Stress: a modulator of memory consolidation and retrieval

From the mechanisms behind memory modulation towards psychopathology

Jeroen Pragt
s3653676

21 December 2021

Supervisor: dr. B. Buwalda

Life Science & Technology
Faculty of Science & Engineering
University of Groningen

Abstract

Stress is experienced continuously in daily life. Peripheral responses towards stressors include the sympatho-adrenomedullary (SAM) system and the hypothalamus-pituitary-adrenal (HPA) axis. The SAM system is responsible for the release of adrenaline and noradrenaline (NA) by the adrenal glands, which can exerts effects on both brain and body. Besides that, the HPA-axis releases cortisol by the adrenal glands after a cascade of reactions via the hypothalamus and pituitary.

Previous research has revealed that these both stress responses are involved in the modulation of emotional memory. Emotional memory is the memory that can be associated with an emotional arousing event, that is caused by stress for instance. Main regions that are involved in the modulation of emotional memory are the amygdala and the hippocampus, of which it has been shown that the amygdala has projections towards the hippocampus. The hippocampus itself is a region that plays a main role in the acquisition and consolidation of spatiotemporal memory. Although this modulation is a very adaptive learning system, maladaptation of the stress responses can also result in pathological conditions. An example of such a disease is the post-traumatic stress disorder (PTSD).

In this thesis, the main mechanisms of the modulation of emotional memory as a response to stress will be described in detail to give an updated overview of the current literature in this field. Furthermore, the onset of these mechanisms can have modulate emotional memory in various ways. Therefore, the timing of the mechanisms will be discussed too. Finally, I will discuss the symptoms and mechanisms of PTSD and translate these findings towards implications for future perspectives on the treatment of PTSD.

Table of contents

Abstract 2
Introduction 4
Importance of the basolateral amygdala and other brain regions in emotional memory modulation 5
Timing of noradrenaline and corticosterones and its influence on memory formation and retrieval 9
The adaptive benefit and possible pathological effects of emotional memory 11
Conclusion 13
References 14

Introduction

Many can think of a stressful experience some point in their life. Typical for such a stressful experience is that many details of the context of that event are easily recalled from memory. The cascade of bodily reactions in response to those experiences are playing an important role in this recollection. In these so-called stress responses, the brain regulates the secretion of peripheral adrenaline and cortisol, via the sympatho-adrenomedullary (SAM) system and the hypothalamus-pituitary-adrenal (HPA) axis respectively. The SAM system exerts the most rapid response and the resulting secretion of adrenaline into the bloodstream can result in various physiological adaptations, like increased heart rate and blood pressure (Tank & Wong, 2015). In the meantime, the HPA-axis is also activated and secretes cortisol through a cascade of reactions that involve the release of corticotropin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH) by the hypothalamus and the pituitary respectively (Smith & Vale, 2006). In addition to this activation of the peripheral stress response, there is extensive evidence that certain brain circuits are activated that play a crucial role in the consolidation of the context of severe stressors that people are experiencing (McGaugh, 2000; Tank & Wong, 2015).

Particularly the role of noradrenalin and glucocorticoids in the modulation of emotional memory has been studied extensively (McGaugh, 2000). Key brain regions that play a role in the consolidation of memory are the hippocampus and the amygdala. The hippocampus has been associated with the storage of declarative memory and is very important for the spatiotemporal context of the experience (what, when and where) (Nadel & Moscovitch, 1997). Besides the hippocampus, the amygdala is perceived as the brain centre of emotion (Baxter & Croxson, 2012). The function of the amygdala has been extensively studied, and it has been found that the amygdala projects to the hippocampus to modulate memory formation (Roozendaal et al., 2009). In human studies, it has been shown that memory consolidation was enhanced when individuals subjectively rated pictures as negatively or positively arousing indicating that emotion facilitates memory consolidation (Fastenrath et al., 2014).

Because the research on mechanisms involved the regulation of emotional modulation of memory is extensive, this thesis provides an overview on the current standings in this field. The main objective of this thesis is to answer the following question: What is the mechanism behind the facilitating effect of stress on emotional memory? Therefore, the main mechanisms of this modulatory effect are explained on the basis of the key brain regions and systems that play a role in this. Although a strong consolidation of emotional memory is highly adaptive from an evolutionary perspective, there are also mental disorders that are related to this formation of emotional memories by stressful events, like post-traumatic stress disorder (PTSD). Therefore, this thesis not only addresses the adaptive properties of emotional memory formation but also includes maladaptive aspects leading potentially to a functional psychopathology.

Importance of the basolateral amygdala and other brain regions in emotional memory modulation

In the formation of memory after a stressful experience, the amygdala is an important brain region. In an imaging study of Cahill et al. (1996), individuals had to recall film clips, either emotionally or neutrally arousing. They found that the activity, measured by the glucose metabolic rate, of the right amygdala was correlated with film recall if they were emotionally arousing. This suggests that recall, or memory, for emotional events is better than emotionally less arousing events and that the right amygdala might play an important role in this. However, they did not find these results for the left amygdala, which might be due to asymmetric functioning or lateralisation. Although this study already provides information that the amygdala is involved in emotional memory, this study does not show how the amygdala is involved. Still, another study found that lesions in the basolateral amygdala (BLA), but not in the central (CEA) and medial (MEA) nucleus of the amygdala, affected glucocorticoid (GC) induced memory modulation (Roozendaal et al., 1996). Furthermore, removal of the adrenal glands by adrenalectomy showed that memory acquisition and retention is not impaired or enhanced if the BLA is lesioned. Adrenalectomy results in the removal of circulating corticosteroids, hence impairing the glucocorticoid induced memory modulation. Lesions in the CEA and MEA blocked the adrenalectomy effect, thereby blocking the memory impairment. The authors suggest that the CEA and MEA therefore only play a role in optimizing the modulatory effects by the GRs and MRs that are present in these regions, while the GCs in the BLA are crucial in emotional memory modulation. I will try to elucidate on the mechanisms in the BLA involved in emotional memory formation and the causal role of mediators of stress like GCs and NA in the next paragraph.

