
Whole night sleep								
Duration (Min)[a]	N1	39.98	14.57	35.60	14.94	-1.25	68.80	.215
	N2	205.14	38.18	207.53	30.81	0.29	68.34	.770
	N3	101.18	32.47	100.97	27.78	-0.03	67.92	.977
	REM	99.10	21.90	109.08	16.49	2.17	64.98	.034
	TST	456.25	23.57	453.18	26.80	-0.51	66.91	.613
Duration (% TST)[a]	N1	9.03	3.82	7.86	3.31	-1.38	68.11	.172
	N2	45.87	7.37	45.73	5.57	-0.09	66.83	.932
	N3	22.48	6.41	22.35	6.23	-0.09	69.00	.931
	REM	21.83	4.19	24.06	3.27	2.50	65.88	.015
Latency (Min)	N3	14.77	7.27	14.65	5.96	-0.08	69.05	.935
	REM	104.95	47.66	92.71	37.11	-1.23	67.78	.225
Sleep efficiency (%)	/	94.11	4.55	93.00	4.27	-1.03	66.00	.305
WASO (Min)	/	9.40	10.40	12.65	14.22	1.08	62.30	.282
SOL (Min)	/	22.61	16.16	18.63	13.24	-1.12	65.59	.268
SWA power (% TP)	N2 + N3	86.67	4.19	86.58	3.54	-0.11	70.00	.915
First hour of sleep								
Duration (Min)	N3	35.06	11.64	35.41	8.73	0.14	66.72	.887
Duration (% TST)	N3	59.15	18.61	59.60	14.31	0.12	67.43	.907
SWA power (% TP)	N2 + N3	89.06	5.20	88.48	3.98	-0.54	67.26	.593

Note. N1 - 3 = non-rapid eye movement sleep stage 1 - 3; REM = rapid eye movement sleep; TST = total sleep time; WASO = wake after sleep onset; SOL = Sleep onset latency; SWA = slow wave activity; TP = total power.
[a] Note that outlier exclusion was performed for each dependent variable. Therefore, descriptive statistics of sleep stage amounts does not correspond to TST amounts.

To explore whether sleep physiology could explain the change in subjective sleep quality from Day 2 to Day 3 in the laboratory subsample, linear regression models with Group as predictor and PSG-based sleep variables as additional predictors were examined. Goodness-of-fit tests did not reveal a significant increase in model fit by including any of the sleep variables. Further explorations on model parameters, however, indicated multivariate outliers

and influential data points. Therefore, robust linear regression models were computed in addition. Goodness-of-fit tests on robust regression models indicated that the amount of time spent in N3, $F(2,65) = 16.24$, $p < .001$, and WASO, $F(2,63) = 7.53$, $p = .023$, significantly improved estimation of the change in sleep quality from Day 2 to Day 3 (see Figure IV-3).[21] Goodness-of-fit tests further indicated that N3 latency and relative SWA power during the first hour of sleep improved model fit (*p*'s =< .007). The regression outputs, however, did not show any significant effects of sleep variables (*p*'s >= .074). An exploratory robust regression analysis including Group and N3 duration revealed a main effect of Group, $b = 0.54$, 95 % CI [0.10, 0.98], $se = 0.22$, $t(65) = 2.45$, $p = .017$, and a main effect of N3, $b = 0.01$, 95 % CI [0.003, 0.01], $se = 0.003$, $t(65) = 2.90$, $p = .005$. No interaction effect was found ($p = .128$). Improvement in sleep quality in the laboratory subsample was associated with hypnosis compared to the control condition and with higher amounts of N3. Another exploratory robust regression analysis including Group and WASO revealed a main effect of WASO, $b = -0.03$, 95 % CI [-0.05, -0.01], $se = 0.01$, $t(63) = -2.70$, $p = .009$. The Group effect did not reach significance ($p = .051$) and no interaction effect was found ($p = .494$). Less time spent awake during the sleep period was associated with an improvement in subjective sleep quality from Day 2 to Day 3 in the laboratory subsample.

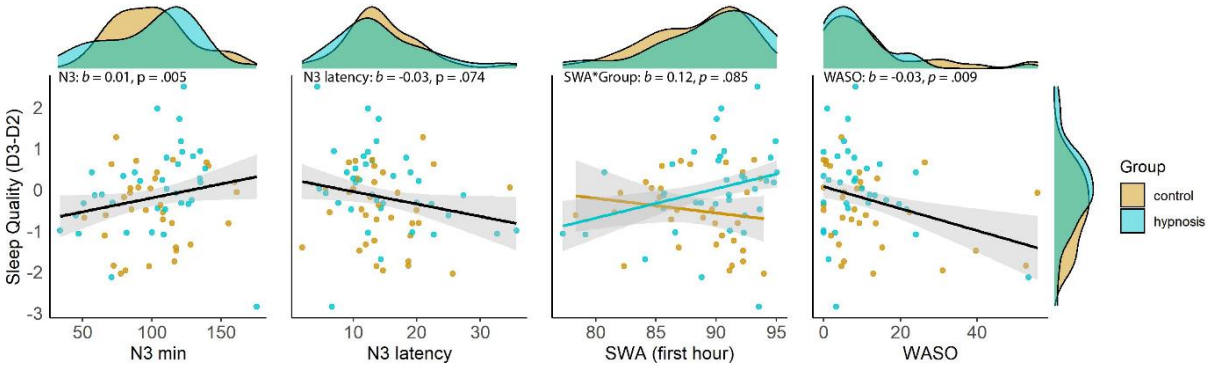

Figure IV-3. Relationship between subjective sleep quality and objective sleep parameters of the sleep period in Night 2 in the laboratory subsample.

Note. Density plots showing the distribution of sleep variables in the control and hypnosis group. Scatter plots illustrating the linear relationships between the change in sleep quality from Day 2 to Day 3 (difference scores) and PSG-based sleep variables across/within the experimental groups. Note that the scatterplots present raw data, whereas the linear slopes were build on robust regression modeling. N3 = non-rapid eye movement sleep stage 3, SWA = slow wave activity, WASO = wake after sleep onset.

[21] When outliers are included, N3 no longer significantly predicted the change in sleep quality ($p = .530$). A regression analysis including Group and N3 latency revealed significant main effects of Group ($p = .015$) and N3 latency ($p = .040$) when including outliers. Another regression analysis including outliers with Group and relative SWA power during the first hour of sleep as predictors revealed a significant Group*SWA interaction effect ($p = .005$). Finally, a regression analysis including Group and WASO revealed significant main effects of Group ($p = .020$) and WASO ($p = .034$) when including outliers.

3.2 Effects of Sleep-Directed Hypnosis on Fear Extinction Recall and Film-Related Intrusions and Rumination

3.2.1 *Fear Conditioning Phases*

3.2.1.1 Manipulation Check – Acquisition

Analyses of CS+ responses during acquisition training revealed no differences between $CS+_{E}$ and $CS+_{U}$ on the final trial of acquisition training for US expectancy across both subsamples (p = .667) and SCR in the laboratory subsample (p = .804). Averaged CS+ ($CS+_{E}$, $CS+_{U}$) and CS- (across blocks) responses were therefore calculated for each trial in the following analysis. LMM analyses of US expectancy including Trial, CS type (CS+, CS-) and Group across both subsamples showed differential elevation of fear expressions for CS+ but not for CS- during acquisition training, indicated by a Trial*CS type interaction effect, b = 7.16, 95 % CI [6.66, 7.66], se = 0.26, t(2709) = 27.97, p < .001. SCR analyses in the laboratory subsample revealed higher SCRs for the CS+ compared to CS-, main effect of CS type: b = 0.09, 95 % CI [0.06, 0.13], se = 0.02, t(1070) = 5.63, p < .001. No Group effects were found (p's >= .252).

3.2.1.2 Manipulation Check – Extinction

LMM analyses of US expectancy including Trial, CS type ($CS+_{E}$, CS-) and Group across both subsamples indicated successful fear extinction, reflected in a significant Trial*CS type interaction effect, b = -3.14, 95 % CI [-3.54, -2.74], se = 0.20, t(2686) = -15.44, p < .001. Successful extinction was also evident in SCR responses in the laboratory subsample, as reflected in a main effect of CS type, b = 0.03, 95 % CI [0.002, 0.06], se = 0.02, t(1067) = 2.11, p = .035, and post-hoc tests, showing that SCRs for $CS+_{E}$ were higher than for CS- at the first trial of extinction training, t(1067) = 2.30, p = .022, whereas no difference was found at the final extinction trial (p = .689). No Group effects were found (p's > = .288).

3.2.1.3 Retention Test

LMM analyses of US expectancy averaged across retention test trials including CS+ type (difference scores for $CS+_{E}$ and $CS+_{U}$) and Group across both subsamples revealed higher US expectancy for $CS+_{U}$ compared to $CS+_{E}$, b = -11.98, 95 % CI [-15.86, -8.11], se = 1.97, t(178) = -6.07, p < .001. This pattern confirms the intended manipulation, i.e., differential extinction of the $CS+_{E}$. No effects of Group were found (p >= .656). For SCR, a LMM analysis including CS+ type and Group in the laboratory subsample similarly showed higher SCRs for $CS+_{U}$ compared to $CS+_{E}$, b = -0.08, 95 % CI [-0.11, -0.04], se = 0.02, t(67) = -4.28, p < .001. No effects of Group were found (p >= .233). These findings suggest no effect of sleep manipulation on extinction recall. Moreover, no significant differences between groups were found when comparing differential $CS+_{E}$ and $CS+_{U}$ responses, which does not support the

hypothesis of extinction generalization promoted by sleep-directed hypnosis. We further explored whether interindividual differences in SWS amount (minutes) could have influenced extinction recall during retention test in the laboratory subsample. Goodness-of-fit tests did not reveal significant improvements in model fit by introducing SWS amount into the LMMs including US expectancy or SCRs as dependent variable (p > .05).

3.2.1.4 Renewal Test

LMM analyses of averaged differential US expectancy across the renewal test including CS+ type and Group across both subsamples revealed a significant effect of CS+ type with higher US expectancy for CS+U compared to CS+E, b = -4.75, 95 % Ci [-8.22, -1.27], se = 1.77, t(177) = -2.68, p = .008. No effects of Group were found (p's >= .878). SCR analyses including CS+ type and Group revealed no significant effects in the laboratory subsample (p's >= .061; see Figure IV-4 for an overview of retention and renewal test performance). These results similarly do not support any impact of sleep-directed hypnosis on extinction recall. Further exploratory tests on whether interindividual differences in SWS amount (minutes) could have influenced performance during renewal test in the laboratory subsample were carried out. Goodness-of-fit tests did not indicate significant improvements in model fit by introducing SWS amount into the LMMs including US expectancy or SCRs as outcomes (p > .05).

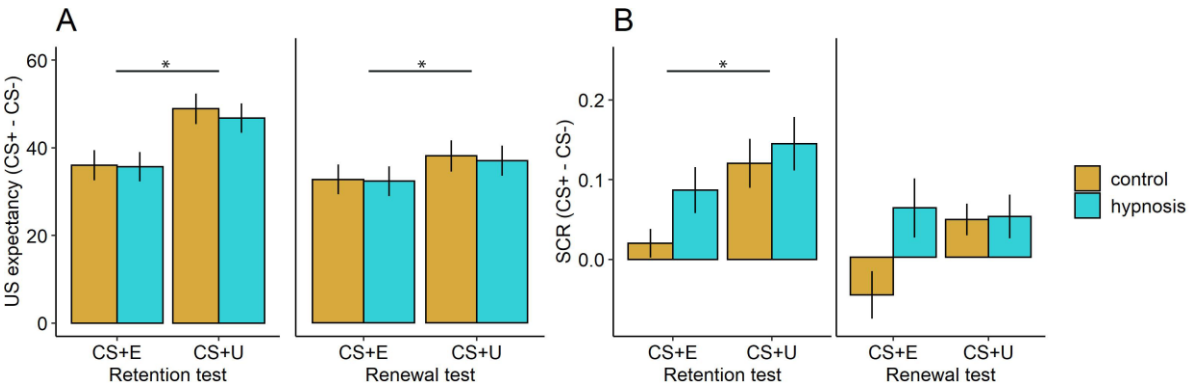

Figure IV-4. Fear expressions during retention test and renewal test.

