

Fading memories : the impact of stress hormones on the retrieval of emotional memories

Tollenaar, M.S.

Citation

Tollenaar, M. S. (2009, May 13). Fading memories: the impact of stress hormones on the retrieval of emotional memories. Retrieved from https://hdl.handle.net/1887/13789

Version: Not Applicable (or Unknown)

License: License agreement concerning inclusion of doctoral thesis in the

Institutional Repository of the University of Leiden

Downloaded from: https://hdl.handle.net/1887/13789

Note: To cite this publication please use the final published version (if applicable).

Chapter 1

General Introduction

We probably all know the feeling of being under pressure or a lot of stress and not being able to recall relevant information (e.g. during an exam) or to give examples of events that happened in the past (e.g. during a job interview). For several decades scientists have studied how it is possible for stress to affect memory in healthy people, but also in people that are diagnosed with stress related disorders like depression or acute and post-traumatic stress disorder. One of the recent findings in healthy populations is that the retrieval of information, particularly emotional information, is affected by stress. This outcome confirmed earlier findings in animal studies. However, the underlying mechanisms of and specific conditions in which these effects appear in humans, as well as the long-term effects on memory, are still unclear. These aspects will be topic of the present thesis.

To understand how it is possible for stress to affect memory, it is first important to precisely state what we mean by stress and by the retrieval of (emotional) memories. In the next paragraphs these issues will be discussed. We will start with a description of our conceptualization of the retrieval of emotional memories and its relevance to daily life. This will be followed by a more general overview of memory theories and the underlying mechanisms in the brain (i.e. the neurobiology) that make memory possible, in particular memory retrieval. We will then turn to the models that may explain how stress can affect memory, with specific details on stress hormones that are involved in this process. An overview will follow of previous research into the effects of stress on memory retrieval, also discussing gaps in the present knowledge regarding this issue.

While impairments in memory can be seen as a negative consequence of stress and stress hormones, a more positive use of this knowledge has been applied to clinical practice. The last part of this introduction will describe how the deliberate suppression of emotional memory retrieval by stress hormones could be useful in disorders characterized by excessive retrieval of emotional memories. However, these studies are still in an early stage and more insight into the effects of stress hormones on different aspects of memory is needed before a safe use of these drugs can be established. Therefore, the present thesis hopes to further elucidate the effects of stress and stress hormones on emotional memory retrieval.

Retrieving emotional memories

What do we mean?

When we reflect upon our life, we usually think of events and social interactions that were important in influencing our life and our sense of self. At the time these events happened, they probably elicited emotions as happiness, sadness, anger or fear. When thinking back of past events it might be that these memories still elicit emotions. For example, when thinking back of a terrible accident that you experienced or witnessed, intense feelings of fear or sadness might still be experienced, including physical responses like an increased heart rate. However, sometimes one can think of an event in the past that was very emotional at the time, but when thinking back of it is only thought of as a negative experience without actually feeling any arousing emotions. For example, you could have a memory of a break up after a short infatuation in high

school or of being embarrassed in front of a group of people. Memories of these experiences can still be important to our sense of who we were and are, but may have changed in the emotional appraisal we give them today. We might even laugh about such events years later on, although they were very distressing at the time. The meaning of memories can thus change over time as well as the associated emotions, or memories can just loose their emotional value over time. So we can think back of emotional events and retrieve these memories either without any of the previously associated feelings, or re-experience (part of) the emotions associated with the event. In the present thesis we will refer to both as emotional memory retrieval, but the distinction will be important in the light of clinical studies, as in certain disorders the reliving of emotional memories and associated emotional experience and responses is excessive and disabling.

On the other hand, a person might also remember an event that was not emotional at all, e.g. taking the train to work yesterday. We will refer to this as neutral memory retrieval. A difference between neutral and emotional memories is that the event(s) that formed an emotional memory elicited an emotional response at the time of formation. Research has shown that an emotional response to an event leads to a favorable position of these events in memory (Cahill & McGaugh, 1998), as they are better stored into long-term memory (LaBar & Cabeza, 2006) and can be remembered for decades. Also, memories of these events usually elicit more vivid and intense reexperiencing. These memories consist of both contextual and factual information and associated emotional responses. It is important to make a distinction between the contents and the emotional experience of a memory, given that different brain areas are thought to be involved in their processing.