GCs can bind to two types of receptors: a mineralocorticoid receptor (MR) and a glucocorticoid receptor (GR). Both MRs and GRs can also bind aldosterone and several other substances. The function and organisation of these receptor types have been extensively studied by Joëls & de Kloet (1994). It seems that MRs have a higher affinity to GCs, while GRs have a much lower affinity to GCs. This means that MRs are generally occupied already to large extent under baseline conditions whereas GRs become occupied particular after a stress response, when GC levels are higher than baseline. Roozendaal et al. (1996) found that administration of a GR antagonist increased the escape latency in a water maze. The water maze is used to study rats that have to escape from the maze by the use of distal cues (Morris, 1984). These cues can be remembered by the rats and therefore, the escape latency is a measure for memory performance here. The findings thus indicate that memory is impaired by blocking GRs. GRs have been found to be a mediator of memory modulation, although other studies have shown that MRs are involved too (Rimmele et al., 2013; Zhou et al., 2010). In a mouse study, pre-training administration of the MR antagonist spironolactone reduces the freezing behaviour in fear conditioning for both contextual memory as tone-cue memory (Zhou et al., 2010). Less freezing behaviour has been associated with reduced fear, indicating that the mice were not conditioned for fear or had impaired fear memory. Because the control group showed increased freezing memory, it can be argued that the latter is the reason that the MR-blocked mice show less freezing. This supports the hypothesis that GCs innervating both GRs and MRs are involved in emotional memory modulation.

Besides GCs, also noradrenalin (NA) plays a role in the consolidation of the details of this experience in memory. Various studies have examined the role of GCs and NA in the BLA with

object recognition training (ORT) (Roozendaal et al., 2006, 2008). Roozendaal et al. (2008) found that injections of NA in the BLA after object recognition training resulted in enhanced memory consolidation compared to saline-administered rats. In these findings, the modulatory effect of NA was dose-dependent, suggesting that there is an optimum NA-dose at which the consolidation enhancement is best. In contrast, administration of the β-adrenoreceptor antagonist propranolol in the BLA, blocked the consolidation enhancement (Fig 1A), also suggesting that the β-adrenoreceptors are involved in memory modulation. In addition, object recognition training, which causes low emotional arousal, was sufficient to activate the glucocorticoid-based memory enhancement, in combination with NA injections in the BLA. Similar results have been found by a previous study (Roozendaal et al., 2006), in which the involvement of the noradrenergic system was studied in more detail. Systemic injections of propranolol in combination with corticosterone after object recognition training impaired memory performance in comparison with saline-treated rats. In this experiment, they used unhabituated rats. Another study namely found that habituated rats did not show a memory enhancement by object cognition training in combination with systemic corticosterone administration (Okuda et al., 2004). To further test the hypothesis that noradrenergic activation is necessary to induce GC-induced memory modulation, Roozendaal et al. (2006) examined whether administering the α2-adrenoreceptor antagonist yohimbine would affect this modulation. α2-adrenoreceptors are presynaptic receptors that exert a negative feedback towards NA release. NA binds to these α2-adrenoreceptors, which impairs further release of NA. Therefore, blockade of α2-adrenoreceptors should stimulate the release of NA. Indeed, systemic administration of yohimbine has been found to increase in extracellular NA (Abercrombie et al., 1988). Roozendaal et al. (2006) found that administration of yohimbine in combination with systemic administration of corticosterone directly post-training caused an enhanced object recognition memory effect in habituated rats (Fig 1B). In contrast, this enhancement was not seen when only yohimbine was administered immediately after the training. The findings of the involvement of β-adrenoreceptors, the stimulatory effects of NA administration and the effects after α2-adrenoreceptor blockade suggest that noradrenergic stimulation of the BLA is necessary for GC-induced modulation, although this still depends on the timing of stimulation. The time-induced effects will be explained more thoroughly in the next chapter.

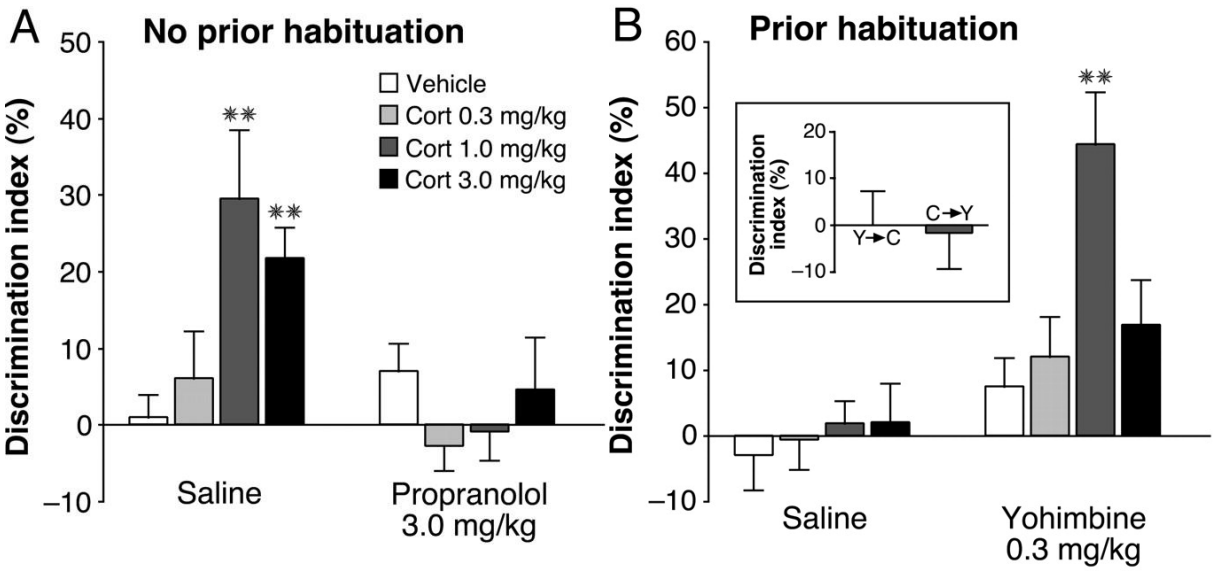

Figure 1 *Performance on object recognition memory after retention period of 24 hours by measure of discrimination index. All administered drugs were dissolved in saline. Corticosterone was*

dissolved in 5% ethanol and saline. A) Effect of systemic coadministration of β*-adrenoreceptor antagonist propranolol with corticosterone or vehicle on object recognition memory in comparison with a saline-treated placebo group. Rats were not previously habituated to object recognition training. B) Effect of the* α*2-adrenoreceptor antagonist yohimbine co-administered systemically with either corticosterone or vehicle solutions on object recognition memory in rats with prior habituation compared to the saline-treated placebo group. Figure from Roozendaal et al. (2006).*