Note. Means and standard errors of differential US expectancy scores (**4A**) and skin conductance responses (SCR in microSiemens, square-root transformed; **4B**) in the laboratory subsample averaged across the respective test phase. Asterisks indicate significant main effects of CS+ type based on linear mixed-effects model (LMM) analyses (*p < .05). No effects of Group were found in any analysis. Note that means and standard errors do not represent all components of the LMMs that were built by the data; plots are shown for illustration.

3.2.2 *Intrusions and Rumination*

To examine the effect of sleep-directed hypnosis on film-related intrusion and rumination, LMM analyses including Group and Day (Day 2, Day 3) were performed across both subsamples. For both measures, the analyses revealed a significant decline across days (main effect), intrusion index: b = -0.81, 95 % CI [-1.15, -0.48], se = 0.17, t(170) = -4.80, p < .001, rumination index: b = -1.24, 95 % CI [-1.90, -0.58], se = 0.34, t(168) = -3.69, p < .001. No significant effects

of Group were found for either measure (*p*'s >= .199). Finally, we examined whether Group effects were evident in intrusions during the IPT on Day 3 across both subsamples. LMM analyses including Group revealed no main effect of Group (p = .577). In contrast to our hypothesis, these findings do not support the assumption that sleep-directed hypnosis has a beneficial impact on intrusions or rumination.

4. Discussion

The current study aimed to investigate potential effects of sleep-directed hypnosis on extinction of trauma-associated fear memories. Analyses revealed a beneficial impact of hypnosis on subjective sleep quality in both subsamples. Although subjective sleep quality was significantly correlated with the amount of N3 sleep and WASO in the laboratory subsample, we found no direct effects of hypnosis on SWS or SWA. Surprisingly, exploratory findings indicate that hypnosis decreased the amount of REM sleep. Neither analyses of extinction retention and generalization nor of trauma-associated intrusions and rumination revealed any effects of hypnosis. As such, the current results indicate that sleep-directed hypnosis is useful for improving subjective sleep quality but not for enhancing extinction memory and reducing analog PTSD symptoms.

Our finding that sleep-directed hypnosis improves subjective sleep quality aligns with previous findings from Cordi et al. (2020) and extends these in important ways: First of all, we were able to show that this enhancing effect is also evident when sleep-directed hypnosis and subsequent sleep take place under ecologically valid conditions, i.e., in the participants' home. Secondly, we were able to demonstrate convergent effects in and across two subsamples with high statistical power. Finally, we found this effect in the context of exposure to a traumatic film clip that may have affected sleep quality beforehand. That is, both groups showed a decline in sleep quality following acquisition training, suggesting a detrimental impact of the traumatic film clip on sleep (see also Richardson et al., 2015; Sopp et al., 2019; Talamini et al., 2013). This effect dissipated after the hypnosis intervention but not after control condition, indicating that sleep-directed hypnosis may have counteracted the effect of exposure to the aversive material on sleep quality. These findings suggest that the effects of sleep-directed hypnosis may also emerge in the context of trauma and other distressing life events, forming an important basis for the application of sleep-directed hypnosis in clinical settings.

In contrast to our assumptions, we did not find any significant impact of hypnosis on SWS parameters. Groups only differed in REM sleep duration, which may be related to numerically higher REM sleep latency in the hypnosis group. This effect may have been driven by increased REM sleep amounts due to the presentation of aversive film clips (Delannoy et al., 2015). This increase may have been normalized by subsequent hypnosis, hence only emerging in the control group. However, since our design did not comprise an assessment of

sleep physiology during the first experimental night after acquisition training, this hypothesis requires further testing in subsequent studies.

In line with earlier findings showing that SWS and SWA were positively associated with subjective sleep quality (Cordi et al., 2014; 2015), exploratory analyses pointed towards a role of SWS in determining the change in sleep quality from pre- to post-intervention. However, it is important to note that only the amount of SWS and not other SWS parameters predicted sleep quality and that this effect did not interact with hypnosis. Inconsistencies between the current results and the findings from Cordi et al. may be related to the fact that we assessed sleep physiology under potentially noisy (ambulatory) conditions in a subsample of participants. Moreover, previous research used within-subjects designs, whereas we used a between-subjects design to accommodate the fear conditioning procedure. Nevertheless, the fact that we did not find direct evidence for increased SWS by hypnosis limits the interpretation of our findings with respect to potential effects on extinction memory.

Our analyses of extinction retention and generalization did not reveal any significant between-group differences, suggesting that hypnosis did not affect the consolidation of extinction memory. Consonantly, we did not observe any group differences in intrusive memories or ruminative thoughts. Hence, our study suggests that while hypnosis enhanced subjective sleep quality, it did not facilitate sleep-related memory reprocessing. Several explanations may account for these results: First, the lack of significant effects of hypnosis on SWS features may have prevented finding a beneficial effect of hypnosis via SWS-induced strengthening of extinction memory. Secondly, sleep-directed hypnosis may not be suited to target memory processes during SWS. Correspondingly, the hypnotic suggestion used in the current study has recently been shown to increase SWS parameters but decrease slow wave-spindle coupling (Beck et al., 2021), which is assumed to underlie memory consolidation during SWS. Finally, another explanation could be that extinction memory is consolidated via a process, which is functionally independent of SWS. This is also supported by additional exploratory analyses on retention and renewal test performance in the laboratory subsample, which did not indicate that SWS amount significantly contributed to the prediction of extinction retrieval. Indeed, previous studies have suggested an involvement of REM sleep rather than SWS in the consolidation of extinction memory (e.g., Menz et al., 2016; Spoormaker et al., 2012). However, this assumption is challenged by our findings that REM sleep amounts varied between groups without having any impact on extinction recall. Moreover, a recent meta-analysis did not show a robust relationship between REM sleep and subsequent extinction recall (Schenker et al., 2021). Nevertheless, future studies should explore the impact of sleep interventions targeting REM sleep on extinction retention and generalization as well as the additive benefits of different interventions targeting subjective and objective sleep quality.

Beyond the limitations mentioned above, several others should be considered. First of all, it is important to note that our design lacked a wake control group. Hence, it is not possible to draw any conclusions regarding the effects of sleep per se but only regarding the effects of sleep-directed hypnosis. Second, previous studies have shown that effects of sleep-directed hypnosis rely on the hypnotizability of participants (Cordi et al., 2014; 2015; 2020). However, additional analyses in the remote subsample, which comprised individuals with different levels of hypnotizability, did not reveal any significant effects of hypnotizability. This contrasts previous reports and could be related to procedural differences between studies (e.g., remote assessment of hypnotizability). Relatedly, it is important to note that the majority of participants of the remote subsample was strongly hypnotizable, which may have prevented us from finding effects of hypnotizability. Third, differences between remote and laboratory assessment may have brought about additional variance in the current analyses. We based this approach on previous research (Kleim et al., 2016) in an effort to further enhance statistical power. Moreover, we used LMM analyses to account for dissimilarities between subsamples. In addition, we tested whether our results differed between the two subsamples. These analyses revealed mostly consistent results between the remote and laboratory subsample (see Supplementary Materials). Fourth, in order to quantify SCRs, we used a non-model-based approach (i.e., trough-to-peak scoring). There has been significant debate on the appropriateness of such approaches (see e.g., Bach & Melinscak, 2020). However, recent research confirms that through-to-peak scoring produces satisfactory effects in terms of CS discrimination (Kuhn et al., 2022). Hence, we believe that, while more research on the issue of SCR quantification is needed, our approach can be considered sufficient for the scope of our research questions. Finally, it is important to note that we used an analog procedure to investigate processes during TF-PT. Although this approach aligns with previous research aiming to shed light on the underlying processes of PTSD symptom development and treatment (Ney et al., 2022), further research is needed to establish whether results replicate in clinical settings. Relatedly, pre-experimental differences in psychological vulnerability may have influenced memory processing during the experimental tasks as well as the impact of hypnosis. Though participants in our two subsamples did not report a history of traumatic events or current mental disorders, we cannot rule out possible effects of (sub)clinical characteristics. To keep assessment as brief as possible, we did not assess such characteristics except for trait anxiety. Additional exploratory analyses including trait anxiety as covariate did not change the direction of our results nor did trait anxiety interact with Group in any of our analyses.

Despite these limitations, our study provides important insights: Although sleep-directed hypnosis did not affect extinction memory and objective sleep quality, it robustly improved subjective sleep quality, which was significantly reduced after fear conditioning including

exposure to a traumatic film clip. These findings indicate that sleep-directed hypnosis could be beneficial for improving subjective sleep quality in traumatized individuals with PTSD symptoms. This is noteworthy since the majority of PTSD patients (i.e., 70-91%) experience difficulties falling and staying asleep (Maher et al., 2006) and sleep problems are a particularly common residual symptom after treatment (Schnurr & Lunney, 2019). Moreover, trauma-induced insomnia severely affects quality of life and overall well-being (Werner et al., 2021). For instance, recent findings indicate that subjective sleep quality moderates the association between trauma exposure and suicide attempts (King et al., 2021). At the same time, standard approached for treating sleep disturbances are not effective in all PTSD patients (see e.g., full remission rate of 41% in Talbot et al., 2014). Sleep-directed hypnosis might thus be a useful addition to treat sleep disturbances in PTSD (Arditte Hall et al., 2021; Galovski et al., 2016). Moreover, due to easy, self-guided implementation, sleep-directed hypnosis could be used as an intervention strategy for trauma survivors, experiencing sleep disturbances in the early aftermath of trauma.

5. Declarations

The study procedures were approved by the local ethics committee of Saarland University (A15-3). The study protocol was registered at the German Clinical Trials Register (DRKS00022369) prior assessment of the laboratory subsample. All participants provided written informed consent in accordance with the Declaration of Helsinki. Data underlying our analyses are accessible via OSF (DOI: 10.17605/OSF.IO/X4T25).

V General Discussion

In the following sections (Chapter V.1), the main results of the three studies are summarized and briefly discussed in the context of the study objectives. In Chapter V.2, I will discuss the findings conjointly and reflect their meaning in light of previous research and theoretical accounts. Chapter V.3 provides an overview on the most important limitations of the present findings and gives suggestions for future research.

1. Summary of Findings

1.1 Study 1

In Study 1, the repeated presentation of a highly aversive film clip as US during acquisition training successfully elicited analog intrusive memories as well as analog ruminative thoughts. In order to increase reliability of quantification of intrusion characteristics featuring PTSD, an index of intrusion load (and rumination load) was built (see Wegerer et al., 2013). As expected, both intrusion and rumination load were positively related to the level of distress caused by the COVID-19 outbreak, measured before analog trauma exposure. COVID-19-related rumination did not correlate with intrusion or rumination load (see Chapter II.3.2). Regarding indices of conditioned fear acquisition, post-acquisition CS+ arousal ratings were positively correlated with distress and rumination related to the COVID-19 outbreak. COVID-19-related distress, furthermore, was positively associated with CS+ fear ratings, whereas valence and US expectancy ratings did not correlate with any COVID-19-related measure (see Chapter II.3.3). It was further hypothesized that interindividual differences in conditioned fear acquisition predict analog PTSD symptoms. The present data confirmed this hypothesis by establishing a positive association between fear, arousal and valence ratings in response to the CS+ after acquisition training and intrusion load. Similarly, post-acquisition fear, arousal and valence ratings for the CS+ were positively associated with rumination load. Notably, US expectancy neither correlated with intrusion nor with rumination load (see Table II-1). Finally, it was expected that the interindividual variability in conditioned fear serves as a mediator in the relationship between COVID-19-related distress and rumination and analog PTSD symptoms. In line with this hypothesis, the present findings showed that post-acquisition fear, arousal and valence ratings for CS+ served as mediators in the relationship between COVID-19-related distress and intrusion load. Fear and arousal ratings did also mediate the association between distress related to the COVID-19 outbreak and rumination load. Notably, these effects emerged while controlling for effects of trait anxiety and differences in subjects' attention during the experiment. Moreover, it should be noted that mediation analyses on $CS_{\mathbf{diff}}$ scores revealed comparable results for intrusion load, whereas results on rumination load were less robust (see Chapter II.3.4).