A view on memory

Memory for events or for information that was learned in the past is often referred to as declarative, or explicit, memory. People can consciously recall declarative memories. When memories are related to a certain place and time, e.g. "the job interview at the University last week", these declarative memories are called episodic memories. On the other hand, declarative memories can also consist of mere facts about the world and oneself, like names of friends and family members or the name of one's high school. This is called semantic memory (Tulving, 1972, 2002). Even though we might still remember meeting a friend and hearing his or her name for the first time, the name belonging to the person is stored as a semantic fact, while the event of meeting is an episodic memory. The present thesis will be about such declarative memories, specifically episodic memories. In most of the chapters, we measured episodic memory retrieval with memories that were created in a laboratory setting (e.g. word pairs or word lists that were learned in the lab on an earlier occasion). But we also studied memories of participants' personal past, which is called autobiographical memory. Autobiographical memories are usually rich memories with vivid images of contextual details and feelings associated with a certain time and place. Autobiographical memories contribute to an individual's sense of self and make us able to keep track of our personal past and goals. Autobiographical memory can be viewed as a form of episodic memory, but also

consists of many semantic elements and general knowledge on life time periods (Conway & Pleydell-Pearce, 2000; Levine, 2004; Williams et al., 2007).

The formation and storage of declarative memories can be divided in several stages (see Figure 1.1). First of all, an event or new information has to be encoded before it can be consolidated, or formed into a long-term memory. However, not all new information will be selected to be consolidated to long-term memory after encoding. Attentional processes and current emotional state might play a role in the (automatic) selection of information to be remembered. Once new knowledge is being consolidated, a memory of this information or event can be retrieved, either intentionally or spontaneously. Retrieval can be repeated many times, as long as the memory is available. The present thesis will investigate the effects of stress specifically on this retrieval stage. However, recently it has become clear that when memories are reactivated by retrieval, they might get into a labile state in which these memories are prone to change. While newly formed memories undergo the process of consolidation to become stable, reactivation might make them labile again (Nader et al., 2000; Przybylawski & Sara, 1997). After reactivation, these memories are then 'reconsolidated' back into long-term memory, potentially affected by the context in which they were retrieved. This is still a controversial matter, but animal and human studies have shown that memories can indeed be affected upon reactivation (Debiec et al., 2002; Hupbach et al., 2007; Nader et al., 2000; Przybylawski & Sara, 1997; Walker et al., 2003). The present thesis will also explore the impact of stress on this post-retrieval stage.

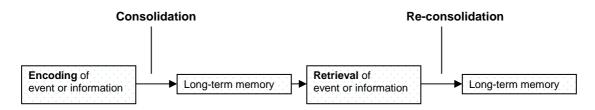


Figure 1.1. Schematic overview of memory stages.

Besides conscious, declarative memory, there is also a more un-conscious, implicit, form of memory. For example, there is memory for learned motor skills (procedural memory), like riding a bike or driving a car. These abilities were learned by repetition but can not easily be verbally described, although a specific driving lesson might be stored as an episodic memory. There is also a more temporary, active memory, referred to as working (or short-term) memory. While declarative memories are stored (consolidated) into long-term memory, which means that they are available long after an event or learning experience occurred, a working memory system is needed to integrate current perceptions and thoughts with knowledge from long-term memory. Information in working memory is temporarily maintained and can be updated and manipulated. This information will sometimes be consolidated into long-term memory, but will often be forgotten again (imagine a phone number you have to remember to dial and forget again as soon have you have used it).

Neurobiology of emotional memory retrieval

Up till now it is still not fully understood how the brain brings about the retrieval of (emotional) memories, but in the next paragraphs a brief overview of recent findings will be given. Knowledge on which brain areas are involved in (episodic) memory retrieval comes from studies in patients, characterized by specific lesions and memory problems, but more recently also from neuro-imaging studies with Electro Encephalography (EEG) and functional Magnetic Resonance Imaging (fMRI).

There are several key structures involved in both the formation and retrieval of memories. The hippocampus and amygdala (both within the medial temporal lobe and limbic system of the brain) and the prefrontal cortex are such key structures (see Figure 1.2). Especially the formation and retrieval of explicit, declarative memories are found to be mediated by the hippocampus as became clear from early studies on patients with lesions in this area (Corkin, 2002; Scoville & Milner, 1957; Steinvorth et al., 2005). Patient studies have further shown that hippocampal and amygdalar structures are involved in the formation of emotional memories (e.g. Phelps, 2004). While the hippocampus seems mostly involved in the formation of declarative (e.g. contextual) knowledge, the amygdala seems involved with implicit, conditioned emotional responses and the vivid recollection of emotional memories (Bechara, 1995; Buchanan et al., 2005; Labar & Cabeza, 2006).