The findings explained above, however, do not show how a stress response of the SAM-system results in the involvement of the noradrenergic system in GC-mediated memory modulation. A study by Williams et al. (1998) showed that systemic injections of adrenaline increased NA levels in the amygdala and that this is mediated via the nucleus of the solitary tract (NTS). Here, adrenaline was administered systemically and NA levels in the BLA were measured before and after adrenaline administration. The results showed that NA levels in the BLA increased significantly after administration of adrenaline. Furthermore, if adrenaline is indeed passed to the brain via the NTS, lidocaine administration into the NTS should block the increase of NA in the BLA. Indeed, NA levels did not significantly increase anymore after systemic injections of adrenaline. These findings suggest that adrenaline is passed to the brain via the NTS. However, this does not fully reflect the mechanism behind the increase of NA in the BLA. To better understand the pathway of NA from the NTS towards the BLA, a study found that projections from the NTS towards the locus coeruleus (LC) are responsible for the release of NA by the LC (McCall et al., 2017; Mello-Carpes & Izquierdo, 2013). Mello-Carpes & Izquierdo (2013) found that injections of muscimol in the NTS until 3 hours after object recognition training resulted in impaired memory performance. Memory performance was measured by the exploration time of a novel object compared to a familiar object. In addition, these results were also found after administration of muscimol into the LC. Thus, both the NTS and the LC are necessary for memory modulation.

As indicated earlier, NA exerts a dose-dependent effect on the GC-induced memory modulation. These results have been found for GC too and is supported by more studies (Okuda et al., 2004; Power et al., 2000). In the study by Roozendaal et al. (2006) various doses of corticosteroid have been administered in combination with either propranolol (Fig 1A) or yohimbine (Fig 1B), which had differential effects on memory performance. Furthermore, systemic administration of various doses of the GC dexamethasone resulted in differential effects too (Power et al., 2000). Already a century ago, the Yerkes-Dodson law was postulated, which has been reviewed by Diamond et al. (2007). In this law, the relationship between arousal and memory performance is indicated as an inversed-u curve (Fig 2). It shows that high arousal can lead to memory enhancement in simple tasks, like single-attention tasks, while in more complex tasks, in which is more demanding, memory is impaired.

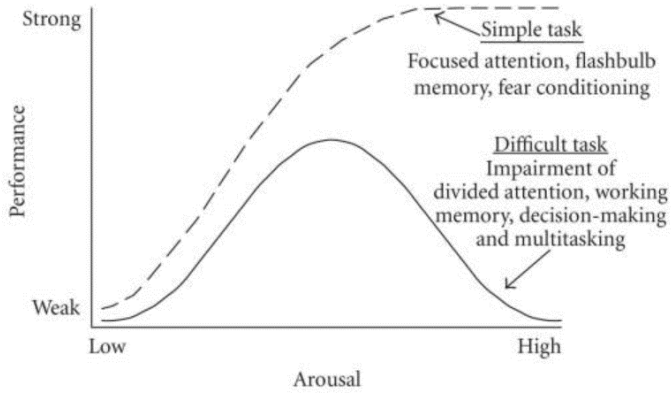

Figure 2 *The original Yerksen-Dodson law, which shows the association between emotional arousal and memory performance. Figure modified from Diamond et al. (2007).*

Although the BLA has been shown to be important in regulating memory performance, it has many projections to other brain regions that play a role in memory performance. In a human study, it has been found that the connection between the amygdala and hippocampus is stronger during the encoding of emotionally arousing pictures that are either negatively or positively arousing (Fastenrath et al., 2014). These connections were measured with fMRI, of which the data was modelled with dynamic causal modelling. Dynamic causal modelling can provide information about the connectivity between brain regions. The findings imply that the amygdala modulates emotional memory by involving at least the hippocampus. Furthermore, BLA injections of atenolol, which is a β-adrenoreceptor antagonist, in combination with a GR agonist in the dorsal hippocampus showed that memory enhancement was blocked. This results was only found ipsilaterally. These findings may indicate that the GRs are necessary for the modulation of memory modulation in the hippocampus (Roozendaal et al., 1999).

In summary, studies have shown that both MRs and GRs in combination with β-adrenoreceptors in the BLA are crucial in GC-induced emotional memory modulation. The finding that the noradrenergic system collaborates with GCs to enhance memory performance has been reviewed by (Roozendaal et al., 2006). In Figure 3, an overview of the mechanisms behind the modulation of emotional memory can be seen. Stress results in the activation of the SAM-system and HPA-axis, inducing the release of adrenaline and cortisol by the adrenal glands. As indicated above, adrenaline is passed to the NTS to activate the noradrenergic system of the LC. The LC then projects to the BLA. GCs can pass the blood-brain barrier by transporters that regulate the influx of GCs (Pariante et al., 2004). The cooperation between NA and GCs results in BLA projections to other brain regions, like the hippocampus.