1.2 Study 2

In Study 2, participants underwent the fear extinction training in the middle of the night after either a 3-hour sleep opportunity or a 3-hour period of wakefulness during the early night half. This experimental manipulation was carried out in order to contrast sleep rich of SWS with wakefulness prior to extinction learning. PSG-based analyses revealed similar amounts of SWS in both experimental groups at their earliest sleep opportunity respectively (i.e., during the early night half in the sleep group and the late night half in the wake group). The sleep group furthermore showed a decrease in SWS in the successive second sleep opportunity (i.e., during the late night half; see Chapter III.3.1.1). These results align with previous observations of SWS amounts changing across sleep cycles in correspondence to homeostatic sleep pressure (Borbely et al., 2016) and support the successful manipulation of sleep in order to investigate early night sleep with high amounts of SWS in the sleep group.

In contrast to the hypothesis that early night sleep facilitates subsequent extinction learning, the present investigation did not reveal any significant group effects in comparison with wakefulness. Specifically, no effects of group were found in subjective fear expressions during extinction training or ROF test or after a sleep opportunity in the late night half for both groups, at retention test (see Chapter III.3.2.1 and Chapter III.3.2.2). Thus, the current findings do not support a beneficial role of pre-learning sleep for the acquisition and later recall of the extinction memory trace. Furthermore, no group difference was found in intrusion frequency during the IPT (see Chapter III.3.2.3). These results were supported by Bayesian inference. Exploratory correlation analyses in the sleep group further suggested no impact of SWS on subsequent extinction performance. In contrast, exploratory findings revealed a positive relationship between REM sleep and success in extinction learning as indicated by a stronger decrement in subjective fear for the CS+ during extinction training. While this finding needs to be confirmed by future studies, the present data point to a beneficial role of REM sleep in subsequent extinction learning.

1.3 Study 3

To investigate the potential effect of boosted SWS on extinction consolidation and recall, sleep after extinction training was manipulated in study 3 by means of a hypnotic suggestion targeting SWS. This intervention has been shown to increase the amount of SWS and SWA power in previous studies (Besedovsky et al., 2022; Cordi et al., 2014; 2015; 2020). In contrast, analyses including the laboratory subsample did not reveal significant group differences in the amount of SWS and relative SWA power, but significantly lower amounts of REM sleep in the hypnosis group compared to the control group. Regarding subjective sleep parameters, sleep-directed hypnosis was associated with an increase in sleep quality. This effect was found in the context of a general deterioration of sleep quality, as indicated by decreasing sleep quality

from Day 1 to Day 2 in both groups and a further decline from Day 2 to Day 3 in the control group. The improvement of sleep quality in the hypnosis group from Day 2 to Day 3 could, therefore, indicate a buffering effect of sleep-directed hypnosis in the context of (analog) trauma exposure. However, future studies are needed to confirm this assumption. Sleep quality was, furthermore, positively related with the amount of SWS and WASO in both groups.

It was hypothesized that sleep-directed hypnosis before nighttime sleep, in contrast to the control condition, should lead to enhanced extinction recall and generalization in the subsequent period of wakefulness. In contrast, the present investigation did not reveal any significant effects of sleep manipulation in subjective and psychophysiological indices of conditioned fear. Specifically, no group effects were found in fear expressions for $CS+_{E}$ or $CS+_{U}$ during retention and renewal test. Finally, the lack of group effects in analog intrusion and rumination indices did not suggest a diminishing effect of sleep on analog PTSD symptoms, which could have been attributed to enhanced extinction consolidation. In summary, Study 3 revealed no empirical evidence for a beneficial effect of sleep-directed hypnosis on extinction consolidation during sleep. However, the lack of effect on SWS parameters limits the interpretation of the fear conditioning data in terms of the expected SWS effects.

2. Integration of Findings

2.1 The Link between Conditioned Fear Acquisition and Intrusion Development and the Role of Stress

In Study 1, the repeated presentation of a highly aversive film clip as US during acquisition training successfully elicited analog intrusive memories. Furthermore, intrusion load was positively related to the level of distress caused by the COVID-19 outbreak, measured before analog trauma exposure. This relationship could reflect the increase in psychopathology in the general population that was associated with the COVID-19 outbreak (Robinson et al., 2022). While the detrimental impact of the COVID-19 outbreak on mental health can be attributed to several mechanisms, the current study design allowed for investigating one of them in particular. The cognitive model by Ehlers & Clark (2000) proposes that, during trauma, the increased arousal caused by the existential threat shifts information processing towards data-driven encoding. This should facilitate the acquisition of conditioned fear towards trauma-related stimuli, triggering intrusive re-experiencing in the aftermath of trauma (see Chapter I.1.4). Fear conditioning could, therefore, be considered as an important peritraumatic process that could mediate pretrauma risks for developing posttraumatic stress symptoms. In line with this assumption, the present data established a positive association between fear expressions in response to the CS+ after acquisition training and subsequent intrusion load. Furthermore,

the interindividual variability in conditioned fear consistently served as a mediator in the relationship between COVID-19-related distress and intrusion load.

The finding that both conditioned fear and intrusion load were positively associated with distress caused by the COVID-19 outbreak aligns with previous findings on the effect of stress on analog intrusions (Hilberdink et al., 2022; Schultebraucks et al., 2019) and fear acquisition (though the effect seem to depend on sex; Peyrot et al., 2020). Although the current experiment did not assess (neuro)biological markers of stress, high-level distress caused by the COVID-19 outbreak has been likely accompanied by (neuro)biological stress responses (see e.g., Haucke et al., 2022; Marcil et al., 2022; Salomon et al., 2021; Šik Novak et al., 2022). As outlined by Pitman and colleagues (2012), the neuronal fear conditioning circuitry is sensitive to the impact of stress hormones. Specifically, high levels of norepinephrine and cortisol are assumed to promote the acquisition and consolidation of conditioned fear by directly acting on the amygdala and hippocampus, as well as indirectly by interfering with prefrontal inhibitory functions (de Quervain et al., 2017; Pitman et al., 2012; see Chapter I.1.8.2). As these effects are dose-dependent (Pitman et al., 2012), the psychosocial stress elicited by the COVID-19 outbreak could have increased the risk for overly strong fear conditioning during analog trauma in an additive manner. Apart from the temporal overlap of stressors, adverse events have the potential to produce lasting changes in the functional network recruited during fear conditioning (e.g., Ansell et al., 2012; Teicher et al., 2016). Such events were shown to cumulatively increase the risk for maladaptive processing during analog trauma, resulting in increased intrusion load (Rattel, Miedl, et al., 2019). The variance in conditioned fear and intrusion load in the present sample might therefore reflect the interaction of previous stressors and the stress elicited by the COVID-19 outbreak that could have promoted pathological memory processing in some individuals. Future studies are needed to explore the exact mechanisms by which psychosocial stressors could affect fear conditioning and analog intrusion development.

It is important to note that previous research has provided competing evidence relating to the current findings and their interpretation. For instance, research also supports the assumption that a disposition to stronger fear acquisition could manifest in higher anxiety in response to a psychosocial stressor such as the COVID-19 outbreak (see Hunt et al., 2022). To date, research has thus provided support for two hypotheses. On the one hand, fear conditioning processes are sensitive to stress (Merz et al., 2016; Peyrot et al., 2020) and effects of chronic stress on fear memory are considered to be a central mechanism underlying the maintenance of PTSD (Maeng & Milad, 2017). On the other hand, pre-trauma conditioned fear expressions were shown to predict PTSD symptom development (Guthrie & Bryant, 2006; Orr et al., 2012). Yet surprisingly little is known of whether these mechanisms may be interrelated. Another point to consider is that current evidence points towards impaired safety learning rather than increased conditionability as specific feature of pathological anxiety and

PTSD (Duits et al., 2015). Accordingly, a recent study found impaired fear discrimination and stronger fear generalization related to elevated COVID-19 anxiety (Hauck et al., 2022), contrasting the present findings (as well as the findings by Hunt et al., 2022). Future research is needed to investigate which mechanisms determine (mal)adaptive processes in terms of fear conditioning.

Study 1 revealed important insights into the role of fear conditioning in intrusion development. The present findings demonstrate that interindividual differences in conditioned fear acquisition predict analog PTSD symptoms. As such, Study 1 provides further support for a causal role of fear conditioning in PTSD etiology. This was not only demonstrated for analog intrusive memories but also, as a novelty in this field, for analog ruminative thoughts. While future studies are necessary to confirm this effect, the current data provide important insights into the potential link between posttraumatic rumination and memory processes during trauma. Finally, by establishing a meaningful, theory-based relationship between fear conditioning, analog symptoms of PTSD and markers of stress occurring from a 'real-world' stressor, the present results support the construct validity of the paradigm used in this dissertation to examine associative learning during and after trauma.

2.2 Methodological Considerations on the Interpretation of Conditioned Fear Indices

The three studies carried out for this dissertation have used fear conditioning protocols. Fear conditioning protocols are used to mimic implicit associative learning during and after trauma that are assumed to underlie PTSD development as well as recovery and relapse (Zuj & Norrholm, 2019). With that, fear conditioning research can bring important insights into the mechanisms by which pre-trauma risk factors could affect trauma processing or provide suggestions for enhancing outcomes from trauma-focused psychotherapy. However, such transfer is limited by methodological constraints, one of which is the experimental investigation of non-observable, i.e., latent, constructs. Latent constructs are tested by measuring behavioral and physiological responses to experimental manipulation that are assumed to affect the underlying latent variables (Bach et al., 2022). Since fear conditioning is not directly observable, fear conditioning protocols are used to make inferences about the underlying memory processes. Therefore, is important to examine the current findings with respect to the validity and robustness of the experimental protocols used in the present thesis. The following sections present no systematic analysis of psychometric properties but rather discuss the current data in the context of certain aspects of construct validity and internal consistency.

2.2.1 Measuring the Construct ‘Associative Strength’ in the Context of Posttraumatic Stress Disorder

When interpreting measures of a latent construct it is important to evaluate to which extent the observed values measure the construct it is supposed to measure, which is termed as construct validation (Cronbach & Meehl, 1955; Strauss & Smith, 2009). In a classical fear conditioning protocol, fear expressions for the CS+ in contrast to the CS- should reflect the associative strength between the CS+ and the US (Bach et al., 2022; Vervliet & Boddez, 2020). Therefore, fear expressions should systematically change through manipulations of the contingency between the CS+ and the US, whereas responses to the unpaired CS- should result in low fear expressions. In all three studies, manipulation checks were carried out in order to test whether these expected effects were established. With regard to subjective ratings (i.e., US expectancy, fear, arousal, and valence), all three studies demonstrated successful acquisition and extinction of conditioned fear (see Chapter II.3.1, Chapter III.3.2, Chapter IV.3.2.1). With regard to SCRs, manipulation checks also suggested successful acquisition and extinction in Study 3 (laboratory subsample; see Chapter IV.3.2.1). In contrast, analyses on SCRs and FPSs during acquisition training in Study 2 did not reveal a differential rise of fear expressions to the CS+ compared to the CS- during acquisition training (see Chapter III.3.2). Consequently, in Study 2, SCRs and FPSs were not considered valid measures of the associative strength between the CS+ and the US and were therefore excluded from further analyses. However, whether these findings indicate that SCRs and FPSs were not indicative of associative learning in the present study or that the experimental manipulation was not sufficient to elicit conditioned responses in those psychophysiological variables, cannot be determined by the present data.

The use of aversive film clips in the present experiments derived from an attempt to investigate whether moderators of fear conditioning processes indirectly affect analog intrusions. This aligns with the assumption that the occurrence of intrusive re-experiencing after trauma relies, at least in part, on fear conditioning processes. Therefore, it was expected that the individual associative strength between the CS+ and the US after fear acquisition predicts subsequent analog intrusions. In accordance with this hypothesis, Study 1 provided evidence that fear, arousal, and valence ratings predicted intrusive re-experiencing (see Chapter II.3.4). Importantly, similar results were found when testing differential fear expressions (CS_{diff}), whereas CS- responses did not predict the occurrence of analog intrusions. The present findings, therefore, support the assumption that fear conditioning protocols can be valid translational models of associative memory processes related to PTSD. Despite the robustness of these findings across different indices of conditioned fear, US expectancy ratings did not correlate with analog intrusions. This discrepancy could be attributed to differences in assessment in Study 1, i.e., trial-wise vs. pre-to-post assessment.