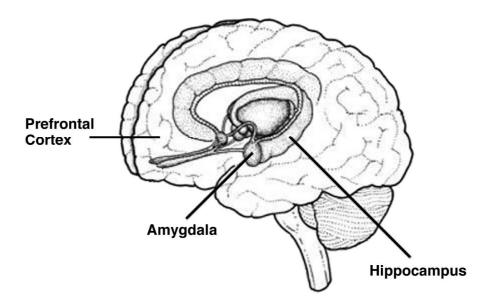


Figure 1.2. Brain structures involved in memory processing

Knowledge on the role of these two structures in memory *retrieval* comes mostly from neuro-imaging studies. Recent studies have shown that retrieving memories elicits activation in both the hippocampus and amygdala, with activity of the amygdala most pronounced in emotional memory retrieval (Dolcos et al., 2005; Smith et al., 2004). Furthermore, the connectivity between the hippocampus and amygdala gets stronger when relevant emotional memories are retrieved (Smith et al., 2006). Emotional memories are generally rated as more vivid, and high in re-experiencing and intensity. These subjective ratings are related to higher activity levels in

hippocampus and amygdala and to stronger feelings of remembering (Addis et al., 2004; Labar, 2007; Sharot et al., 2004). The emotionally driven activity in the amygdala, caused by attempts to retrieve memories, can also help to select memories or facilitate the retrieval of associated contextual information belonging to the memory (Buchanan, 2007; Labar, 2007). This may then lead to a full emotional experience (LeDoux, 2000; Tsuchiya & Adolphs, 2007)

The prefrontal cortex is also implicated in the successful retrieval of memories (Greenberg et al., 2005; Svoboda et al., 2006) and is thought to be involved in the initiation and control of the retrieval process (Buchanan, 2007; Simons & Spiers, 2003), as well as the maintenance of the retrieved information (a function related to working memory). In addition, the prefrontal cortex seems to be involved in the storage and retrieval of semantic information, even about emotions. That is, the prefrontal cortex is implicated in memories that are negatively or positively valenced, but do not elicit emotional arousal (Kensinger & Corkin, 2004). Therefore, patients with damage to the amygdala may still show enhanced memory for emotional information, but based more upon semantic knowledge of emotions, as generated by the prefrontal cortex.

The prefrontal cortex mainly has a controlling function, necessary for the correct retrieval of past events, especially remote events (Rudy et al., 2005). The prefrontal cortex might even inhibit the role of the hippocampus over time (Frankland & Bontempi, 2005; Takashima et al., 2006). That is to say, the role of the hippocampus in the retrieval of remote memories is not without controversy. For long, it was the norm to think that the medial temporal lobe (MTL; including the hippocampus) was only temporarily involved in the formation of memories. It would become unnecessary after the consolidation of information into long-term memory (Squire, 1992; Squire & Alvarez, 1995). This is called the Standard Model of Consolidation. The role of the MTL would be to activate brain regions in the neocortex that contain the information that was experienced, creating strong interconnections between these cortical sites, leading to memories independent of and no longer activating the hippocampus. According to this model, retrieval of both semantic memories and episodic memories would only be temporarily mediated by the hippocampus. Studies in patients with MTL damage have shown that remote memories are usually preserved, while recent memories are affected (e.g. Bayley et al., 2003), indicating the standard consolidation theory might be correct. A model that challenged the consolidation model is the Multiple Trace Theory (MTT; Moscovitch et al., 2005; Nadel & Moscovitch, 1997). This model proposes that the MTL remains necessary for the retrieval of episodic memories, while semantic memories become independent of the MTL over time. To store episodic memories, the hippocampus will bind representations in neocortical neurons via memory traces in the hippocampus, and every time a memory is reactivated, new traces are formed that bind together these representations. Older memories will thus have more memory traces in the hippocampus, making them less vulnerable to (partial) lesions of the MTL. In line with this model, recent findings have shown that the retrieval of remote episodic memories is less detailed in patients with extensive medial temporal lobe damage (Moscovitsch et al., 2006; Steinvorth et al., 2005). Imaging studies have furthermore revealed that remote memories can indeed show activation of the MTL, so long as the

memories are still vivid and rich in quality (Addis et al., 2004; Gilboa et al., 2004). It might well be that especially remote emotional memories, which are more vivid and re-experienced more intensely during retrieval, still need hippocampal structures to be retrieved, so long as they elicit emotional reactions. Once memories do no longer elicit emotional responses or vivid images, they might become independent of the hippocampus (like semantic memories), although this still needs to be elucidated.