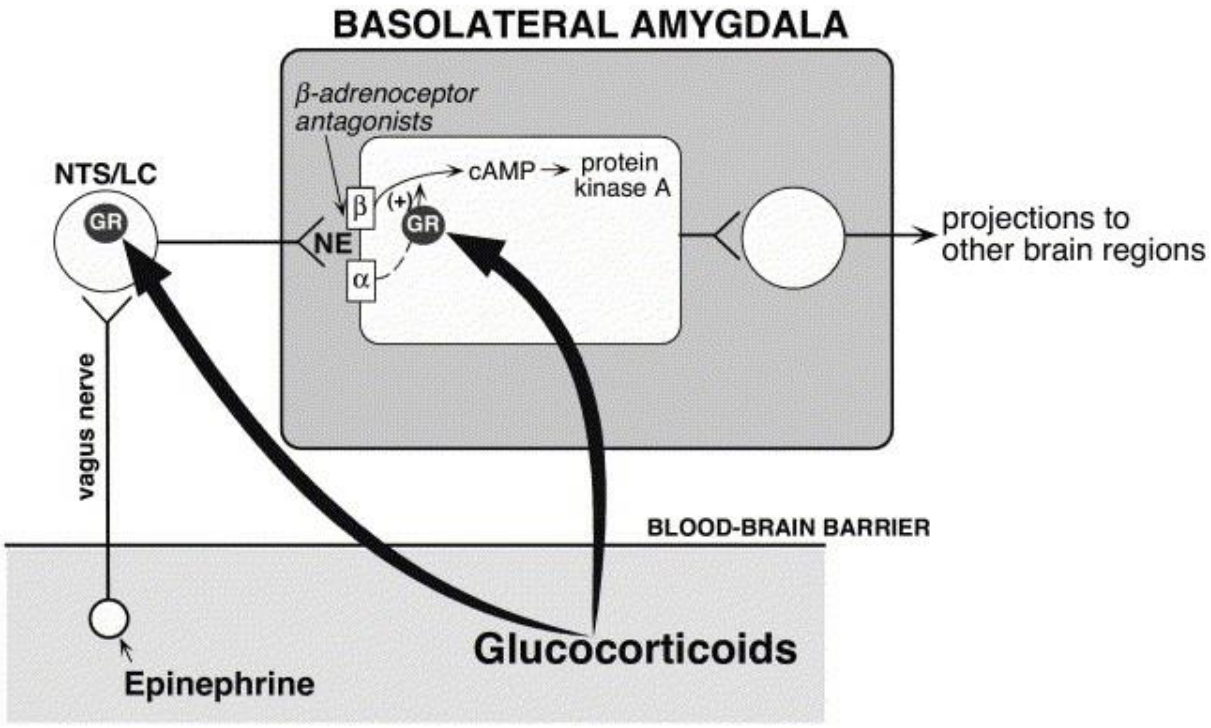

Figure 3 *Overview of the mechanism behind stress-induced memory modulation in the brain. NTS: Nucleus of the solitary tract; LC: Locus coeruleus. Figure from B. Roozendaal et al. (2006)*

Timing of noradrenaline and corticosterones and its influence on memory formation and retrieval

Stress can act on different processes within the domain of emotional memory and, therefore, has differential effects on memory performance. It has been shown that contextual memory is impaired if MRs or GRs are systemically blocked during the acquisition phase (Zhou et al., 2010) and if circulating GCs are removed by an adrenalectomy (Roozendaal et al., 1996). The study by Zhou et al. (2010) with mice reports that MR blockade before training induces less freezing behaviour 3-4 hours after training, in contextual and tone-cue memory respectively. Furthermore, these mice were again tested on contextual and tone-cue memory 24 or 25 hours after the training phase. Here, no difference in freezing behaviour was observed between the control group and the MR-blocked group (Zhou et al., 2010). These findings indicate that pre-training MR blockade only impairs memory on short-term. Similar findings have been found for olfactory fear conditioning, in which MR blockade by administration of spironolactone subcutaneously 60 minutes before training resulted in a less-defending strategy, implicating that memory acquisition was impaired (Souza et al., 2014). Moreover, subcutaneous administration of an MR antagonist before olfactory fear conditioning, in which the rats store this new information in memory, resulted in a higher approach time to the odour, a decrease in hide time and by reducing the time for risk assessment. These findings suggest that MRs in general are highly involved during the acquisition phase, although it has not become clear where the MRs were being blocked. However, this memory effect by blocking MRs may also be an effect of deficiencies in locomotor activity, since memory was assessed by approach and hide time. Post-training MR blockade does not show differences in memory performance, measured by the approach and hide time again, suggesting that locomotor

activity has not been interfered (Roozendaal et al., 1996; Zhou et al., 2010). Because the affinity of GCs with MRs is higher than with GRs, this results in an earlier occupation of MRs by GCs. If GCs increase during peak periods, for instance as a response to stress, GRs are being occupied too, because the MRs are already completely occupied. Therefore, it might be that MRs are involved in short-term memory modulation, while GRs are involved on the long-term.

To find out, whether this might be case, the involvement of GRs in the acquisition phase has been studied too. Zhou et al. (2010) found that administration of a GR antagonist in the peritoneum 1 hour before the training phase resulted in more freezing behaviour in contextual memory only 24 hours after training, suggesting that memory is only improved on the long-term. Furthermore, these authors also performed a tone-cue memory task. During this tone-cue memory task, freezing behaviour increased only 4 hours after training. Therefore, it might be that MRs are mainly occupied if GRs are blocked, thereby stimulating memory consolidation. Post-training injections of GR agonists, however, affect memory modulation too. This suggests that GRs are not definitively necessary during the acquisition phase, although it seems that post-training GR stimulation facilitates learning if GRs are stimulated shortly after training (Roozendaal et al., 2006).

Besides the effects on memory acquisition, stress can also affect memory retrieval. In a study by Tollenaar et al. (2009), humans were treated with cortisol, propranolol or placebo 75 minutes before testing memory by means of free recall of neutral or emotionally words, cued recall and a digit span forward and backward task. The words that the individuals needed to recall were already learned one week earlier. The results of this study show that the cortisol-group had an impaired free recall compared to both the placebo- as the propranolol-group. Similar results were obtained one week later, when the individuals were tested on memory retrieval again, now without treatment. These results suggest that cortisol can impair memory retrieval. Furthermore, both MRs and GRs are involved in the modulation of memory retrieval and it has been found that those have an opposite function (Rimmele et al., 2013). Free recall of emotional and neutral pictures and texts was improved in humans after blocking GRs, while free recall was impaired after blocking MRs. MR and GR antagonists were administered orally directly before retrieval testing, so the blockade of MRs and GRs did not involve memory acquisition and consolidation and the antagonists did not block MRs and GRs in one particular brain region. The reason for the opposing effects of MR and GR antagonism is not fully clear, but it might be that the stimulation of MRs induce a retrieval improving effect. In this scenario, MR blockade would indeed lead to retrieval impairments, while GR blockade would overstimulate the MRs and, thus would improve retrieval. This is in line with another study (Yau et al., 2011), which argues that GR antagonism or reducing GC levels in the brain blocked memory impairments, although this was explicitly found in aged rats and not in young rats. Therefore, it might be that at least part of these results can be explained by ageing-related memory deficiencies.

In summary, the timing of stress in combination with the learning event have differential effects on memory performance. Memory consolidation is improved during stress if stress appears in approximately one hour before the learning event (Souza et al., 2014; Zhou et al., 2010). According to a review by Schwabe et al. (2012), memory is improved if the stress is related to the learning event (Figure 4). If stress appears simultaneously with the learning event, the information is better consolidated in long-term memory by the influence of NA and GCs by the mechanisms explained

above. GCs seem to activate a long-term action of the GRs, inducing gene-mediated memory suppression by GRs (Schwabe et al., 2012).

