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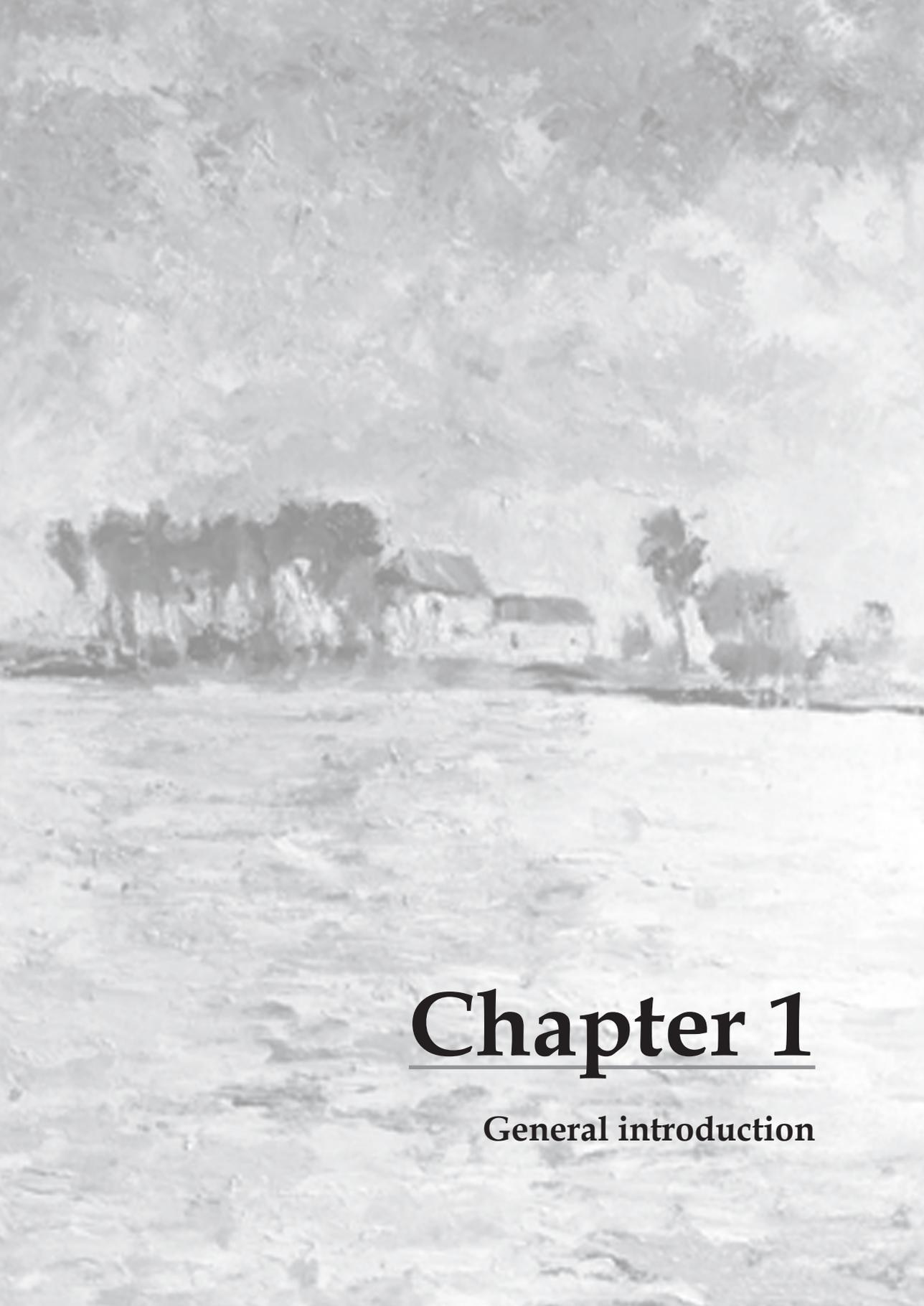
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Chapter 1