To summarize, the hippocampus is mostly found to be involved in the formation of declarative memories and is active during retrieval. The amygdala is involved in the emotional strengthening of memories and is more active and in concordance with the hippocampus during emotional memory retrieval. The prefrontal cortex mainly has a controlling function and is necessary for the correct retrieval of past events. The prefrontal cortex might even inhibit or take over the role of the hippocampus over time, although there is still a considerable debate on the temporary role of the hippocampus in the retrieval of remote events.

Stress and stress hormone effects on memory retrieval

Stress hormones

When a person experiences stress, either physically or mentally, the body reacts in diverse ways to cope with the situation at hand. Here, we will focus on hormonal responses that are initiated by stress. When stress is experienced we can differentiate between a fast and a slow hormonal response. The fast response is mediated by the autonomic (sympathetic) nervous system (ANS) and the slower response by the hypothalamic pituitary adrenal (HPA) axis (Joels et al., 2006). The ANS system leads to the release of adrenaline and noradrenaline (or epinephrine and norepinephrine) in the body by the adrenal medulla, which leads to increases in e.g. heart rate, blood pressure and sweat production. (Nor)adrenaline is also released as a neurotransmitter in the brain and leads to a state of alertness and modulates the processing of emotional information via the amygdala (van Stegeren, 2008). We are often aware of this stressed ANS reaction as we can feel our body prepare to take action. On the other hand, through a cascade of hormones, the HPA axis leads to the release of cortisol into the blood stream by the adrenal cortex. The release of cortisol is not consciously noticeable and is involved in the re-mobilization of energy after the start of a stressful experience (Sapolsky, 2003; Sapolsky et al., 2000). It is also involved in the negative feedback regulation of the HPA axis, and cortisol levels will therefore decrease again after the end of the stressor (Lupien & LePage, 2001). Like (nor)adrenaline, cortisol is active both in the body and the brain, as it is able to cross the blood-brain barrier (BBB). Within the brain 2 types of cortisol receptors have been found that are differentially spread over brain areas, the minoralocorticoid (MR) and glucocorticoid (GR) receptors. Both receptors are abundantly present in the hippocampus and can hence influence cognitive processes mediated by the hippocampus like memory (De Kloet et al., 1999; Lupien & Lapage, 2001). In reaction to acute stressors, these hormonal effects might be adaptive to the present state, but when prolonged or chronic can lead to health problems in the long run (McEwen, 1998).

The amount of stress that is experienced by a person is dependent on several individual differences, like the way a person evaluates a stressor and available coping strategies. Furthermore, the stressor itself can have different properties that can lead to a strong or relatively mild stress reaction. In a meta-analysis, Dickerson and Kemeny (2004) investigated variables that can lead to stress. Situations that are new or unpredictable, uncontrollable or (socially) threatening will lead to the highest cortisol responses. A paradigm that includes all of these processes is the Trier Social Stress Task (Kirschbaum et al., 1993). This is a laboratory stressor that can be repeatedly used and is shown to lead to significant increases in cortisol in the majority of people over time. It includes a public speaking task preceded by an anticipation phase and followed by a cognitive task while being socially evaluated. In the present thesis, we have made use of this stress protocol.

One difficulty that arises when studying cortisol reactions to stress and its effects on memory is the fact that women and men respond with different physiological and cognitive responses to stress. For example, cortisol reactivity is mediated by the use of oral contraceptives and female hormones in different phases of the menstrual cycle (Kirschbaum et al., 1995, 1999), and memory functions are also differently affected by stress in females and males (Wolf, 2003; Wolf, Schommer et al., 2001). To avoid this variance, in the present thesis we have decided to only examine the effects of stress on memory retrieval in men. We acknowledge this as a shortcoming, since most stress related disorders (like PTSD and depression) are more prevalent in women than men. However, studying these effects in a homogenous group is a first step in further understanding the relation between cortisol and memory.