Alternatively, rating measures are suggested to be susceptible to demand characteristics of the experiment (Lipp, 2006). That is, instructed fear acquisition protocols, such as the one used here, allow the participant to acquire a conscious awareness about the contingency after relatively few trials. Thus, a participant's response after explicitly asking about their US expectation could be particularly prone to effects of demand. This may also relate to descriptively lower variance found in US expectancy ratings compared to other subjective ratings (see Chapter II.4). While US expectancy is considered a valuable measure of associative strength during fear conditioning in general (Boddez et al., 2013), the present findings should be acknowledged and further investigated. Specifically, the findings could reflect multiple processes underlying conditioned fear acquisition that are, in the context of trauma exposure, not equally related to intrusion development.

2.2.2 Convergence and Divergence in Fear Conditioning Protocols with Multiple Outcome Measures

Within and across the three studies, multiple outcome measures were assessed during the conditioning phases. This common methodological approach reflects the attempt to observe learned fear in its various forms of responding (see Lang, 1968) in order to provide a more holistic understanding of the processes of interest. Yet the field of fear conditioning research is quite diverse in its preference for specific outcome measures and, to date, no consensus exists on whether there is a single, most ideal index of conditioned fear (Bach et al., 2022; Lonsdorf et al., 2017). It has therefore been a matter of debate if different outcome measures reflect different processes of fear conditioning and are therefore only comparable to a limited extent (see e.g., Blechert et al., 2008; Fanselow & Pennington, 2018; Hamm & Weike, 2005; LeDoux & Pine, 2016). If multiple outcome measures are assumed to reflect dissimilar processes during fear conditioning, these measures could be likely affected differently by experimental manipulation, leading to divergent results.

In the present dissertation, no specific hypotheses were defined according to different fear expressions. Therefore, all outcome measures should reflect the associative strength between the CS+ and the US and were expected to show sufficient convergence. In order to examine whether the present findings support this conceptualization, intercorrelations of post-acquisition differential fear expressions were calculated for the remote subsample included in Study 1 and 3. As can be seen in Table V-1, subjective fear and arousal ratings correlated highly, indicating good convergent validity (see Carlson & Herdman, 2012). Valence ratings further correlated moderately with fear and arousal ratings, whereas US expectancy intercorrelations where of a minor extent, indicating no sufficient convergence between US expectancy and the other three subjective ratings. Notably, this divergence between US expectancy and fear, arousal and valence could be observed throughout Study 1. That is, all

CS+ and CS_{diff} scores aside from US expectancy predicted analog intrusions and served as mediators in the relationship between COVID-19-related distress and analog intrusions (besides from CS_{diff} arousal scores; see Chapter II.3.4 and the Supplementary Materials). As described above, the divergence between US expectancy and the other ratings might be linked to methodological issues (e.g., trial-by-trial assessment, restricted variance, demand characteristics; see Chapter II.4 and Chapter V.2.1.2). Likewise, the present findings could suggest two distinct latent constructs underlying US expectancy in contrast to fear, arousal and valence. For instance, US expectancy could reflect associative learning, whereas fear, arousal and valence could reflect evaluative learning (see e.g., Constantinou et al., 2021; Öhman & Mineka, 2001). Considering this, the present findings might reflect dissimilar relationships between different indices of conditioned fear and intrusive re-experiencing. However, since no hypotheses according to different fear expressions were made, further confirmatory research would be needed to prove distinct effects of evaluative vs. associative learning in analog intrusion development.

Table V-1. Intercorrelations of post-acquisition differential fear expressions in the remote subsample included in Study 1 and 3.

Measures	1	2	3	4
1. Post-ACQ CS_{diff} Fear	-			
2. Post-ACQ CS_{diff} Arousal	*r* = .81 [+]	-		
3. Post-ACQ CS_{diff} Valence	*r* = -.63	*r* = -.55	-	
4. Post-ACQ CS_{diff} US expectancy[a]	*r* = .45 [-]	*r* = .37 [-]	*r* = -.42 [-]	-

Note. Interpretation of intercorrelations in brackets according to the benchmarks: [-] no sufficient convergent validity (<0.50), recommended convergent validity (≥0.70; see Carlson & Herdman, 2012). ACQ = Acquisition training; US = unconditioned stimulus; CS_{diff} = [CS+]–[CS-]. [a] Final trial of the acquisition training.

As shown in the present exemplary analysis, conditioned fear indices may diverge. In the context of sleep effects on fear conditioning processes, divergent outcomes regarding conditioned fear indices are not unusual. For instance, Straus et al. (2017) found better extinction recall in subjects who were well rested before extinction training in contrast to subjects who were sleep-deprived prior to extinction training. Notably, the authors found this effect only for FPS but not for subjective anxiety ratings. The present findings also showed divergent outcomes in Study 2. While exploratory results indicated that REM sleep plays a role in subjective fear, no effects were found in US expectancy (see Chapter III.2.4). Again, these findings could either be attributed to methodological issues in assessing US expectancy or they could reflect differential effects of REM sleep on different latent processes underlying extinction training. However, since no a-priori hypotheses were specified according to different conditioned fear indices, this divergence rather challenges the robustness of the current finding on REM sleep and extinction learning.

2.2.3 Examining the Internal Consistency of Fear Expressions

Internal consistency is conceptualized as the extent to which the items of a test measure the same construct (Revelle, 1979). High internal consistency indicates low measuring error by maximizing the shared variance between items that is assumed to display the 'true score' of a latent variable (Cortina, 1993; Moriarity & Alloy, 2021). In fear conditioning paradigms, fear expressions should reflect the associative strength between the CS+ and the US changing through experimental manipulations of the CS-US contingency (Bach et al., 2022; Vervliet & Boddez, 2020). For this dissertation, internal consistency of fear expressions during acquisition and extinction training was evaluated using the methodological approach by Klingelhöfer-Jens et al. (2022).[22] Overall, the results (presented in Table V-2) indicated satisfactory internal consistency for subjective outcomes in all samples and studies, ranging from acceptable to excellent (see Kline, 2013). With regard to SCRs, the analyses indicated acceptable to excellent internal consistency for measuring CS+ and CS-, whereas Pearson's correlation coefficients for differential fear expression (i.e., CS_{diff}) during both acquisition and extinction training could be considered unacceptable. As such, the present findings suggest generally robust internal consistency of fear and US expectancy ratings as well as SCRs within acquisition and extinction training.

One notable exception concerns the internal consistency of the CS_{diff} scores in SCR in Study 3 (laboratory subsample), which indicate low precision in measuring the associative strength between the CS+ and the US. This is of importance since, in Study 3, the main research question was tested by means of examining CS_{diff} scores (see Chapter IV.3.2.1). This methodological approach is based on previous research (see Pace-Schott, Rubin, et al., 2015). Furthermore, CS_{diff} scores in US expectancy did not suggest any divergent results at retention or renewal test in Study 3. Notwithstanding, the current findings limit the interpretation of the findings in Study 3 based on SCR. Notably, these findings reflect the results of a previous investigation. That is, Klingelhöfer-Jens et al. (2022) reported internal consistency for CS+ and CS- ranging between acceptable and good, whereas internal consistency for CS_{diff} during acquisition and extinction training were considered poor to unacceptable. This may be related to the fact that difference scores have less meaningful variance than the raw variables on which they were built (see Klingelhöfer-Jens et al., 2022; Moriarity & Alloy, 2021). However, internal consistency was low for differential scores of SCRs but not for US expectancy or fear ratings (see Table V-2). Whether these findings indicate that SCRs may be more sensitive to the described reduction in meaningful variance cannot be determined by the present data.

[22] Internal consistency of fear expressions during the conditioning phases was calculated with the odd-even approach, which builds on the assumption that adjacent trials during acquisition/extinction training should be more similar than nonadjacent trials (see Klingelhöfer-Jens et al., 2022). For each individual, phase and CS type, odd and even trials were averaged and Pearson's correlation coefficients between odd and even trials were calculated. Due to the different number of measurements, internal consistency calculation was restricted to outcomes that were assessed trial-by-trial during acquisition and extinction training.

Table V-2. Internal consistency of fear conditioning outcomes during acquisition and extinction training

Outcome measure	Sample (Study)	Phase	CS type	Internal consistency[a]	95% CI lower	95% CI upper	Interpretation[b]
US expectancy rating	Remote (Study 1 & 3)[c]	Acquisition training[d]	CS+	0.87	0.82	0.91	Good
			CS-	0.96	0.94	0.97	Excellent
			CS_{diff}	0.93	0.91	0.95	Excellent
		Extinction training[e]	CS+	0.97	0.96	0.98	Excellent
			CS-	0.90	0.86	0.93	Excellent
			CS_{diff}	0.95	0.93	0.97	Excellent
	Laboratory (Study 3)	Acquisition training[d]	CS+	0.73	0.60	0.82	Acceptable
			CS-	0.91	0.86	0.94	Excellent
			CS_{diff}	0.89	0.82	0.93	Good
		Extinction training[e]	CS+	0.97	0.95	0.98	Excellent
			CS-	0.96	0.94	0.98	Excellent
			CS_{diff}	0.96	0.94	0.98	Excellent
Fear rating	Laboratory (Study 2)	Acquisition training	CS+	0.99	0.98	0.99	Excellent
			CS-	0.98	0.97	0.99	Excellent
			CS_{diff}	0.98	0.96	0.99	Excellent
		Extinction training	CS+	0.99	0.99	0.99	Excellent
			CS-	0.99	0.99	0.99	Excellent
			CS_{diff}	0.99	0.99	0.99	Excellent
SCR	Laboratory (Study 3)	Acquisition training[d]	CS+	0.91	0.86	0.95	Excellent
			CS-	0.76	0.64	0.84	Acceptable
			CS_{diff}	0.37	0.14	0.56	Unacceptable
		Extinction training[e]	CS+	0.84	0.76	0.90	Good
			CS-	0.77	0.66	0.85	Acceptable
			CS_{diff}	0.20	-0.04	0.41	Unacceptable

Note. CS = conditioned stimulus; CI = confidence interval; US = unconditioned stimulus; SCR = skin conductance response; ROF = return of fear; CS_{diff} = [CS+] – [CS-]. [a] Pearson's correlation coefficients (*r*) between averaged odd and even trials reflecting internal consistency. [b] Interpretation of internal consistency scores according to the benchmarks: unacceptable (<0.50), poor (0.50-0.59), questionable (0.60-0.69), acceptable (0.70-0.79), good (0.80-0.89); excellent (≥0.90; see Kline, 2013). [c] In Study 1, only acquisition trials were analyzed. [d] Fear expressions during acquisition training were averaged across CS+ type ($CS+_E$, $CS+_U$) or Block ($CS-_1$, $CS-_2$). [e] Fear expressions during extinction training include $CS+_E$ and CS-.

2.3 The Effect of Sleep on Extinction Learning and Consolidation

2.3.1 Slow Wave Sleep Effects on Subsequent Extinction Learning

One major aim of the present dissertation was to investigate whether SWS-rich sleep prior to extinction training has a beneficial impact on extinction learning. In Study 2, this was tested by contrasting sleep with prolonged wakefulness during the early night half and examining fear expressions at subsequent extinction training, ROF test and retention test. The results did not confirm this hypothesis. That is, no effects of experimental group were found at any conditioning phase. Likewise, no group effects emerged for intrusion frequency during the IPT.

Hence, Study 2 did not suggest a diminishing effect of sleep on analog intrusions originating from enhanced fear extinction. The present findings differ from previous research, showing that sleep, compared with sleep deprivation, promotes subsequent learning and retrieval, which has been robustly shown for declarative and procedural memory (Newbury et al., 2021). As for fear extinction, however, research has provided mixed evidence regarding the role of preceding sleep. One study showed that pre-extinction sleep, in contrast to sleep deprivation, facilitated extinction recall (Straus et al., 2017). Another study did not report any effects of a daytime nap, compared with wakefulness, at extinction or reacquisition training (Pavlov et al., 2022). It should be noted that methodological differences between the studies limit the comparability of the present results and existing research, for example due to differing outcome measures or differing sleep manipulations. Nevertheless, the current findings provide important information as they challenge the assumption that sleep during the early night half, in contrast to prolonged wakefulness, is beneficial for subsequent extinction learning.