General introduction

Memories in context

You are what you remember. A bold statement. But do we not draw on past experiences to guide our thoughts and behavior, whether it is consciously or unconsciously? We seem to be a conglomeration of impressions that have accumulated while our lives progressed, impressions built out of images, smells, sounds, feelings, all tied together in sometimes chaotic cobwebs of associations. The sound of a particular song can make us instantly travel back years in time, making us to relive a seemingly forgotten holiday of which that particular song was the soundtrack. For those who know their classics, the sound of venomously shrieking violins can reinstate a black-and-white scene of a fear-provoking assault through a shower curtain, in the movie *Psycho*. One does not have to be a scientist to realize the significance of memories for who we are as human beings. Marcel Proust contemplates the phenomenon when he tastes a madeleine that unsuspectingly overwhelms him with the way “love has of filling with a precious essence”, before he even realizes that it was the madeleine, the taste of his youth, that had brought back these sensations.

The above examples clearly describe how memory can easily be reinstated by cues from the environment. A study conducted in the early seventies that is now classical Psychology textbook-material provided the first experimental evidence that information is indeed better recalled when the retrieval environment resembles the previous learning environment. In this study, Godden and Baddeley (1975) asked divers to learn lists of words either on dry land or underwater and tested memory for these words subsequently either in the same or the opposite environment. Those divers who had to recall the words in the original environment remembered significantly more words than those who were required to switch from learning to testing environments. Thus, context congruency enhances memory. Context-dependent memory explains why for instance pictures, music, and madeleines are so imperative to people: these help us to retrieve - often precious- memories. But what exactly defines a context? Broadly, it can be defined as the internal (cognitive and hormonal) and external (environmental and social) backdrop against which psychological processes operate (Spear, 1973). Contexts can thus shape and define the perception of sensory traces, memories of episodes past, the content of thought, the meaning of words and the goals of purposive behavior. In this broader sense, contexts enable the flexible representation and retrieval of information, thereby playing a core role in resolving ambiguity, all of which are necessary for adaptive behavior (Maren et al., 2013).

When context indeed plays such a pivotal role in the flexible representation and retrieval of information and in resolving ambiguity regarding the meaning of stimuli, it is not difficult to fathom that deficits in contextual processing often lead to inflex-

ible, rigid and inappropriate behavioral responses. In humans, these responses can in turn lead to various symptoms — from paranoid beliefs or intrusive thoughts to compulsive behaviors — that are seen in a variety of psychiatric disorders, including schizophrenia, PTSD, depression and drug addiction (Maren et al., 2013). Thus, various forms of psychopathology that involve disorders of affect may be best conceptualized as disorders of the context-regulation of affect (Davidson et al., 2000). With regard to memory more specifically, the ability to store declarative memories into their original encoding context (i.e., memory *contextualization*) is highly adaptive as it can help to retrieve memories that are likely to be appropriate in a specific context, while preventing undesired memories from intruding into consciousness. This ability seems to be impaired in several anxiety disorders, especially posttraumatic stress disorder (PTSD). These patients frequently report repeated visual or other sensory intrusions corresponding to a small number of real or imaginary events, usually extremely vivid, detailed, and with highly distressing content. For this reason it has been proposed that dysregulation of contextualization processes might play a key role in the generation of PTSD symptoms (Acheson et al., 2012; Ehlers et al., 2004; Liberzon and Sripada, 2008).

The hippocampus and memories

Several lines of evidence suggest that the hippocampus aids in encoding associations among stimuli, actions, and places that compose discrete events. Animal research showed that selective hippocampal damage results in deficits in forming a memory for the context or location where items were previously experienced. Gaffan (Gaffan and Parker, 1996) trained monkeys on a set of discrimination problems composed of objects presented on a computer screen with different kinds of background patterns. Animals with the hippocampus disconnected did learn object discriminations at the normal rate when the background was irrelevant for the task. But the same animals were seriously impaired when the background context predicted the location of the rewarded object. Perhaps the strongest evidence that the hippocampus is critical for learning the context of important events comes from studies of fear conditioning. These studies are based on associative fear learning in which a tone and shock (unconditioned stimulus, US) are paired repeatedly instigating rats to become fearful of the tone (conditioned stimulus, CS). In addition to conditioned fear for the tone cue, animals also develop fear for the context in which the tones and shock were presented, as is evidenced by fearful responses (such as freezing) when the animal is returned to the context where conditioning occurred. One representative study indeed showed that damage to the hippocampus eliminates this contextual fear without affecting conditioned fear to the tone (Phillips and Ledoux, 1992).