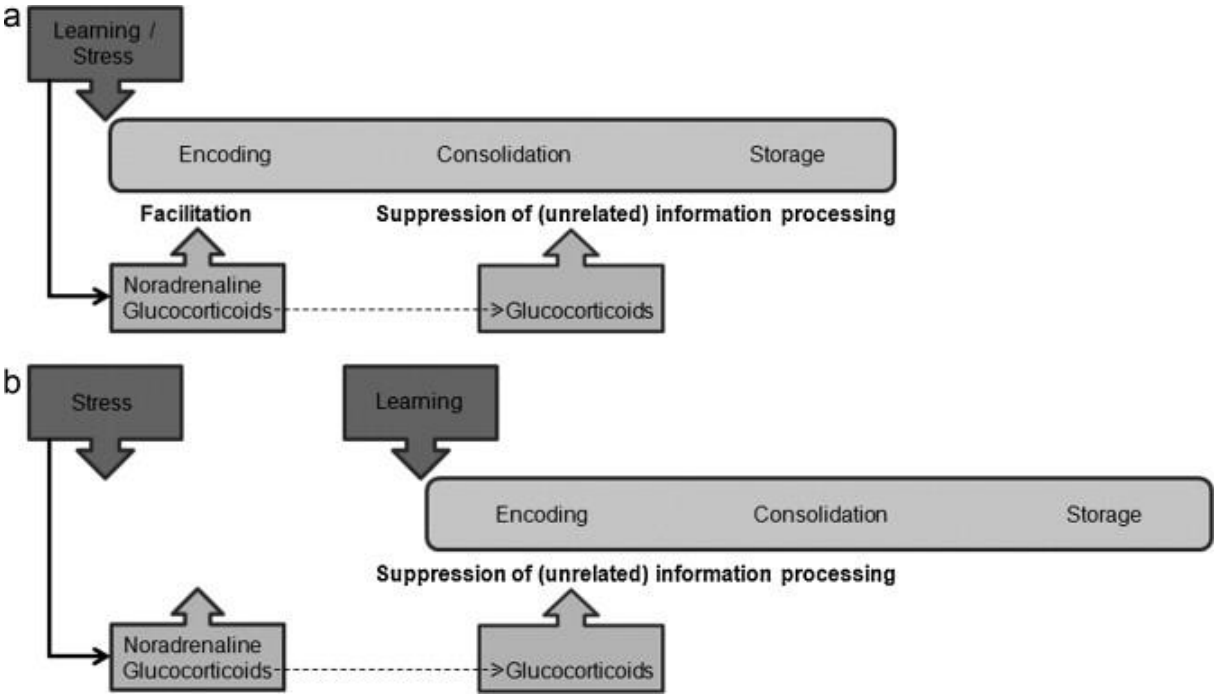

Figure 4 *Mechanisms of action of stress on memory performance. A) If the learning event is timed simultaneously with a stressful experience, the information will be better acquired by the influence of noradrenaline and glucocorticoids. On the long-term memory acquirement will be impaired to reduce the consolidation of (unrelated) information. B) If the stressful experience takes place earlier than the learning event, these events are not synchronized. Therefore, the short-term improvement of memory acquisition has no consequences, while the encoding of the learning event is impaired because of the long-term effect of glucocorticoids. Figure from Schwabe et al. (2012).*

The adaptive benefit and possible pathological effects of emotional memory

PTSD is a stress-related disorder which can be developed by people that have experienced one or more traumatic events in the past. According to the DSM-5 criteria, PTSD is diagnosed by the following symptoms: (1) exposure to a traumatic stressor; (2) anxiety-related or psychological stress symptoms that can be associated with the traumatic experience; (3) avoidance of stimuli that is related to the traumatic experience; (4) the starting or worsening of mental problems related to the traumatic experience; (5) the starting or worsening of arousing behaviour which can be associated to the traumatic experience (American Psychiatric Association, 2013). Furthermore, the symptoms that are being shown by the individual need to be present for more than a month and may not be attributable to abuse or medical disorders. In the following paragraphs I will explain how an adaptive form of emotional memory can shift towards psychopathology in PTSD.

Emotional memory consolidation mechanisms are beneficial and adaptive in life, because it can prevent life-threatening events in the future. However, the development of PTSD is not likely to be an adaptive mechanism and it might be that PTSD is just the cost. Our brains can adapt to new stimuli and associations, which makes our brains vulnerable to make wrong associations (Marks & Nesse, 1994). As explained in the previous chapters, the formation of emotional memory is induced by stress responses of the HPA-axis and the noradrenergic system. For PTSD-patients it has been found that the HPA-axis shows alterations and that plasma cortisol levels are lower (Yehuda et al., 1994). A study by Yehuda et al. (1996) found indeed that baseline plasma cortisol levels were lower in PTSD-patients compared to normal people. Here, baseline levels were measured by taking blood samples every 30 minutes starting at 10 AM. The measurements were stopped 24 hours later, to have data for a complete day-night cycle. The largest drop in baseline cortisol levels between PTSD-patients and normal people were in the evening and early morning. This finding suggests that the HPA-axis is dysregulated in patients with PTSD and the authors imply that lower cortisol levels might be caused due to a higher negative feedback loop for cortisol. In line with this finding is the study performed by McFarlane et al. (2011), in which the regulation of the HPA-axis was studied by a dexamethasone suppression test. In this test, dexamethasone is administered orally to the participants at 8 AM and 4 PM. Normally, dexamethasone reduces salivary cortisol levels via feedback inhibition at the level of the pituitary and the hypothalamus mediated by GR (Cole et al., 2000). This inhibits the HPA-axis and thus, reduces cortisol release (McFarlane et al., 2011). The dexamethasone suppression test resulted in a larger reduction in salivary cortisol in PTSD-patients compared to controls at 8 AM (McFarlane et al., 2011).

The decline in cortisol levels in PTSD patients is thus shown, with an implication of the dysregulation of the HPA-axis. However, the decline in cortisol levels does not show that the HPA-axis is indeed dysregulated. Therefore, a study aimed to find whether CRH levels deviate in PTSD patients compared to controls (de Kloet et al., 2007). Plasma CRH levels were measured in PTSD patients, healthy controls and, trauma controls. The results show that plasma CRH levels are higher in PTSD patients, compared to both healthy and trauma controls. This shows that the elevated CRH levels are characteristic to PTSD and not to the experience of traumatic events in the past, because the trauma controls do not show this elevation. However, the authors note that plasma CRH levels may have an additional source besides the release by the hypothalamus. Therefore, CRH levels in the cerebrospinal fluid are measured in a study by Baker et al. (1999). This study measured the CRH levels in the cerebrospinal fluid for six hours in PTSD patients and healthy controls. Here, CRH levels were also found to be elevated in the cerebrospinal fluid, suggesting that the HPA-axis might be involved in the decline of cortisol levels in PTSD patients. To find out at which level the HPA-axis is dysregulated, ACTH needs to be involved in this investigation too. Yehuda et al. (2004) studied the effects of dexamethasone on ACTH and cortisol levels. A previous study by McFarlane et al. (2011) already showed that cortisol levels were declined after the administration of dexamethasone, but the ACTH response was not included. In the study of Yehuda et al. (2004), the authors hypothesised that dexamethasone administrated orally would decrease the cortisol levels again and that either ACTH levels would decline too or ACTH levels would not deviate. In the first scenario, the drop in ACTH levels would suggest a dysregulation of the negative feedback system of the HPA-axis, focussing on the pituitary and ACTH-release. The second scenario would, however, indicate that the adrenal gland works less well in PTSD patients. The results show that ACTH levels are stronger declined in PTSD patients compared to healthy controls, while the ACTH-to-cortisol ratio did not differ between pre- and post-treatment with dexamethasone. This