Research on the effects of stress and stress hormones on memory retrieval

Both cortisol and (nor)adrenaline are thus active in the brain after stress. They are able to strengthen the consolidation of memories into long-term memory by their effects on the hippocampus and amygdala (McGaugh, 2000), especially when stress is experienced in the context of or around the time of the events to be remembered (Joels et al., 2006; Smeets et al., 2007). However, the effects of stress and stress hormones on the retrieval of memories seem to be in the opposite direction. Memory retrieval has mostly been found to be impaired by acute psychosocial stressors (Domes et al., 2004; Kuhlmann, Piel et al., 2005; Smeets et al., 2008). Interestingly, especially emotional memories have been found to be sensitive to the effects of stress (Domes et al., 2004; Kuhlmann, Piel et al., 2005; Smeets et al., 2008). Stress thus seems to impair memory retrieval and this is thought to be due to increases in cortisol levels. Although stress elicits endogenous cortisol increases, and the individual differences in these increases could in some cases be related to memory retrieval (Domes et al., 2004; Smeets et al., 2008), the idea that cortisol may affect memory retrieval is also tested more directly by exogenous administration of cortisol. Recent studies have found that cortisol administration indeed impairs memory retrieval in humans (first study: de Quervain et al., 2000; for an overview see: Het et al., 2005), and again this effect is in some studies found to be most pronounced for the retrieval of (moderate) emotional information (Buchanan, Tranel et al., 2006; Kuhlmann, Kirschbaum et al., 2005; for an overview see Wolf, 2008).

The finding that mostly emotional memory retrieval is affected by stress and cortisol is in line with an animal model proposed by Roozendaal et al. (2003, 2006), in which noradrenergic activity is a prerequisite for cortisol effects on memory. That is, when noradrenergic signaling from the basolateral amygdala is blocked in rodents, cortisol no longer affects memory retrieval. Similar preventive effects on the impairing effects of cortisol on memory retrieval by a beta-adrenergic blocker (propranolol) are found in humans (de Quervain et al., 2007). As mentioned earlier, emotional memory retrieval is found to elicit amygdala activity and might thus supply the necessary noradrenergic activity that is needed for cortisol to impair memory retrieval. However, previous animal studies (Okuda et al., 2004) and preliminary studies in humans (Elzinga & Roelofs, 2005; Kuhlmann & Wolf, 2006b) have also shown that memories don't need to be emotional for cortisol to impair retrieval, so long as the environment elicits enough arousal. More research is needed to clarify the circumstances in which cortisol can impair memory retrieval.

We should note that when studying emotional memory retrieval, both negatively and positively valenced memories can be investigated. In the present thesis however, we will focus merely on the retrieval of negative memories, since these are most relevant in the field of clinical psychology, where problems are usually related to negative memories (e.g. depression and PTSD).

During stress, not only cortisol levels increase, but also (nor)adrenergic signaling is increased. The effects of stress might thus also be partly mediated by this hormone / neurotransmitter. While there is strong evidence that noradrenergic signaling is a prerequisite for cortisol effects on memory, the direct effects of (nor)adrenaline on memory retrieval in humans are basically unknown (Chamberlain et al., 2006). Increases in noradrenergic signaling might lead to a higher level of attention and vigilance, potentially increasing memory retrieval (Sara, 2000), but this will have to be specifically tested. On the other hand, blocking adrenergic activity by a drug called propranolol has only been done once in the context of a memory retrieval task, but did not show any effects (de Quervain et al., 2007). Animal research does show a role for (nor)adrenaline in extinction or reconsolidation processes (Debiec & LeDoux, 2004; Przybyslawski et al., 1999). That is, blocking of adrenergic activation with propranolol directly after reactivation was found to disrupt spatial and conditioned fear memories in rodents. Not much is known yet on the effects of blocking or enhancing (nor)adrenergic activity on human memory retrieval and reconsolidation. Therefore, more research in this area is needed.

Another issue that remains unclear is whether recent and remote memories are equally affected by stress. That is, retrieval of recent and remote memories is possibly mediated by different brain areas, and may hence be differentially affected by stress. If remote memories become less dependent on the hippocampus over time (as the consolidation theory states), they might also become less vulnerable to the effects of cortisol. However, animal studies have shown that GR receptors are also present in prefrontal and neocortex areas (Sanchez et al., 2000), the place where remote memories are stored according to consolidation theory. In that respect, even remote memories might be vulnerable to cortisol influences, as would be predicted from the Multiple Trace Theory as well. The only study till now that investigated retrieval of remote memories was by Wolf et al. (2002). He did not find any effects of stress on

the retrieval of these remote memories, but the learned information was all neutral, implicating there might not have been enough arousal for cortisol to affect memory. Studies on the effects of stress hormones on memory retrieval should try to make more distinction between recent and remote memories.