Study 2 was particularly focused on investigating extinction learning and recall after sleep that is rich of SWS. In line with the main results, secondary correlation analyses in the sleep group did not suggest an association between pre-extinction SWS amount or the number of slow waves and subsequent performance during extinction training, ROF test or retention test. These findings are contrary to former research, suggesting a role of SWA, in particular, for encoding (e.g., Antonenko et al., 2013; Nissen et al., 2021; Van Der Werf et al., 2009; but see Mander et al., 2011, for contrasting findings). In terms of fear extinction, a recent meta-analysis did not find an association between the amount of SWS and the efficacy of fear extinction (Schenker et al., 2021). Notably, the authors did report that less SWS and more N2 sleep were associated with higher SCRs for CS- at extinction training. Further sub-analyses, however, suggested effects only in clinical populations with PTSD or insomnia, whereas no significant effects of single sleep stages were found in healthy participants. Moreover, it should be noted that the calculated effects were built on very few studies (i.e., $k = 5$ for samples of healthy participants and $k = 2$ for clinical populations; see Schenker et al., 2021). In contrast to the hypothesis that particularly SWS promotes subsequent extinction learning, secondary correlation analyses revealed a positive relationship between REM sleep and the success in extinction learning. This aligns with previous findings suggesting that REM sleep, instead of SWS, might be critical for sleep-dependent encoding (e.g., Cousins et al., 2018; but see Kaida et al., 2015; Mander et al., 2011). Regarding extinction learning, however, the meta-analysis by Schenker et al. (2021) did not show a significant correlation between pre-extinction REM sleep and subsequent extinction performance. Taken together, the present results suggest that SWS-rich sleep does not affect subsequent extinction learning. Exploratory correlation analyses further indicated no association between the amount of SWS and subsequent performance during extinction training, which aligns with the findings from a recent meta-

analysis (Schenker et al., 2021). In contrast to the meta-analytic findings as well as our a-priori hypothesis, the analyses suggested that pre-extinction REM sleep could be positively associated with successful fear extinction.

The hypothesis that early night sleep promotes extinction learning was based on the assumptions of the SHY (Cirelli & Tononi, 2022; Tononi & Cirelli, 2003). The SHY proposes that prolonged wakefulness deteriorates learning capacities, whereas sleep restores these capacities by synaptic down-selection and by re-building cellular functions. While the latest version of the SHY (Cirelli & Tononi, 2022) suggests that both NREM and REM sleep could contribute to synaptic renormalization, it emphasizes the role of SWA. Therefore, Study 2 contrasted prolonged wakefulness with sleep during the early night half, in which the amount of SWS is typically highest (Yaroush et al., 1971). The absent group effects in fear expressions and intrusion frequency in Study 2 do not support the hypothesis that SWS-rich sleep promotes extinction learning. Several explanations may account for this null effect. First, extinction learning, as a unique form of implicit non-declarative emotional memory, might be unaffected by sleep-dependent synaptic down-selection (and potentially also by synaptic saturation during wakefulness, in the first place). This may explain why the current evidence for an impact of sleep on subsequent fear extinction is rather mixed (see e.g., Pavlov et al., 2022; Schenker et al., 2021; Straus et al., 2017), whereas empirical findings have brought robust evidence for sleep-dependent encoding of declarative and procedural memory (Newbury et al., 2021). In contrast, it is assumed that synaptic plasticity is a universal mechanism in memory formation (Magee & Grienberger, 2020), suggesting that the assumptions of the SHY should also apply on fear extinction (Pace-Schott, Germain, et al., 2015).

Second, the null results in terms of sleep manipulation may point towards a more prominent role of REM sleep, rather than SWS, in synaptic down-selection. This aligns with the exploratory finding that the amount of pre-extinction REM sleep was positively related to fear extinction success in Study 2. In fact, several recent conceptualizations of sleep-dependent synaptic renormalization propose a role of both NREM and REM sleep (Cirelli & Tononi, 2022; Navarro-Lobato & Genzel, 2019; Niethard & Born, 2019). A prominent perspective (see Niethard & Born, 2019) on how SWS and REM sleep could contribute to restoring synaptic plasticity, is that depending on previous neuronal activity, synaptic strength could be either strengthened or weakened (or remain unchanged) during SWS. During REM sleep, however, synaptic weakening is assumed to be more widespread. In accordance with the ASCT (Diekelmann & Born, 2010; Klinzing et al., 2019), the synapses that are strengthened during NREM sleep are considered to be protected from weakening in the subsequent REM phase (Niethard & Born, 2019). As a result, the succession of NREM and REM sleep allows for selectively sustaining newly encoded information and restoring synaptic plasticity, allowing optimal information processing during wakefulness. This may explain why, in Study 2, REM

sleep was associated with higher rates of extinction learning while the overall amount of REM sleep during the early night half was low.

Third, the present findings should be also reflected in the context of theoretical accounts questioning the assumptions of the SHY (see e.g., Frank, 2011; 2021; Puentes-Mestril & Aton, 2017). For instance, while there is evidence for a beneficial effect of sleep on subsequent cognitive performance during wakefulness, clear evidence that this effect can be attributed to the mechanisms proposed by the SHY is currently lacking (Puentes-Mestril & Aton, 2017). Therefore, the manipulation of sleep in Study 2 may not have targeted the mechanisms that are causally related to restoring capacities necessary for extinction learning. Another explanation for the present results is that a sufficient amount of REM sleep is necessary for promoting efficient fear extinction by facilitating the regulation of fear rather than through weakening net synaptic strength. Nevertheless, it is important to note that no general effect of sleep was found in Study 2. Therefore, further studies are necessary to examine whether these exploratory findings on REM sleep effects are robust and of significance.

2.3.2 Slow Wave Sleep Effects on Extinction Consolidation

A major research goal of this dissertation was to investigate the role of SWS in extinction consolidation. Study 3 investigated whether boosting SWS has a beneficial impact on extinction recall by contrasting sleep-directed hypnosis, designed to increase SWS, with normal nighttime sleep after extinction training. In contrast to the hypothesis of this study, no group effects were found in subjective and psychophysiological indices of conditioned fear for $CS+_E$ during retention and renewal test. Thus, the current findings suggest that sleep-directed hypnosis does not facilitate extinction consolidation during sleep and therefore does not lead to improved extinction recall and stronger resistance to ROF. Furthermore, sleep-directed hypnosis, compared to the control condition, did not affect indices of conditioned fear for $CS+_U$, whereas fear expressions were higher in presence of the $CS+_U$ compared to $CS+_E$ during retention test irrespective of the experimental group. These findings align with the conceptual distinction of fear and extinction recall (Milad et al., 2007). However, they do not indicate effects of sleep manipulation on any of these processes. Finally, no effects of group were found for analog intrusions and rumination. Whether the results of Study 3 reflect contradictory evidence against an effect of enhanced SWS on extinction consolidation, cannot be established by the current findings since the experimental manipulation (i.e., hypnosis vs control condition) did not result in significant group differences in SWS parameters. Previous research suggests that interventions stimulating SWS can improve subsequent memory performance (Zhang & Gruber, 2019), though the effects are suggested to be small (Wunderlin et al., 2021). With regard to sleep-directed hypnosis, however, former research did not indicate improved memory performance (Cordi et al., 2014) or even suggest detrimental effects (Cordi et al.,

2020). Hence, it is unclear whether sleep-directed hypnosis, which would have had a significant effect on SWS, would result in improved extinction recall.

To date, it is assumed that sleep promotes the consolidation and generalization of fear extinction and both SWS and REM sleep are supposed to be involved in these processes (Pace-Schott et al., 2023). None of the studies presented in this dissertation contrasted sleep with wakefulness after extinction training. It is therefore not possible to use the present findings to draw conclusions on the effect of sleep as such. Nevertheless, the results of Study 2 and 3 are of interest in terms of interindividual differences in sleep stage characteristics and their relevance for subsequent extinction recall. In Study 2, due to the experimental manipulation (sleep vs. wakefulness) targeting the early night half, the two groups showed significant differences in their sleep architecture during the second night half. In particular, the sleep group had less SWS and higher REM sleep amounts than the wake group. With respect to behavioral parameters, no differences between groups were found at subsequent retention test or during the IPT. In Study 3, the experimental manipulation did not result in SWS effects while the groups showed differences in their amount of REM sleep. Specifically, the hypnosis group showed less REM sleep compared to the control group in the laboratory subsample. As in Study 2, however, no effects of group were found in extinction recall or generalization as well as for intrusion or rumination indices. Furthermore, secondary analyses on post-extinction SWS amounts and performance at retention and renewal test did not reveal any associations between SWS and extinction recall in the laboratory subsample. With that, the findings from Study 2 and 3 do not suggest an effect of specific sleep stages on extinction consolidation and recall. This corresponds to the findings of a recent meta-analysis, which did not reveal any robust associations between post-extinction sleep and extinction recall (Schenker et al., 2021). Notably, further sub-analyses of the meta-analysis pointed towards an association between the amount of REM sleep and subsequent extinction recall that is moderated by sex. It is important to note that the interpretation of findings from Study 2 and 3 in terms of relationships between sleep stages and markers of extinction recall is foremost post-hoc and therefore limited. However, the overall lack of group effects in Study 2 and 3 do not suggest an association between different sleep stage amounts and extinction recall.

The assumption that SWS is critical for the consolidation and recall of fear extinction is based on the ASCT (Diekelmann & Born, 2010; Klinzing et al., 2019). According to this account, sleep promotes the strengthening and integration of newly encoded memories into pre-existing long-term memory storage. SWS in particular is supposed to be crucial in this process by actively supporting the reactivation and redistribution of memory representations across neuronal networks. Corresponding to this account, research has shown that early night sleep, which is rich of SWS, but not late night sleep, which has low amounts of SWS, promotes memory consolidation (see Cordi & Rasch, 2021a; Rasch & Born, 2013). Based on this

research, it was hypothesized that higher amounts of SWS facilitate the consolidation of previously encoded extinction memories, which should manifest in a positive relationship between SWS and extinction recall. In contrast to this hypothesis, both Study 2 and 3 do not indicate a significant correlation between SWS amounts and subsequent extinction recall. Notably, some large-scale studies (Ackermann et al., 2015; Cordi & Rasch, 2021b) likewise did not report significant correlations between the amount of SWS or SWA and subsequent memory performance, suggesting that more SWS not necessarily leads to improved memory retention (Cordi & Rasch, 2021a). In accordance with this, previous studies on sleep-directed hypnosis showed increased SWS and SWA but no improvement in memory retention (Cordi et al., 2014; 2020). A recent study (Beck et al., 2021) thus investigated the impact of sleep-directed hypnosis on sleep microarchitecture and showed that while sleep-directed hypnosis increases SWA, it did not affect the amount of sleep spindles. Sleep spindles, however, are central to sleep-dependent memory consolidation (Kumral et al., 2023). According to the ASCT (Diekelmann & Born, 2010; Klinzing et al., 2019) slow wave-spindle coupling is supposed to be a key mechanism of systems consolidation during sleep. Therefore, the fact that SWS was not associated with extinction recall in Study 2 and 3 may point toward a more complicated role of SWS and SWA in systems consolidation.