suggests that the HPA-axis is dysregulated at the level of the pituitary. In addition, ACTH release was impaired after a DEX-CRH test (Ströhle et al., 2008). In this study, dexamethasone was administered orally to both PTSD patients and healthy controls in the late evening before the intervention day. On the intervention day, CRH (solved in HCl and saline) was infused into the forearm, after which plasma ACTH and cortisol levels were measures. ACTH was found to be significantly declined after the DEX-CRH test in PTSD patients. Cortisol levels did not differ between the PTSD and healthy group. These results illustrate that the ACTH release is therefore declined in the HPA-axis, although the authors remark that the group size was very small. Another study still found similar results (Smith et al., 1989). Here, CRH was infused in the forearm without dexamethasone administration. These results also show a reduced ACTH release in PTSD patients after CRH administration. So, these two studies show that the HPA-axis is dysregulated at the level of the pituitary and ACTH release (Fig 5).

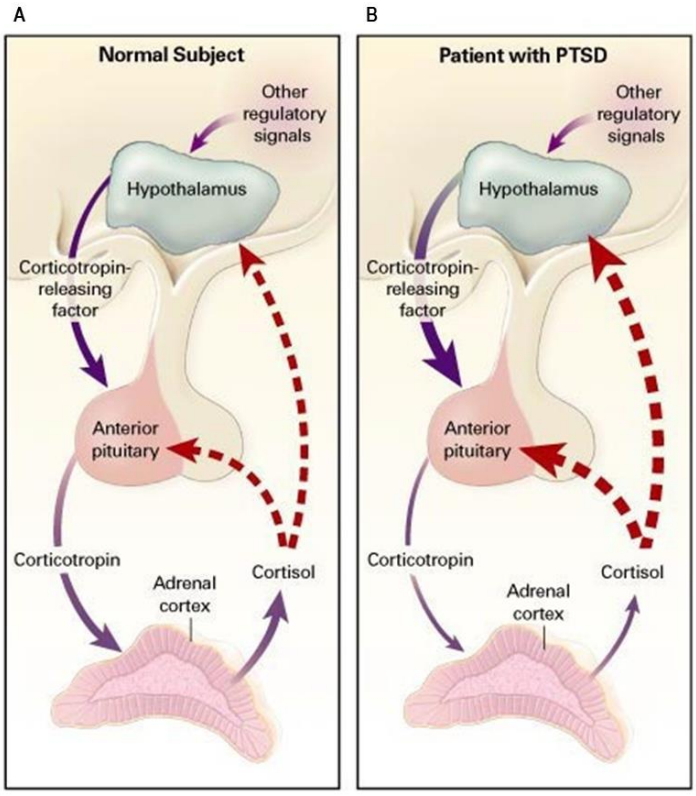

Figure 5 *Comparison of the HPA-axis regulation in normal (A) and in PTSD (B) humans. Normal regulation of the HPA-axis is through the negative feedback loop of cortisol, which impairs the release of CRH by the hypothalamus and ACTH (corticotropin) by the pituitary. In PTSD can be seen that CRH levels are elevated, while ACTH levels are reduced, which illustrates that the release of ACTH is blunted. Furthermore, cortisol levels are also lower in PTSD humans, while the negative feedback of cortisol is even stronger than in normal humans. Figure adapted from Yehuda (2002).*

Conclusion

In the previous sections, it has been shown that emotional memory is affected by the involvement of stress responses that are mediated via both the HPA-axis and the SAM-system. The HPA-axis

results in the release of cortisol by the adrenal gland after a cascade of reactions. Cortisol is transferred to the brain, because it can pass the blood-brain barrier. In the brain, it binds to the GRs and MRs that are present throughout the brain. The most important areas that are targeted by cortisol are the BLA and hippocampus. It could be seen that either removal of GCs or blockades of MRs and GRs around one hour before training resulted in memory impairments. In addition, infusions of GCs into the BLA enhanced memory performance. Besides this, the adrenaline release by the adrenal gland is necessary for cortisol to enhance memory consolidation. Adrenaline is transferred to the NTS via the vagus nerve, where it projects to the LC to release NA into the brain circuits. Based on these findings, it can be concluded that the modulation of emotional memory consolidation is mediated through the release of cortisol by the HPA-axis and the noradrenergic system prior to a learning event.

Although stress enhances the consolidation of memory, retrieval is impaired under stress circumstances. Elevated cortisol or GC levels within 75 minutes before retrieval testing reduced the performance on retrieval. In addition, blocking GRs also resulted in less retrieval performance, while MR blockade did not. In conclusion, cortisol has a long-term functioning by reducing retrieval performance after a stressful event.

Complementary to these findings is the pathological side of emotional memory modulation. In PTSD-patients it has been found that the HPA-axis is dysregulated at the pituitary level, thereby reducing the cortisol release by the adrenal glands. This might be the reason for the onset of several PTSD-symptoms, like high arousal and anxiety, because the reduced cortisol levels may abolish the retrieval impairment that is normally induced by long-term cortisol. Therefore, this might be a target for treating PTSD symptoms, namely by administering low levels of cortisol. A study has already suggested that this indeed could relieve certain PTSD symptoms such as reexperiencing and reducing traumatic experiences (Aerni et al., 2004). However, this study has been performed in 3 human patients only. Therefore, this could be studied more extensive in future, and it could be studied in combination with regular psychotherapy, to study whether cortisol administration might increase the efficacy of co-therapy with psychotherapy. Additionally, the genetic part underlying PTSD onset has not been included in this thesis, although it might be of interest for further treatments or even prevention by finding genes that might be a good predictor for PTSD onset in the future.