Furthermore, almost all studies on the effects of stress hormones on memory retrieval have used word list or short stories as experimental memory material instead of real autobiographical memories. Although memories created in the lab are better controlled than real life memories, conclusions might not fully generalize to autobiographical memory processes. And as the retrieval of autobiographical memories might be mediated by slightly different brain areas than simpler information about e.g. word pairs or pictures that were learned before (Gilboa, 2004), effects of stress might differ. A single study on the effects of cortisol on autobiographic memory retrieval did show a retrieval impairment, but this was most pronounced for neutral memories (Buss et al., 2004), contrasting studies using neutral and emotional words. When studying autobiographical memory retrieval, memories are usually not evaluated on accuracy, but on the level of specificity they reach. The model of Conway and Pleydell-Pearce (2000) may help to elucidate the mechanisms which explain why autobiographical memories can become over-general instead of specific. This model assumes that autobiographical memories are reconstructed in a dynamic and iterative process from stored autobiographical knowledge and semantic knowledge. Autobiographical knowledge is stored and accessed hierarchically, with upper layers containing general life-time information, narrowing down to lower layers, where detailed sensory and perceptual situation-specific information is found. According to this model, deliberate retrieval of autobiographical memories follows a hierarchical process starting with retrieval of life time periods involving general events, followed by the retrieval of event specific knowledge of one event. In the process of reconstructing autobiographical memories patients with stress-related disorders may get stuck in the intermediate level of this model and are unable to retrieve specific details that concern self-relevant information. Using a specificity measure (e.g. the Autobiographical Memory task (AMT), first described by Williams & Broadbent, 1986), the effects of stress on autobiographical memory can be studied.

The bright side of attenuating emotional memory retrieval

Clinical implications of fundamental knowledge

As described in the previous paragraph, emotional memory retrieval seems to be impaired by stress hormones like cortisol. While this might seem a negative consequence, in some situations it can be adaptive. That is, in some situations it might be desirable to block emotional memory retrieval. As described in the first paragraph, in some disorders, emotional memories elicit very strong emotions and sometimes so strong that they can disable normal life. For example, patients with post-traumatic stress disorder (PTSD) experience flashbacks and intrusions of the trauma, a sense of reliving the trauma and hyper reactivity to traumatic cues. But also depressed patients can have a bias in memory for the retrieval of negative memories (Leppanen, 2006). If

it is possible to impair the retrieval of emotional memories, or make memories less emotionally intense, this could enhance the efficacy of treating these disorders.

Pitman and Delahanty (2005) have proposed a model that might explain the pathogenesis of PTSD. During a traumatic experience, a strong stress response can lead to the release of an excessive amount of stress hormones like adrenaline and cortisol. This can lead to strong memories that are often and vividly relived. Every time the memory is relived stress hormones are released again and might strengthen the memory, leading to a cycle of over-consolidated memories. As described before, this process of memories being affected by their retrieval is also called reconsolidation. If we can attenuate either the excessive retrieval, or the strong reconsolidation of these memories, it might be possible to break this cycle. As cortisol is found to impair emotional memory retrieval, and preliminary studies in animals and humans have shown that propranolol can reduce reconsolidation of emotional memories (Brunet et al., 2008; Debiec & LeDoux, 2004; Przybyslawaki et al., 1999), these drugs are of interest to clinical practice. At this moment several studies with cortisol and propranolol in clinical populations have been performed or are being conducted, showing promising results (Aerni et al., 2004; Pitman et al., 2002; Soravia et al., 2006; Vaiva et al., 2003; Weis et al., 2006). As the mechanisms through which these drugs work are still largely unclear, the present thesis will explore the impact of both cortisol and propranolol on memory retrieval and reconsolidation in healthy people. While these results might not be directly applicable to clinical groups (with far stronger emotional, traumatic memories), it is a start to understand the working mechanisms of these drugs.