The hypothesis that enhanced SWS could facilitate extinction consolidation and, as a consequence, extinction recall is countered by accounts proposing that REM sleep rather than SWS is central to sleep-dependent consolidation of fear extinction (e.g., Colvonen, Straus et al., 2019; Davidson & Pace-Schott, 2020; Pace-Schott, Germain, et al., 2015). These accounts are originally based on the assumption that distinct mechanisms of sleep-dependent consolidation exist for different memory systems and that emotional memories are predominantly processed during REM sleep (see Pace-Schott, Germain, et al., 2015). Specifically, it has been argued that REM theta activity promotes emotional memory (including extinction memory) consolidation by facilitating synchronized activation of the amygdala, hippocampus, and vmPFC (Genzel et al., 2015). However, it should be noted that neuronal memory reactivations, as indicated by ripple activity in the hippocampus *and* the amygdala, were reliably found during NREM sleep but not during REM sleep in animal studies (Trouche et al., 2020). In line with this, first evidence exists for coordinated amygdala-hippocampal ripple activity during NREM sleep in humans (Cox et al., 2020). With regard to behavioral studies of sleep effects on fear extinction, some reported evidence is in line with a specific role of REM sleep in extinction consolidation and recall (Menz et al., 2016; Spoormaker et al., 2012). However, no robust relationship between REM sleep amounts and subsequent extinction recall was found in a recent meta-analysis (Schenker et al., 2021). It should, however, be considered that further sub-analyses in this meta-analysis pointed towards a relationship between REM sleep and extinction recall moderated by sex. In both Study 2 and Study 3 (laboratory

subsample), post-extinction REM sleep amounts differed between groups. Analyses of extinction recall, however, did not reveal any significant differences between groups. These findings do not support a role of REM sleep in extinction consolidation. However, when interpreting the present data, it should be noted that neither Study 2 nor Study 3 were designed to investigate REM sleep effects and no a-priori hypotheses were made for this purpose. Fear expressions at retention test and analog intrusions and rumination were found independent of any between-group differences in post-extinction sleep architecture in Study 2 and 3; these findings contradict the hypothesis of sleep-dependent extinction consolidation. This is of importance, since, in contrast to the abundant evidence supporting sleep-dependent consolidation of declarative and procedural memory (e.g., Hu et al., 2020; Newbury et al., 2021; Schimke et al., 2021; Schmid et al., 2020), evidence for sleep-dependent consolidation of fear extinction is rather mixed (e.g., Menz et al., 2013; Pace-Schott et al., 2009; Schenker et al., 2021; Straus et al., 2017). Therefore, it should be also taken into consideration that it has yet to be proven if extinction memories undergo a consolidation process which necessitates sleep.

3. Limitations and Outlook

3.1 Study 1

In Study 1, COVID-19-related distress and rumination were assessed in order to estimate the interindividual stress elicited by the COVID-19 outbreak. This was done by means of questionnaires, modified to the specific circumstances of the COVID-19 pandemic and successfully used in a previous investigation (see Schäfer et al., 2020). The assessment did not include a detailed evaluation of the stressor per se. More specifically, information about the perceived intensity, timing and duration of the stressor is lacking. Previous research, however, suggests that these parameters are important moderators of the effect of stress on fear conditioning processes (Merz et al., 2016). Furthermore, whether the participants were exposed to pandemic-related trauma, e.g., sudden loss of a loved one by a COVID-19 infection, was not recorded systematically. Therefore, it is not possible to distinguish between distress occurring as a response to a large-scale psychosocial stressor and distress occurring in conjunction with an additional traumatic stressor. Finally, no correlates of (neuro)biological stress responses were assessed alongside the psychological stress responses. The effect of stress on conditioned fear acquisition, however, is supposed to be driven by alterations in the neuronal fear conditioning circuitry due to stress hormones (de Quervain et al., 2017; Pitman et al., 2012). Hence, the interpretation of the findings in terms of the mechanisms by which stress may have influenced information processing during the acquisition training and exposure to the aversive film clip is limited. Related to this, no causality is established for the

relationship between stress responses related to the COVID-19 outbreak and conditioned fear acquisition based on the present methods of Study 1. That is, COVID-19-related distress and rumination as well as indices of conditioned fear were assessed in a cross-sectional design. Therefore, it is not possible to draw strong conclusions on the direction of the effect. This is of importance since research has also provided support for the hypothesis that a disposition to stronger conditioned fear acquisition could result in higher sensitivity to stressors, such as the COVID-19 pandemic (see Hunt et al., 2022). Future studies should address these issues, for instance, by means of a cross-lagged panel design including psychological and (neuro)biological correlates of stress caused by an experimental stress induction and indices of conditioned fear that are sensitive to interindividual differences in the associative strength of CS-US associations.

Another limitation of Study 1 concerns the role of conditioned fear acquisition as a potential pathogenic process. Accumulating evidence suggests impairments in safety learning and extinction rather than enhanced conditionability as specific features of anxiety disorders and PTSD (Duits et al., 2015; Lissek & Van Meurs, 2015; Scheveneels et al., 2021). However, it is difficult to disentangle acquisition and retention of conditioned fear, and the latter could contribute to deficits in extinction learning and recall (Lissek & Van Meurs, 2015). Furthermore, previous analog studies on fear conditioning and intrusions have consistently shown that intrusions are linked to fear expressions in response to the CS+ (see Espinosa et al., 2022; Franke et al., 2021; Streb et al., 2017; Wegerer et al., 2013). In correspondence with this, the findings of Study 1 indicate a positive relationship of analog intrusions with CS+ as well as $CS_{\mathbf{diff}}$ responses but not with CS- responses. Whether this relationship is of relevance for persistent intrusive re-experiencing, however, cannot be determined by the present data. A recent study (Franke et al., 2021), for instance, showed a positive correlation between conditionability and intrusions after acquisition training, but this relationship turned negative when the individuals subsequently underwent extinction training. Thus, further research is needed to examine which mechanisms determine (mal-)adaptive processing of aversive events. Specifically, future studies should investigate the relationship between conditioned fear acquisition, safety learning, and extinction as well as intrusion development. Such studies may use the fear conditioning protocol from Milad et al. (2007) to disentangle fear from extinction recall and their association with (analog) PTSD symptoms. Furthermore, future studies may examine the association between fear conditioning processes and (analog) intrusions for a longer period of time (see Espinosa et al., 2022, for an example).

3.2 Study 2

In Study 2, sleep was manipulated before extinction training in the middle of the night. While the sleep group had a 3-hour sleep opportunity during the early night half, the wake group

remained awake during this time period. This experimental design was chosen in order to contrast SWS-rich sleep with prolonged wakefulness before extinction learning. There are several potential confounds regarding the sleep manipulation that should be considered. First, although the first hours of sleep are typically dominated by SWS, sleep also consists of other sleep stages, which alternate in cycles across night-time (Dijk, 2009; Shrivastava et al., 2014). Hence, drawing conclusions on mechanisms specific for a single sleep stage is limited. Second, the wake group was partially sleep deprived during the early night half. Sleep deprivation is linked to detrimental effects on attention and working memory (Krause et al., 2017), which might have influenced the performance of the wake group during extinction training and subsequent ROF test. Indeed, the wake group showed significantly higher sleepiness, but no decrements in psychomotor vigilance during the second and third experimental session in comparison with the sleep group. Though secondary analyses did not suggest that sleepiness had a substantial impact on extinction learning, such effects cannot be fully ruled out by the present data. Third, sleep architecture is strongly influenced by accumulating sleep pressure (Borbely et al., 2016; Dijk, 2009). Correspondingly, the wake group, which had its earliest sleep opportunity at approximately 3 AM, had comparable amounts of SWS to the sleep group during their earliest sleep opportunity at approximately 11 PM. This, however, had an effect on the sleep architecture during the late night half, resulting in differences in the relative amount of SWS, REM sleep and N2 sleep between the experimental groups. This constitutes a constraint in the interpretation of retention test performance as well as analog intrusions during the IPT, since research indicates that sleep, and particularly REM sleep, plays a role in the consolidation of conditioned fear (e.g., Marshall et al., 2014; Menz et al., 2013; but see Davidson et al., 2016). Moreover, this limits comparability of the data from Study 2 with the findings of Straus et al. (2017), who implemented a full recovery night in all experimental groups before testing extinction recall. Another limitation when comparing the results of Study 2 with previous findings concerns psychophysiological measures. For example, in Study 2, manipulation checks did not support successful differential fear acquisition in both experimental groups and no further analyses were performed. Consequently, it was not possible to test if sleep, compared with wakefulness, facilitates extinction recall specifically in FPS responding, as has been shown by Straus et al. (2017). However, the present data did replicate the findings of Straus et al. (2017) as well as Pavlov et al. (2022) by showing no effects of sleep manipulation on subjective indices of extinction recall. Finally, a limitation that should be considered when interpreting the results of Study 2 regards the relationship between REM sleep amount and fear ratings during extinction training. The study was designed in order to investigate sleep that is rich of SWS and is, therefore, not well suited to examine effects of REM sleep. Furthermore, the analyses of sleep stage effects on extinction learning were made on an exploratory basis. Therefore, further

confirmatory research is needed to replicate the present findings. Future investigation of REM sleep effects, for instance, could contrast sleep with wakefulness during the late night half, which is rich of REM sleep (Dijk, 2009; Shrivastava et al., 2014), and test whether this manipulation influences performance during extinction training and subsequent retention test.

3.3 Study 3

In Study 3, sleep after extinction training was manipulated by means of a hypnotic suggestion designed to induce more SWS and was compared to a control condition, in which participants listened to a neutral control text before sleep. This hypnotic suggestion has been shown to reliably increase SWS and SWA during NREM sleep (Cordi et al., 2014; 2015; 2020). Since it was hypothesized that sleep-directed hypnosis facilitates extinction recall indirectly by enhancing SWS-dependent consolidation of extinction memory, it was a necessary precondition to replicate the findings from Cordi and colleagues. The present results of Study 3, however, deviate from their results in multiple ways. First, no differences between the experimental groups were found in the amount of SWS or relative SWA power. Previous findings suggest that the effect of hypnosis is most prominent in the first sleep cycle (see Cordi et al., 2020), but no effect was evident in analyses performed over the whole sleep phase as well as during the first hour of the night. Hence, Study 3 failed to replicate the effect of boosted SWS through sleep-directed hypnosis. In contrast to our hypothesis as well as the findings from Cordi et al., the hypnosis group had less REM sleep. Second, based on previous research, it was expected that the effect of the hypnotic suggestion is restricted to highly hypnotizable individuals (see Cordi et al., 2014; 2015; 2020). Therefore, only highly hypnotizable participants were included in the laboratory subsample of Study 3 (see Besedovsky et al., 2022, for a similar account). In the remote subsample, also less hypnotizable participants were included in order to increase the sample size. Analyses on whether hypnotizability may have influenced the outcomes of the remote subsample did not reveal effects of hypnotizability, which can be considered a shortcoming of the study as it did not replicate the findings of Cordi et al. (2014; 2015; 2020). It should be noted that the majority of participants in the remote subsample were highly hypnotizable, which may have prevented us from finding an effect of hypnotizability. Notwithstanding, these deviations restrain the interpretation of the present data in terms of effects of sleep-directed hypnosis as a potential intervention to enhance extinction recall. Furthermore, since no differences between experimental groups were found in SWS, no conclusions on the role of SWS in extinction consolidation and recall can be drawn on the basis of between-group comparisons. The analyses unexpectedly revealed a difference in REM sleep amount between the two groups. Since none of the previous studies on sleep-directed hypnosis have reported effects on REM sleep parameters (see Cordi et al., 2014; 2015; 2020) and no a-priori hypothesis was

formulated regarding REM sleep, the interpretation of REM sleep effects in Study 3 should be made with caution. Another point that should be considered in the interpretation of the present findings is that the study design did not include a wake control group. Therefore, Study 3 does not provide any information on whether sleep, in general, affects subsequent extinction recall. Finally, Study 3 combines data of two subsamples, which include different individuals at different time points and partly deviating methods. For instance, data of the remote subsample was collected in early 2020, data of the laboratory subsample was collected in 2021. As has been indicated by Study 1, the COVID-19 outbreak in early 2020 might have had an impact on fear conditioning processes. Furthermore, secondary analyses on subjective sleep quality showed that the remote subsample had higher subjective sleep quality than the laboratory subsample (see Supplementary Materials). This finding does not correspond with recent meta-analytic evidence on the impact of the COVID-19 outbreak on sleep quality (e.g., Limongi et al., 2023). It may, however, reflect considerable variance in the size and direction of the effect depending on pre-pandemic sleep quality (see Kocevska et al., 2020). Most importantly, the effect of subsample did not interact with the effect of sleep-directed hypnosis on subjective sleep quality. In order to account for variability between subsamples, LMM analyses were performed including subsample as random effect. Moreover, additional analyses were carried out for all main results with subsample and its interactions as fixed effects. These analyses revealed mostly consistent results between the remote and the laboratory subsample. The fact that sleep-directed hypnosis did not increase SWS parameters strictly limits the interpretation of Study 3 and challenges the robustness of the intervention's effect in general. Future studies, including at other labs, should aim to replicate the findings by Cordi et al. (2014; 2015; 2020). Furthermore, future studies may investigate the effect of other interventions boosting SWS on extinction recall, such as phase-locked acoustic stimulation, which is considered a promising tool to target sleep-dependent memory consolidation (Wunderlin et al., 2021).