Functional neuroimaging (fMRI) studies in humans have examined whether the hippocampus is more activated during the encoding or retrieval of associations among many elements of a memory—a characteristic of context rich episodic memories (Tulving, 1985). For example Davachi et al. (2003) showed their subjects several adjectives and instructed them to either generate a mental image of a spatial scene (“image”), or to pronounce the word backwards (“read”). During subsequent memory testing outside the scanner, the subjects were asked to recognize an item as previously encountered (item recognition) and recollect specific contextual details about the prior encounter (source recollection). Encoding activation in hippocampus and in posterior parahippocampal cortex predicted later source recollection, but was uncorrelated with item recognition. In contrast, encoding activation in perirhinal cortex predicted later item recognition, but not subsequent source recollection. In another comparable study independent analyses for item and associative memory formation revealed brain activity that appeared selectively related to item memory formation in the posterior inferior temporal, posterior parahippocampal, and perirhinal cortices. In contrast, hippocampal and inferior prefrontal activity predicted successful retrieval of newly formed inter-item associations (Qin et al., 2009b). Neuropsychological studies in amnesic patients who had suffered from damage to the hippocampus proper confirm these observations, by showing that recognition of associations (i.e., among faces and occupations) is impaired even when recognition for single items is spared (Turriziani et al., 2004). Findings like these have been incorporated in models that distinguish between the hippocampal contributions critically important for associative memories and the perirhinal contributions sufficient for item memory (Brown and Aggleton, 2001; Davachi, 2006; Eichenbaum, 2004; Yonelinas et al., 2002), though these are not undisputed (Squire et al., 2007).

If the hippocampus is indeed imperative for contextualization processes, then how does it accomplish contextualization? Two regions of the hippocampus, that is, the dentate gyrus and CA3 region (DG-CA3 network), have been suggested to mediate a dynamic competition between two complementary processes of an associative memory system: pattern completion (or generalization) and pattern separation (Guzowski et al., 2004; Leutgeb, 2004; Vazdarjanova, 2004). Pattern completion on the one hand enables to respond to a degraded input pattern with the originally stored pattern. Pattern separation on the other hand aids in making the stored representations of two similar input patterns more dissimilar (Guzowski et al., 2004). In animals, responses in DG-CA3 are typically measured while exposing rats sequentially to two environments in which certain cues are altered. If the neural response to the second environment is different from the first, pattern separation is the stronger process. If, on the other hand, the two responses are very similar, pattern completion

is said to dominate. In this case, context will be a less potent way to differentiate memories, leading to generalization of stored associations across contexts. It has been proposed that impairments in pattern separation may underlie overgeneralization of fear in anxiety disorders and may therefore be an endophenotype of anxiety disorders such as PTSD and panic disorder (Kheirbek et al., 2012a). In conclusion, the context dependency of memories may develop when two similar input patterns are made more dissimilar (Guzowski et al., 2004), preventing memory generalization from occurring.

Altered memory contextualization: stress and concomitant hormones

Considering all these lines of research suggesting that the hippocampus underlies memory contextualization, then how may alterations in these processes come to generate PTSD-like memory symptoms (Acheson et al., 2012; Ehlers et al., 2004; Liberzon and Sripada, 2008)? Several models for the etiology of anxiety disorders incorporate stress and associated stress hormones such as cortisol as important vulnerability factors (Elzinga and Bremner, 2002; Korte, 2001; Shin and Liberzon, 2009). When environmental cues signal a potential threat to an organism's well being, the brain produces a coordinated set of behavioral, autonomic, and metabolic changes that promote an adaptive response aimed at restoring homeostasis and that enable the appropriate behavioral response to cope with the challenge at hand. These systems can not only be activated by acute physical threats such as an attacker in a dark alley, but can for example also be activated by threats to self-esteem or social status, which are more likely to occur in current society. Here, the magnitude of the stress response depends on psychological appraisal processes like the loss of control or of predictability. The stress response involves activation of two main neuroendocrine pathways: the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis. Activation of the ANS leads to the rapid release of adrenaline from the adrenal medulla and noradrenaline from sympathetic nerve endings via activation of the locus coeruleus. The release of these catecholamines leads to increases in heart rate, blood pressure, respiration rate and pupil dilation resulting in a state of heightened alertness, vigilance and arousal which prepares for immediate attempts to cope with the stressor, characterized as the 'fight-or-flight response' (Cannon, 1929). On a slightly slower timescale a second major stress system, the HPA axis, is activated. The HPA axis leads to hormonal changes that underlie the more sustained components of the stress response, like the normalization of homeostasis (de Kloet et al., 2005). Importantly, cortisol and adrenaline play a critical role in the expression of emotions and modulate memory resulting in enhanced memory for emotional experiences (Cahill and McGaugh, 1995; McGaugh and Roozendaal,