References

Abercrombie, E. D., Keller, R. W., & Zigmond, M. J. (1988). Characterization of hippocampal norepinephrine release as measured by microdialysis perfusion: Pharmacological and behavioral studies. *Neuroscience*, *27*(3), 897–904. https://doi.org/10.1016/0306-4522(88)90192-3

Aerni, A., Traber, R., Hock, C., Roozendaal, B., Schelling, G., Papassotiropoulos, A., Nitsch, R. M., Schnyder, U., & De Quervain, D. J. F. (2004). Low-dose cortisol for symptoms of posttraumatic stress disorder. *American Journal of Psychiatry*, *161*(8), 1488–1490. https://doi.org/10.1176/APPI.AJP.161.8.1488/ASSET/IMAGES/LARGE/N126F1.JPEG

American Psychiatric Association. (2013). Trauma- and Stressor-Related Disorders. In *Diagnostic and Statistical Manual of Mental Disorders*. American Psychiatric Association. https://doi.org/10.1176/APPI.BOOKS.9780890425596.DSM07

Baker, D. G., West, S. A., Nicholson, W. E., Ekhator, N. N., Kasckow, J. W., Hill, K. K., Bruce, A. B., Orth, D. N., & Geracioti, T. D. (1999). Serial CSF corticotropin-releasing hormone levels and adrenocortical activity in combat veterans with posttraumatic stress disorder. *American Journal of Psychiatry*, *156*(4), 585–588. https://doi.org/10.1176/AJP.156.4.585/ASSET/IMAGES/LARGE/AL13F1.JPEG

Baxter, M. G., & Croxson, P. L. (2012). Facing the role of the amygdala in emotional information processing. *Proceedings of the National Academy of Sciences*, *109*(52), 21180–21181. https://doi.org/10.1073/PNAS.1219167110

Cahill, L., Haiert, R. J., Fallon, J., Alkirei, M. T., Tangii, C., Keatorii, D., Wuii, J., & Mcgaugh, J. L. (1996). Amygdala activity at encoding correlated with long-term, free recall of emotional information. *Neurobiology*, *93*, 8016–8021.

Cole, M. A., Kim, P. J., Kalman, B. A., & Spencer, R. L. (2000). Dexamethasone suppression of corticosteroid secretion: evaluation of the site of action by receptor measures and functional studies. *Psychoneuroendocrinology*, *25*(2), 151–167. https://doi.org/10.1016/S0306-4530(99)00045-1

de Kloet, C. S., Vermetten, E., Geuze, E., Lentjes, E. G. W. M., Heijnen, C. J., Stalla, G. K., & Westenberg, H. G. M. (2007). Elevated plasma corticotrophin-releasing hormone levels in veterans with posttraumatic stress disorder. *Progress in Brain Research*, *167*, 287–291. https://doi.org/10.1016/S0079-6123(07)67025-3

Diamond, D. M., Campbell, A. M., Park, C. R., Halonen, J., & Zoladz, P. R. (2007). The Temporal Dynamics Model of Emotional Memory Processing: A Synthesis on the Neurobiological Basis of Stress-Induced Amnesia, Flashbulb and Traumatic Memories, and the Yerkes-Dodson Law. *Neural Plasticity*, *2007*. https://doi.org/10.1155/2007/60803

Fastenrath, M., Coynel, D., Spalek, K., Milnik, A., Gschwind, L., Roozendaal, B., Papassotiropoulos, A., & de Quervain, D. J. F. (2014). Dynamic Modulation of Amygdala–Hippocampal Connectivity by Emotional Arousal. *Journal of Neuroscience*, *34*(42), 13935–13947. https://doi.org/10.1523/JNEUROSCI.0786-14.2014

Joëls, M., & Ronald de Kloet, E. (1994). Mineralocorticoid and glucocorticoid receptors in the brain. Implications for ion permeability and transmitter systems. *Progress in Neurobiology*, *43*(1), 1–36. https://doi.org/10.1016/0301-0082(94)90014-0

Marks, I. f. M., & Nesse, R. M. (1994). Fear and fitness: An evolutionary analysis of anxiety disorders. *Ethology and Sociobiology*, *15*(5–6), 247–261. https://doi.org/10.1016/0162-3095(94)90002-7

McCall, J. G., Siuda, E. R., Bhatti, D. L., Lawson, L. A., McElligott, Z. A., Stuber, G. D., & Bruchas, M. R. (2017). Locus coeruleus to basolateral amygdala noradrenergic projections promote anxiety-like behavior. *ELife*, *6*. https://doi.org/10.7554/ELIFE.18247

McFarlane, A. C., Barton, C. A., Yehuda, R., & Wittert, G. (2011). Cortisol response to acute trauma and risk of posttraumatic stress disorder. *Psychoneuroendocrinology*, *36*(5), 720–727. https://doi.org/10.1016/J.PSYNEUEN.2010.10.007

McGaugh, J. L. (2000). Memory - A century of consolidation. *Science*, *287*(5451), 248–251. https://doi.org/10.1126/SCIENCE.287.5451.248/ASSET/708969E9-5128-42DA-AB08-0CCB17B17BC0/ASSETS/GRAPHIC/SE0108182002.JPEG

Mello-Carpes, P. B., & Izquierdo, I. (2013). The Nucleus of the Solitary Tract → Nucleus Paragigantocellularis → Locus Coeruleus → CA1 region of dorsal hippocampus pathway is important for consolidation of object recognition memory. *Neurobiology of Learning and Memory*, *100*, 56–63. https://doi.org/10.1016/J.NLM.2012.12.002

Morris, R. (1984). Developments of a water-maze procedure for studying spatial learning in the rat. *Journal of Neuroscience Methods*, *11*(1), 47–60. https://doi.org/10.1016/0165-0270(84)90007-4

Nadel, L., & Moscovitch, M. (1997). Memory consolidation, retrograde amnesia and the hippocampal complex. *Current Opinion in Neurobiology*, *7*(2), 217–227. https://doi.org/10.1016/S0959-4388(97)80010-4

Okuda, S., Roozendaal, B., & McGaugh, J. L. (2004). Glucocorticoid effects on object recognition memory require training-associated emotional arousal. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(3), 853. https://doi.org/10.1073/PNAS.0307803100

Pariante, C. M., Thomas, S. A., Lovestone, S., Makoff, A., & Kerwin, R. W. (2004). Do antidepressants regulate how cortisol affects the brain? *Psychoneuroendocrinology*, *29*(4), 423–447. https://doi.org/10.1016/J.PSYNEUEN.2003.10.009

Power, A. E., Roozendaal, B., & McGaugh, J. L. (2000). Glucocorticoid enhancement of memory consolidation in the rat is blocked by muscarinic receptor antagonism in the basolateral amygdala. *European Journal of Neuroscience*, *12*(10), 3481–3487. https://doi.org/10.1046/J.1460-9568.2000.00224.X