3.4 Further Considerations on the Experimental Investigation of Sleep Effects on Fear Extinction

Besides the limitations specific to the methodology of the respective experiment, there are several other important limitations which address more general aspects of experimental research on fear conditioning processes and sleep-dependent memory processing. The three studies presented here investigated implicit associative learning processes that are assumed to underlie the development of (pathological) anxiety. Fear conditioning protocols model these processes in well controlled designs with generally high internal validity (Scheveneels et al., 2021). In Chapter V.2.2, the present findings were discussed with regard to certain aspects of validity and reliability. Overall, the data suggest successful manipulation of the strength of the CS-US association during acquisition and extinction training in all three studies (but see

Chapter V.2.2.1, for deviating results in SCR and FPS in Study 2). Analyses of internal consistency further indicated reliable measurement of associative strength by the present variables (besides from SCR for CS_{diff} in Study 3, see Chapter V.2.2.3). Moreover, evaluation of convergent validity between the outcome measures suggest satisfactory convergence for most of the variables. Notably, US expectancy did not correlate with analog intrusions and did not converge with other indices of conditioned fear in Study 1, indicating that US expectancy might represent a latent construct different from the other subjective ratings. These findings emphasize the need for making a-priori hypotheses on whether the investigated variables measure the same or different forms of conditioned fear (see Lonsdorf et al., 2017). Common research approaches, however, are using multiple outcomes interchangeably to assess the same latent construct (Bach et al., 2022), which makes it difficult to interpret findings diverging between outcome measures. As noted in Chapter V.2.2.2, this also applies to investigations of sleep effects on fear extinction including the present studies, and may explain the heterogeneous evidence in this research field. Future studies should report a-priori decisions, which outcome measures will be used, and what latent construct(s) they are assumed to reflect. Furthermore, other studies may also report retrospective evaluation of validity and reliability of the collected data to inform theoretical models and inspire future confirmatory research (Constantinou et al., 2021).

Another point that should be considered when interpreting fear conditioning data is whether the present findings can be translated to pathological fear and its recovery. In order to increase ecological validity of memory processes during and after trauma (Ney et al., 2022), the fear conditioning protocol was modified by using naturalistic stimuli as CS and highly aversive film clips as US. In all experiments, participants reported intrusive memories of the US that was presented during acquisition training. Furthermore, analog intrusions in Study 1 were predicted by the strength of fear associations, indicating overall sufficient validity in measuring the construct of associative learning during and after analog trauma. Nevertheless, transfer to real-life trauma and PTSD is limited as the present results are based on examinations of analog symptoms from healthy, individuals without prior trauma exposure. Future research should also test if the effects proposed here can be examined in different kinds of samples, including individuals with lifetime trauma exposure with and without PTSD. Moreover, fear conditioning protocols are criticized for being too simplistic for the aim of modeling memory processing during and after trauma (see Bienvenu et al., 2021; Dunsmoor et al., 2022). This, on the one hand, concerns processes of fear conditioning itself, which are less commonly investigated (e.g., retrospective revaluation) and, on the other hand, processes that are related to fear conditioning but not well addressed by the current paradigms (e.g., episodic memory or emotion regulation; Dunsmoor et al., 2022; Dunsmoor & Kroes, 2019).

Future research may construct new analog designs that address fear conditioning in real-life more holistically.

Another important aspect that should be considered here is that while Study 2 and 3 were based on assumptions of sleep-dependent memory processing, several related research questions remained unaffected by these studies. For example, neither Study 2 nor Study 3 did investigate if sleep, in general, promotes extinction memory processes. This, however, is of importance since research has to date brought mixed evidence regarding sleep effects on extinction learning (see Chapter I.3.2) as well as on extinction consolidation (see Chapter I.3.4). The present studies attempted to test effects of SWS in particular. That is, in Study 2 sleep was contrasted with wakefulness during the early night half before extinction training, since SWS is typically dominant in the first sleep cycles (Dijk, 2009). In Study 3, night-time sleep was manipulated by a hypnotic suggestion, designed to increase SWS and SWA during sleep (Cordi et al., 2014), and was contrasted with a control condition without hypnotic suggestion after extinction training. If the manipulation is successful, such designs allow for investigating effects that are assumed to reflect processes underlying sleep-dependent encoding or consolidation. However, even if Study 2 and 3 had brought evidence in favor of the hypotheses that SWS promotes extinction learning and recall, whether these effects emerged from the specific processes that have been theoretically assumed would still have remained elusive. Future research may target these processes more directly. For instance, in order to investigate the assumptions of the SHY in the context of fear conditioning processes, future studies could use interventions to boost SWA (such as the one used in Study 3, or alternative forms, e.g., Antonenko et al., 2013) before extinction training.

Alternatively, studies could investigate if the capacity for extinction learning varies along with net synaptic strength. In fact, previous research has indicated facilitated extinction learning in the morning (Pace-Schott et al., 2013) and suggested that the relationship between fear extinction and PTSD symptoms is moderated by the time of day at which extinction training was scheduled (Zuj, Palmer, Hsu et al., 2016). However, it is complicated to disentangle effects of time awake from circadian factors such as cortisol, which are also assumed to influence extinction learning (Lass-Hennemann & Michael, 2014; Pace-Schott, Germain, et al., 2015). With respect to the assumptions of memory consolidation during sleep, few studies have investigated the mechanisms specific to the ACST in the context of fear conditioning (Ai et al., 2015; Hauner et al., 2013; He et al., 2015). These studies rely on ‘targeted memory reactivation’ (TMR; see Rasch et al., 2007; Schouten et al., 2017), which uses sensory stimuli as cues that were previously associated with newly learned information as targets and represent these cues during sleep in order to bias neuronal reactivation of the associated targets. A recent meta-analysis demonstrated that TMR during SWS significantly improved declarative and procedural memory retrieval during subsequent wakefulness (Hu et al., 2020).

As a first study, Ai et al. (2015) carried out a TMR protocol in which a tone was intermittently presented during the extinction training, serving as an auditory contextual stimulus. Subsequently, the sleep groups received a nap opportunity during which the same tone, an unknown tone, or no tone was presented during SWS; similar stimulus conditions were further applied to three wake control groups. While the authors did not find any effects of sleep in comparison to wakefulness in general, the presentation of the contextual tone from extinction training was linked to higher differential fear in the sleep and lower differential fear in the wake group during retention test. These contradicting findings suggest that TMR during SWS interfered with extinction consolidation while it strengthened extinction recall in the wake group. However, it should be considered that the presentation of a contextual stimulus during extinction training but not during acquisition training and retention test could have provoked a contextual renewal, which may have confounded the effects.

In order to replicate the study by Ai et al. (2015) and to further investigate whether extinction memory undergoes consolidation during SWS, Study 4 was conducted.[23] During the acquisition training in Study 4, three different colored lamps (CS) were presented, of which two (CS+) were followed by an unpleasant electric stimulus (US). The CS were shown in a specific room and were accompanied by background sound, typical to the scenery (e.g., typing on a keyboard if the room showed a workspace), both serving as contextual details of the specific conditioning phase. In addition, the lamp turning on was accompanied by a short auditory cue, also semantically related to the context (e.g., sound of a phone ringing in the workspace scenery). The extinction training was divided into two phases with different contextual information and auditory cues, in which the two CS+ were presented without the US. Subsequently, one of these auditory cues from extinction training was presented during SWS in a group that had a 2-hour sleep opportunity during the early night half. Another group received the auditory cue while they were awake during the early night half. Recall of both extinction memories was tested within their respective extinction contexts (retention test) as well as in an unknown context (renewal test). This design was chosen to test if auditory cueing during SWS promotes strengthening of memory of the extinction context, resulting in improved extinction recall for the cued CS+ in the sleep group. By testing recall of extinction in the original extinction context as well as in a new context, this designs further allows the examination of potential effects of contextual renewal, which were likely present in the previous study by Ai et al. (2015). Currently, Study 4 is in preparation and no data analysis has been carried out yet.

The present dissertation aimed at investigating effects of SWS in fear extinction, thereby focusing on SWS-dependent memory processing. The present findings from Study 2 and 3 did not suggest a role of SWS in the encoding or consolidation of extinction memory. Notably,

[23] Study 4 is currently in preparation. Data collection has been finished, but no data analysis has been carried out yet. The pre-registration of Study 4 was published in the Open Science Framework (see Appendix; https://doi.org/10.17605/OSF.IO/83U7A).

current evidence questions the robustness of evidence from research on sleep-dependent memory processing, in general (Cordi & Rasch, 2021a). This may be linked to methodological issues. In an attempt to improve replicability and robustness of future research on the role of sleep effects on memory, Cordi and Rasch (2021a) have given several practice recommendations. These include general aspects of empirical research such as reporting null findings, performing replication studies and meta-analytic research as well as pre-registering studies before data collection. In the present dissertation, the findings of Study 2 and 3 can be considered null findings in terms of the main research questions. Both studies were pre-registered. Study 4, which has been planned during the course of this dissertation project, has also been pre-registered. Study 1, however, was not pre-registered as the conceptualization of the study took place under time pressure. Cordi and Rasch (2021a) furthermore suggest a-priori estimation of sample size and particular attention to whether the research question could be tested by means of within-subjects or between-subject comparisons. Within-subjects designs are preferable as they have higher statistical power. However, fear conditioning research does usually use between-subjects designs to prevent potential carry-over effects. Future studies might overcome this methodological obstacle. For example, in Study 4, two CS+ were presented separately from each other during acquisition as well as during extinction training (see Appendix). This method was based on Milad et al. (2007) and was further modified in order to create distinct acquisition and extinction memory traces of the two CS, respectively.

The fact that the present findings of Study 2 and 3 rather question the role of SWS in fear extinction could also suggest that other mechanisms are of greater importance. These include other sleep stages, such as REM sleep, as well as other features of NREM sleep, such as sleep spindles. For instance, recent studies have suggested alterations in spindle activity in PTSD patients (Denis et al., 2021; van der Heijden, Hofman et al., 2021; Wang, Laxminarayan, et al., 2020; but see Wang, Ramakrishnan, et al., 2020). Furthermore, these studies reported a positive relationship between spindle activity and intrusive re-experiencing (van der Heijden, Hofman et al., 2021) as well as overall PTSD symptomatology (Denis et al., 2021), suggesting that alterations in spindles might resemble a specific characteristic of pathological processing in PTSD. Another explanation could be that additional, third variables moderate the relationship between sleep and fear extinction, such as sex (see Schenker et al., 2021). Alternatively, the relationship between sleep and PTSD may relate to processes apart from encoding and consolidating extinction memory and maybe also beyond memory in general (see e.g., Pace-Schott et al., 2023; Van Someren, 2021). A detailed discussion of these aspects would have exceeded the scope of the present thesis. Nonetheless, they should be considered in future research on the role of sleep in fear extinction.

VI References

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VII Statement of Author's Contribution to Joint Work

This dissertation is based on three studies, which have been published as articles in international peer-reviewed journals. I am the first author of the manuscripts presented in Chapter II and III. In the production of the manuscript presented in Chapter IV, Marie Roxanne Sopp and I contributed equally and share first authorship. In all three manuscripts, other authors contributed substantially to the work and are listed below. The three manuscripts are presented here in their original form, apart from minor changes in formatting and language.

Chapter II

Friesen, E., Michael, T., Schäfer, S. K., & Sopp, M. R. (2022). COVID-19-related distress is associated with analogue PTSD symptoms after exposure to an analogue stressor. *European Journal of Psychotraumatology, 13*(2), 2127185.
https://doi.org/10.1080/20008066.2022.2127185

I conceived and designed the study together with Marie Roxanne Sopp and Tanja Michael. Sarah Katharina Schäfer provided resources and promoted the investigation. I and Marie Roxanne Sopp performed the experiment and analyzed the data. The first draft of the manuscript was written by me, on which Marie Roxanne Sopp provided critical revisions. All authors read, edited and approved the manuscript for publication.