2002). Corticosteroids exert their effects on central stress circuitry through binding to two nuclear receptors, which influence brain function primarily by modulating gene transcription (de Kloet et al., 2005): the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). GRs and MRs differ in both their localization in the brain and their affinity for corticosteroids. Though ubiquitously present in the (animal) brain, both MR and GR receptors are especially densely situated in the hippocampus (Joëls and Baram, 2009), which we now know, is critical for memory contextualization processes. Indeed, PTSD, stress and the hippocampus are closely related.

PTSD is accompanied by alterations in the stress response, which is not surprising since the disorder generally develops after exposure to a severe stressor. Cross-sectional literature on cortisol alterations in PTSD has been complex and somewhat inconsistent, but many findings demonstrate hypocortisolism in PTSD, such that individuals with PTSD experience lower resting levels of peripheral cortisol and enhanced negative feedback mechanisms (Yehuda and LeDoux, 2007). Predictive studies have revealed that low cortisol responses early after trauma predicted increased risk for PTSD symptoms (McFarlane, 1989), while cortisol administration reduces risk (Schelling et al., 2004). In contrast to the finding of reduced basal cortisol levels, there is evidence that the cortisol response to psychological stress is enhanced in PTSD patients (Heim et al., 2000) and prospective studies suggest that lower cortisol levels shortly after trauma exposure are a risk factor for the subsequent development of PTSD (McFarlane, 1989). Together, studies like these give strong evidence for altered cortisol regulation mechanisms in PTSD, but they do not directly provide evidence for alterations in the hippocampus. Other studies did focus on the relationships with stress and the hippocampus. Severe and chronic stress, with concurrent elevations in circulating glucocorticoids, have been shown to induce hippocampal atrophy in rodents and primates (Sapolsky, 2003). These effects of stress on hippocampal volume have also been shown to result in poor hippocampal-dependent memory performance (Luine et al., 1994). In humans, high cortisol levels (e.g. Cushing's Disease) are associated with low hippocampal volume and cognitive deficits (Grillon et al., 2004b), which are reversed with successful treatment (Starkman et al., 2003). Based on these studies it has been hypothesized that trauma exposure induces HPA axis dysregulation, resulting in hippocampal atrophy in vulnerable individuals (Elzinga and Bremner, 2002).

A triangular relationship between memory contextualization, cortisol, and the hippocampus?

Even though a vast amount of research into relationships with PTSD, hippocampus, stress and/or cortisol has been conducted, there are still some important gaps in knowledge. The above-described relationships are mostly correlational in nature, involve generally severe and chronic stress paradigms, and never entirely uncovered the complicated triangle that consists of PTSD-like memory impairments, cortisol and the hippocampus. For instance, animal models of traumatic memories and PTSD principally focus on what may be called the quantitative aspect of fear memories: an increased and persistent fear response (Tronel and Alberini, 2007). Others have explicitly modeled the trauma itself, by using chronic stress manipulations (e.g., Shansky et al., 2009) or unpredictable and uncontrollable qualities of stress (e.g., Foa et al., 1992), others aimed at replicating specific neurobiological alterations in HPA-axis activity, or behavioral characteristics such as enhanced startle or impaired extinction learning (for an overview see: Cohen and Zohar, 2004). Thus, in the animal literature, no clear consensus has yet been reached on what are the most significant parameters that should be focused upon. Only one study so far analyzed whether PTSD-like memory impairments, characterized by impairments in memory contextualization, are mediated by the hippocampus (Kaouane et al., 2012). The authors injected the stress hormone corticosterone into the hippocampus of mice submitted to either a cue fear conditioning paradigm in which a cue predicted the US, or a context conditioning paradigm, in which a cue was present but not predictive of the US. The next day, the cue-conditioned animals did not show alterations in fear responses to the cues, but the context conditioned group generalized fear responses to the cue that was present during original conditioning, but not predictive of the shock (Kaouane et al., 2012). Thus, hippocampal corticosterone infusions impaired the ability of the subject to restrict fear responses to the appropriate predicting signal (i.e., the context).