We can hypothesize on the mechanisms that are affected by cortisol and propranolol. Neuro-imaging studies have shown that the impairing effects of cortisol on memory retrieval might be largely mediated by the hippocampus (de Quervain et al., 2003; Oei et al., 2007). Cortisol might thus diminish the recall of emotional memories, but can possibly also reduce the emotional impact of the memory as the emotional reactions belonging to the memory are not fully accessed. However, unconscious automatic reactions to memory cues might possibly still elicit emotional responses (for a debate on conscious versus unconscious memories see Mitchell et al., *in press*). Whether cortisol can reduce the emotional impact of memories thus remains to be elucidated. Furthermore, if memories are not or not fully reactivated due to cortisol, less reconsolidation might take place, potentially leading to a less strong memory trace. Propranolol on the other hand is thought to mostly affect the amygdala (Strange & Dolan, 2004; van Stegeren, Goekoop et al., 2005). During the retrieval of emotional memories, propranolol might block the access to the emotional responses normally elicited by the amygdala in response to a memory, and could thus lead to a memory of an emotional event without the emotional experience. As the memory is remembered less intense, it might also be reconsolidated to a lesser extent, which could potentially also impact the conscious recall of the declarative components on the long-term.

In summary, while cortisol might block more declarative recall of memories mediated by the hippocampus, there is a possibility that it also affects the emotional experience of these memories. Propranolol on the other hand might block the retrieval of emotions associated with memories mediated by the amygdala, but possibly also

leads to less strong memories. In the present thesis we will explore the immediate and long-term impact of cortisol and propranolol administration both on declarative memories and on the emotional reactions to memories to examine these hypotheses. Understanding the effects of cortisol and propranolol on memory is important to assess both the potential positive effects of these drugs, but also possible side-effects and ethical consideration of the use of these drugs. That is, will factual memories actually be forgotten, or only become less emotional, and how long will those effects last? It might very well be that patients are better helped by a good processing of the memories instead of forgetting those memories (McCleery & Harvey, 2004). Before these considerations and implications can be fully discussed, more knowledge is needed on the effects of cortisol and propranolol on memory retrieval and reconsolidation. The present thesis will try to unravel some of these processes.

Outline of this thesis

Main aims

The main aim of the present thesis is to study the effects of stress hormones, in specific cortisol, on the retrieval of emotional memories in healthy humans. In addition, we were interested in the effects of stress hormones on post-retrieval processes like reconsolidation. Previous research has shown that the retrieval of emotional information is negatively affected by stress. However, the specific conditions in which these effects appear, as well as the long-term effects, are still unclear. Several of these issues are investigated in the present thesis. More knowledge on the effects of cortisol, as well as propranolol, on the retrieval of declarative memories and emotional reactions to memories, could be useful in clinical practice that is involved with disorders characterized by excessive retrieval of emotional memories.

Chapters

In this introduction, background information was given on the field of emotional memory retrieval and the possible influences of stress and stress hormones on this process, as well as the potential useful implications for clinical practice. In the next five chapters, data from three studies that were conducted between September 2004 and 2008 will be described.

In chapter 2, the effects of a psychosocial stress task on memory retrieval of neutral and emotional words is described, in which the effects of cortisol increases during and after the stress task are related to memory performance. This was done to further explore the different effects of cortisol on the retrieval of neutral and emotional memories in both an arousing and a non-arousing setting. Furthermore, the memories were created in the lab either 1 day or 5 weeks before retrieval to asses whether retrieval of recent and remote memories is differentially affected by stress.

In chapter 3 a follow-up of the study from chapter 2 is described, for which all participants were contacted again 6 months after the start of the original study. As it might be possible to affect the retrieval of emotional memories by stress, it might also be possible that these memory traces are affected in their reconsolidation. It is thus

interesting to see whether retrieval impairments due to stress and stress hormones are temporary or have long-term effects.

Chapter 4 describes the immediate and prolonged effects of exogenous cortisol and propranolol administration on declarative memory retrieval of neutral and emotional words, to investigate the effect of these drugs both on retrieval and post-retrieval processes.

Chapter 5 describes a study on the effects of stress on the specificity of autobiographical memories, to test whether findings on laboratory memory tasks can be generalized to real life memories.

Chapter 6 is also directed to autobiographical memory and investigates the immediate and prolonged effects of cortisol and propranolol administration on the subjective experience of personal memories, as well as on the physiological reactivity to these memories. Chapter 6 is based on the same study as chapter 4, but chapter 4 measured effects on declarative memory retrieval with a different task.

Finally, chapter 7 will give an overview of the findings in chapters 2 to 6 and discuss the implications of these findings for memory models and clinical practice. The chapter will conclude with some suggestions for future research.