Chapter III

Friesen, E., Sopp, M. R., Brueckner, A. H., Ferreira de Sá, & Michael, T. (2022). Investigation of early night sleep effects on subsequent fear extinction learning and recall. *Journal of Experimental Psychopathology, 13*(2), 1-16.
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I conceptualized the study together with Marie Roxanne Sopp, Alexandra Heike Brueckner and Tanja Michael. I, Marie Roxanne Sopp, Alexandra Heike Brueckner, Tanja Michael and Diana Ferreira de Sá designed the methodology. Tanja Michael and Diana Ferreira de Sá provided study materials and computing resources. I and Marie Roxanne Sopp coordinated the project, performed the experiment and analyzed the data. I visualized the data and wrote the first draft of the manuscript. Marie Roxanne Sopp and Tanja Michael provided critical revisions on the manuscript and supervised me in all steps of the production of this study. I, Marie Roxanne Sopp, Tanja Michael and Alexandra Heike Brueckner were involved in the acquisition of the financial support for the project leading to this publication.

Chapter IV

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(**shared first authorship*)

I conceptualized the study and designed the methodology together with Marie Roxanne Sopp, Tanja Michael, Maren Jasmin Cordi and Björn Rasch. Tanja Michael, Maren Jasmin Cordi and Björn Rasch provided study materials and computing resources. I and Marie Roxanne Sopp coordinated the project and performed the experiment. We both further visualized and analyzed the data. The first draft of the manuscript was written jointly by me and Marie Roxanne Sopp. I wrote the method and results section and Marie Roxanne Sopp wrote the introduction and discussion section. All authors provided critical revisions on all parts of the manuscript. Tanja Michael supervised me in all steps of the production of this study. Marie Roxanne Sopp and Tanja Michael acquired the financial support for the project leading to this publication.

VIII Abbreviations

AASM	American academy of sleep medicine
ANOVA	Univariate analysis of variance
ASCT	Active systems consolidation theory
BF	Bayes factor
BLA	basolateral amygdala
BOLD activity	blood oxygen level dependent activity
CBT-I	Cognitive-behavioral therapy for insomnia
CC	Control condition
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CR	Conditioned response
CS	Conditioned stimulus
CS+	Conditioned stimulus that is paired with an unconditioned stimulus
$CS+_{E}$	Extinguished conditioned stimulus
$CS+_{U}$	Unextinguished conditioned stimulus
CS-	Safety stimulus
CS_{diff}	Difference score between CS+ and CS-
dACC	dorsal anterior cingulate cortex
EEG	Electroencephalography
EMG	Electromyography
EOG	Electrooculography
FPS	Fear-potentiated startle
HPA axis	Hypothalamic-pituitary-adrenal axis
IMQ	Intrusive memory questionnaire
IPT	Intrusion provocation task
LC-NE system	Locus coeruleus-norepinephrine system
LMM	Linear mixed-effects modeling
NREM	Non-rapid eye movement
NREM1-3/N1-3	Non-rapid eye movement sleep stages 1-3
NS	Neutral stimulus
PSG	Polysomnography
PTSD	Posttraumatic stress disorder
PVT	Psychomotor vigilance task
REM	Rapid eye movement

ROF	Return of fear
SCR	Skin conductance response
SG	Sleep group
SHY	Synaptic homeostasis hypothesis
SOL	Sleep onset latency
SSS	Stanford Sleepiness Scale
SWS/N3	Slow wave sleep
SWA	Slow wave activity
TF-CBT	Trauma-focused cognitive behavioral therapy
TF-PT	Trauma-focused psychotherapy
TMR	Targeted memory reactivation
TST	Total sleep time
UR	Unconditioned response
US	Unconditioned stimulus
vmPFC	ventromedial prefrontal cortex
WASO	Wake after sleep onset
WG	Wake group

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X Appendix

1. Pre-Registration of Study 4. Effects of Auditory Cueing During Non-Rapid-Eye-Movement Sleep on Fear Extinction Memory

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Description

We will study the effects of auditory cueing during non-rapid-eye-movement (NREM) sleep on fear extinction memory. Research on human sleep strongly suggests that NREM sleep promotes memory consolidation by reactivating memory engrams and integrating them into long-term memory storage. Cueing experiments, which aim to bias these processes (by means of so-called targeted memory reactivation, TMR), have proven a causal relationship between neuronal activity during sleep and memory performance in humans. However, first studies on the effects of TMR on fear conditioning processes (acquisition and extinction of fear memories) reported mixed results. To our knowledge, only a single study examined fear extinction-related cueing during sleep and showed rather a reinstatement of fear than a strengthening of extinction memory (Ai et al., *Neurobiology of Learning and Memory*, 2015). Besides the need for a replication of this unexpected finding, this study leaves questions regarding the role of the learning context unanswered. Research on fear renewal effects has shown that the recall of extinction memory is dependent on the encoding context. TMR studies frequently use context cues to establish and re-activate associative memories. Hence, studies on the relationship between sleep and fear extinction memory should take context-dependent fear learning processes into account. We hypothesize that the re-presentation of an auditory stimulus which is associated with the extinction context during NREM sleep strengthens fear extinction compared to a non-cued condition as well as to cueing during wakefulness. Furthermore, by presenting an unknown context, we expect a return of fear (ROF) that is assumed to be lower in the cued condition compared to the non-cued condition and to cueing during wakefulness.

Study procedure: On the first day of the experimental procedure, a habituation phase and acquisition training will take place. During acquisition training, participants will be presented with different colored lamps (conditioned stimuli, CS), of which two (CS+) will be followed by

an unpleasant electric stimulus (unconditioned stimulus, US) while one (CS-) will not be followed by the US. By showing the colored lamps in a room accompanied by background noises, the CS will be embedded into a multisensory context. The following day, participants will undergo extinction training, during which the CS will be presented without the US. Afterwards, they will be assigned to one of two experimental groups. One group will receive a sleep opportunity of 2 hours in the early night in which the auditory stimulus from the extinction context will be presented during NREM3 sleep. The other group will be presented with the same stimuli in a 2-hour wake interval. Subsequently, both groups will perform a retention test in the respective extinction contexts and a ROF test which will entail re-presentation of the CS in an unknown context (renewal).

Fear conditioning procedure: During the habituation phase, three colored lamps (CS) will be presented in four different rooms with different background noises to the participants. The rooms (i.e., bathroom, living room, kitchen, workspace) in combination with typical background noises (e.g., sound of typing on a keyboard with the image of a workspace) serve as multisensory contexts (CXTs). The acquisition training procedure is divided in two halves. In one half, participants will repeatedly see the CS- and the CS+cueing. The latter will be followed by the US. In the other half of the procedure, the CS- and the CS+no-cueing will be repeatedly presented and the latter will be followed by the US. Both halves will be presented without interruption and the order of the presentation will be balanced across participants. During each trial, participants will first see the CXT in which the lamp is presented without any color. After a short period of time, the light of the lamp will turn on (CS onset) in one of the three colors, accompanied by a short additional sound (e.g., sound of a phone ringing in the CXT of a workspace and the typing noise in the background). During extinction training, all CS will be presented unreinforced and in two halves. In each half, the CS+ and CS- will be presented in different CXTs (CXTcueing/CXTno-cueing) with different images, background noises and single auditory sounds at each CS onset. During the retention test, the subjects will be re-exposed to the CS in two halves within their respective CXT and with the auditory stimuli from extinction training. Similar to acquisition training, extinction training and retention test halves will be presented without interruption and the order will be balanced across participants. Finally, all CS will be randomly re-presented in a new CXT during the ROF test.

Auditory cueing procedure during sleep/wakefulness: Participants in the sleep group will receive a sleep opportunity of 2 hours. However, total sleep time will be restricted to 1½ hours (the start of the sleeping period is defined as the first onset of NREM2 sleep). Polysomnographic recordings will be monitored online. Auditory cueing will be started manually whenever stable NREM3 sleep occurs. If no NREM3 sleep occurs for more than 60 minutes, the cueing phase will be started at clear signs of NREM2 sleep. Cueing will be immediately interrupted when arousals, movements, or transitions into other sleep stages are

detected. In the wake group, classical music will be presented to the participants. After a short period, the cues will be faded into the background music. The duration of the cueing phase in the wake group will be individually matched to the duration of cueing in the sleep group.

Data collection

[Have any data been collected for this study already?] No data have been collected for this study yet.

Hypothesis

Main hypothesis (directional): Cueing during NREM sleep - in contrast to no cueing during NREM sleep and to cueing during wakefulness – strengthens fear extinction memory which leads to stronger reductions in fear expressions during the retention test and the ROF test.

Dependent variable

Fear Conditioning: Fear expressions will be measured online (during each CS presentation) by collecting skin conductance responses (trough-to-peak amplitude, microSiemens) and US expectancy ratings on a visual analog scale (US-E; 0 - 100). In addition, we will assess subjective fear and arousal ratings towards the CS on visual analog scales (0 100) in a pre/post-learning design. Indices of contingency awareness will be measured during the final trials of the two acquisition phases (US-E) and after acquisition training has been completed (explicit contingency questionnaire).

Sleep measures: During the sleep/wake manipulation on day 2, polysomnographic recordings (EEG; EMG; EOG) will be conducted. Total sleep time, relative sleep stage durations, as well as cueing-associated changes in spectral power will be analyzed. Baseline sleep quality will be assessed using the Pittsburgh sleep quality index (PSQI). Subjective sleep parameters (sleep quality; total sleep time) will be assessed on both days of the experiment. Furthermore, psychomotor vigilance (Psychomotor vigilance task, PVT) and subjective sleepiness (Stanford Sleepiness Scale, SSS) will be recorded prior to each test phase.

Conditions

[How many and which conditions will participants be assigned to?] See above.

Analyses

Data will be analyzed using mixed-effects modelling. The models will include random intercepts and - dependent on the analyzes - within-subjects fixed effects (CS type, trial, and cueing condition) and the between-subjects fixed effect of group. Quadratic effects and by-subject random slopes will extend the term whenever they result in a significant increase in

model fit. According to our hypotheses, we expect a significant effect of cueing on fear expressions within the sleep group in the retention test, resulting in higher fear expressions towards the CS+no-cueing compared to the CS+cueing. This effect should be also found differentially, hence the cueing factor is expected to interact with fear expressions dependent on CS type (CS+ vs CS-). Furthermore, we assume no such cueing effect in the wake group. Consequently, an interaction between the cueing and the group factor is expected. In the ROF test, we assume reduced fear expressions towards the CS+cueing in comparison to the CS+no-cueing exclusively within the sleep group. Hence, we expect an effect of cueing and an interaction of the cueing with the group factor, these effects should also be found differentially for CS types. Moreover, changes in spectral power of NREM as well as sleep spindles and slow waves associated to the cueing during sleep are expected to predict fear expressions in the sleep group during subsequent wakefulness. Post-hoc contrasts as well as correlation analyses (sleep parameters, fear expressions) will be performed to examine the main research questions.

Outliers and Exclusions

Data with technical errors, extreme artifacts, and from physiological non-responders (SCRs) are considered missing data and will be retained if the analyzes permit. Data sets will be excluded if one of the following conditions apply: - Dropouts: Participants who abort the experiment - No sleep/wakefulness in the respective experimental group - No contingency awareness at the end of the acquisition phase

Sample Size

Our targeted sample size is N = 80 participants (n = 40 in each group, healthy undergraduates), including an assumed dropout of 5%.

Other

In addition, we will explore differences in vigilance and sleepiness due to the sleep/wake manipulation. Effects of sleep vs. wakefulness on fear extinction memory (group effects within the no-cueing condition) will also be examined. Furthermore, we will carry out manipulation checks and tests of basic assumptions. Follow-up analyses will be conducted if these assumptions (see below) are violated. - Successful sleep/wake manipulation - Successful cueing during NREM3 (or NREM2) in the sleep group - Successful fear learning during the acquisition phase (differential elevation of fear responses for each of the CS+ compared to the CS-) - No differences between groups regarding age, gender, trait anxiety, depressive symptoms, sleep parameters (prior to experimental manipulation), fear learning (during acquisition phase), etc.