In humans, studies have focused on single items to be memorized, such as words or pictures. It has been shown that stress typically enhances consolidation (Buchanan and Lovallo, 2001), and can enhance encoding (Cornelisse et al., 2011b; de Quervain et al., 2009; but see Elzinga et al., 2005). Such alterations in memory have indeed been shown to relate to stress-induced cortisol levels (Cornelisse et al., 2011b; Smeets et al., 2008), and indeed seem to be mediated by the hippocampus (Henckens et al., 2009; Qin et al., 2012). As has been pointed out in the beginning of this introduction, memories are often interrelated in complex associative networks rather than stored in isolation. Therefore, investigating the effects of stress on memory contextualization might be a more ecologically valid approach to investigating stress effects on

memory. Taken together, in humans, an open question is whether cortisol can alter memory contextualization processes, presumably mediated by the hippocampus. If we are able to experimentally demonstrate such a causal relationship, this would provide important insight into the pathways by which cortisol ultimately may lead to altered memory contextualization, as is characteristic of PTSD-like memory impairments.

Experimental models of stress effects on memory contextualization

As outlined before, human studies to contextual binding have focused on associations among elements of a memory, indeed a characteristic of context rich episodic memories (Tulving, 1985). For instance, studies presented one element of a memory and probed for associations with the original source (i.e., source memory). Importantly however, context in these studies refers to scenes that were explicitly associated with objects or nouns. A shortcoming of these studies is that they did not address the effects of implicitly encoded contexts on retrieval, but rather the mechanisms of explicit associative memory. Another disadvantage of this approach is that these paradigms have less clear parallels with the rich existing animal literature investigating hippocampal function. In addition, these studies did not investigate the effects of stress (or stress hormones) on such associations. Studies that did investigate stress effects on contextual binding have operationalized context in more implicit ways though. These studies took a broad definition of context, defined as the internal (cognitive and hormonal) and external (environmental and social) backdrop against which psychological processes operate (Spear, 1973). One study demonstrated that social stress enhanced memory for words related to personality, but not a category unrelated to personality, which was interpreted as enhanced context congruent memory by stress. These effects were positively related to cortisol (Smeets et al., 2007). Another study manipulated thematic arousal independently of the to-be remembered material, and showed that social stress specifically enhanced high arousing themes. In addition, this memory-enhancing effect was most pronounced for elements central to the to-be-remembered event (Echterhoff and Wolf, 2012), which was again positively associated with cortisol. Another study did not report possible relationships of cortisol with stress effects on contextual dependency of memory. Context was manipulated by the physical environment in which encoding and retrieval took place (i.e., change of room and odor) and found that stress impaired the typical memory enhancement by context congruency (Schwabe et al., 2009). A second study showed that social stress enhanced memory for objects that were central to the stressor, but not for unrelated items (Wiemers et al., 2013). Summarizing the above findings, cortisol likely plays an important role in the relationship

between stress and memory contextualization, though the exact direction of cortisol effects is not entirely clear. However, an important disadvantage of operationalizing context in the broad sense is that due to the high overlap between the different items within the same global (environmental) context, no unique cue-context associations are formed. Consequently, these cues typically produce less robust context effects (Dalton, 1993). Therefore, by switching to an entirely new context after learning, subtle differences in contextualization versus generalization may not be challenged, and thus overlooked.

Aim and outline of the present thesis

The aim of the present dissertation was to investigate the means by which cortisol can alter context dependent memories. We tried to overcome difficulties associated with broader manipulations of context on the one hand, while increasing parallels with existing animal research on the other hand. We hereto built on a previously used memory task that has revealed robust context effects (Talamini et al., 2010). It manipulates contextual congruence at a local level, and uses subtle context switches that are perhaps more likely to challenge pattern separation versus completion in the hippocampus. During the encoding phase of the task, participants are typically presented with central stimuli (words or faces) against unique background pictures. Approximately 24 hours later, memory contextualization is assessed: half of the stimuli is tested in intact contexts, while the other half is tested in rearranged context combinations. Furthermore, since especially emotionally arousing experiences are well remembered (McGaugh and Roozendaal, 2002) and since it has been suggested that the critical mechanism underlying the role of emotional arousal are interactions between stress hormones and arousal-induced noradrenergic activity in the amygdala (de Quervain et al., 2009), we manipulated arousal by using emotional stimuli in addition to neutral ones. We also used a fear-conditioning paradigm paralleling the context task, and one other fear-conditioning paradigm that likewise is thought to target hippocampal-dependent fear memory (i.e., trace conditioning).

In the first chapter of this thesis, we investigated whether cortisol mediates social stress effects on memory contextualization (**Chapter 2**). Then, if cortisol indeed plays a fundamental role in memory contextualization, we wanted to more closely describe the specific role of cortisol. Basic neuroscientific research has shown that cortisol via memory circuitry receptors induces rapid non-genomic effects followed by slower genomic effects, which are thought to modulate cognitive function in opposite, complementary ways (Joëls et al., 2011). In **Chapter 3** we therefore targeted these time-dependent effects of cortisol during memory encoding, and tested subsequent contextualization of emotional and neutral memories. In order to understand

how abnormalities in memory contextualization contribute to development and/or maintenance of PTSD, an important question is furthermore whether altered memory contextualization is a trait in vulnerable individuals for PTSD. Interestingly, there is a range of known vulnerability factors for anxiety disorders that have typically been associated with alterations in hippocampal functioning and/or alterations in memory as well. Theoretically, if impaired memory contextualization indeed is a vulnerability factor for the development of anxiety these factors should then be able to alter memory contextualization processes too. In **Chapter 4** we tested relationships with memory contextualization and some known vulnerability factors for PTSD.

The first three chapters of this thesis assessed declarative memories, while the predominant model for the pathogenesis of anxiety disorders is that these disorders originate from a learned association between a previously neutral event (Conditioned Stimulus or CS, e.g., gaze) and an anticipated disaster (Unconditioned Stimulus or US). The strength of associative learning and memory can be assessed by measuring the psychophysiological expression to the CS. Therefore, in the second part of this thesis, we tested in another study (**Chapter 5**) how cortisol affects contextual control over expression of fear. The purpose of the study was threefold: first, we aimed to develop an experimental paradigm specifically capable of capturing contextual modulation of the expression of fear. Second, we tested whether cortisol would alter the contextualization of fear expression. Finally, we aimed at assessing whether alterations in contextualization due to cortisol were different for men and women. In **chapter 5** we were interested in the acute effects of cortisol on fear expression. However, in order to construct a more valid experimental model for the etiology of anxiety disorders, retention of long-term fear expression should be tested as well. Therefore, we conducted another fear-conditioning experiment (**Chapter 6**) in which we tested how time-dependent effects of cortisol affect fear memory of delay and trace conditioning the following day. This distinction is of special interest because the neural substrates underlying these two types of conditioning (i.e., the amygdala or hippocampus, respectively) may be differently affected by time-dependent cortisol effects.

In the final part of this thesis, **Chapter 7** takes a broader perspective and aimed to review cortisol effects on learning and memory. A number of factors that alter cortisol's effects on learning and memory are well-known. For instance, effects of cortisol can be modulated by emotional arousal or the memory phase under study. Despite great advances in understanding factors that explain variability in cortisol's effects, additional modulators of cortisol effects on memory exist that are less widely acknowledged in current basic experimental research. The goal of the current review

was to disseminate knowledge regarding less well-known modulators of cortisol effects on learning and memory, such as context. Finally, in **Chapter 8**, the main findings of the studies presented in this thesis are summarized, synthesized and discussed.