Rimmele, U., Besedovsky, L., Lange, T., & Born, J. (2013). Blocking Mineralocorticoid Receptors Impairs, Blocking Glucocorticoid Receptors Enhances Memory Retrieval in Humans. *Neuropsychopharmacology*, *38*(5), 884. https://doi.org/10.1038/NPP.2012.254

Roozendaal, B., Okuda, S., De Quervain, D. J. F., & McGaugh, J. L. (2006). Glucocorticoids interact with emotion-induced noradrenergic activation in influencing different memory functions. *Neuroscience*, *138*(3), 901–910. https://doi.org/10.1016/J.NEUROSCIENCE.2005.07.049

Roozendaal, Benno, Castello, N. A., Vedana, G., Barsegyan, A., & McGaugh, J. L. (2008). Noradrenergic activation of the basolateral amygdala modulates consolidation of object recognition memory. *Neurobiology of Learning and Memory*, *90*(3), 576–579. https://doi.org/10.1016/J.NLM.2008.06.010

Roozendaal, Benno, McEwen, B. S., & Chattarji, S. (2009). Stress, memory and the amygdala. *Nature Reviews. Neuroscience*, *10*(6), 423–433. https://doi.org/10.1038/NRN2651

Roozendaal, Benno, Nguyen, B. T., Power, A. E., & McGaugh, J. L. (1999). Basolateral amygdala noradrenergic influence enables enhancement of memory consolidation induced by hippocampal glucocorticoid receptor activation. *Proceedings of the National Academy of Sciences of the United States of America*, *96*(20), 11642. https://doi.org/10.1073/PNAS.96.20.11642

Roozendaal, Benno, Okuda, S., Van Der Zee, E. A., & McGaugh, J. L. (2006). Glucocorticoid enhancement of memory requires arousal-induced noradrenergic activation in the basolateral amygdala. *Proceedings of the National Academy of Sciences*, *103*(17), 6741–6746. https://doi.org/10.1073/PNAS.0601874103

Roozendaal, Benno, Portillo-Marquez, G., & McGaugh, J. L. (1996). Basolateral amygdala lesions block glucocorticoid-induced modulation of memory for spatial learning. *Behavioral Neuroscience*, *110*(5), 1074–1083. https://doi.org/10.1037/0735-7044.110.5.1074

Schwabe, L., Joëls, M., Roozendaal, B., Wolf, O. T., & Oitzl, M. S. (2012). Stress effects on memory: An update and integration. *Neuroscience & Biobehavioral Reviews*, *36*(7), 1740–1749. https://doi.org/10.1016/J.NEUBIOREV.2011.07.002

Smith, M. A., Davidson, J., Ritchie, J. C., Kudler, H., Lipper, S., Chappell, P., & Nemeroff, C. B. (1989). The corticotropin-releasing hormone test in patients with posttraumatic stress disorder. *Biological Psychiatry*, *26*(4), 349–355. https://doi.org/10.1016/0006-3223(89)90050-4

Smith, S. M., & Vale, W. W. (2006). The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. *Dialogues in Clinical Neuroscience*, *8*(4), 383–395. https://doi.org/10.31887/DCNS.2006.8.4/SSMITH

Souza, R. R., Dal Bó, S., De Kloet, E. R., Oitzl, M. S., & Carobrez, A. P. (2014). Paradoxical mineralocorticoid receptor-mediated effect in fear memory encoding and expression of rats submitted to an olfactory fear conditioning task. *Neuropharmacology*, *79*, 201–211. https://doi.org/10.1016/J.NEUROPHARM.2013.11.017

Ströhle, A., Scheel, M., Modell, S., & Holsboer, F. (2008). Blunted ACTH response to dexamethasone suppression-CRH stimulation in posttraumatic stress disorder. *Journal of Psychiatric Research*, *42*(14), 1185–1188. https://doi.org/10.1016/J.JPSYCHIRES.2008.01.015

Tank, A. W., & Wong, D. L. (2015). Peripheral and Central Effects of Circulating Catecholamines. *Comprehensive Physiology*, *5*(1), 1–15. https://doi.org/10.1002/CPHY.C140007

Tollenaar, M. S., Elzinga, B. M., Spinhoven, P., & Everaerd, W. (2009). Immediate and prolonged effects of cortisol, but not propranolol, on memory retrieval in healthy young men. *Neurobiology of Learning and Memory*, *91*(1), 23–31. https://doi.org/10.1016/J.NLM.2008.08.002

Williams, C. L., Men, D., Clayton, E. C., & Gold, P. E. (1998). Norepinephrine release in the amygdala after systemic injection of epinephrine or escapable footshock: contribution of the nucleus of the solitary tract. *Behavioral Neuroscience*, *112*(6), 1414–1422. https://doi.org/10.1037//0735-7044.112.6.1414

Yau, J. L. W., Noble, J., & Seckl, J. R. (2011). 11β-Hydroxysteroid Dehydrogenase Type 1 Deficiency Prevents Memory Deficits with Aging by Switching from Glucocorticoid Receptor to Mineralocorticoid Receptor-Mediated Cognitive Control. *The Journal of Neuroscience*, *31*(11), 4188. https://doi.org/10.1523/JNEUROSCI.6145-10.2011

Yehuda, R., Teicher, M. H., Levengood, R. A., Trestman, R. L., & Siever, L. J. (1994). Circadian regulation of basal cortisol levels in posttraumatic stress disorder. *Annals of the New York Academy of Sciences*, *746*, 378–380. https://doi.org/10.1111/J.1749-6632.1994.TB39260.X

Yehuda, Rachel. (2002). Post-traumatic stress disorder. *The New England Journal of Medicine*, *346*(2), 108–114. https://doi.org/10.1056/NEJMRA012941

Yehuda, Rachel, Golier, J. A., Halligan, S. L., Meaney, M., & Bierer, L. M. (2004). The ACTH response to dexamethasone in PTSD. *American Journal of Psychiatry*, *161*(8), 1397–1403. https://doi.org/10.1176/APPI.AJP.161.8.1397/ASSET/IMAGES/LARGE/N112F1.JPEG

Yehuda, Rachel, Teicher, M. H., Trestman, R. L., Levengood, R. A., & Siever, L. J. (1996). Cortisol regulation in posttraumatic stress disorder and major depression: A chronobiological analysis. *Biological Psychiatry*, *40*(2), 79–88. https://doi.org/10.1016/0006-3223(95)00451-3

Zhou, M., Bakker, E. H. M., Velzing, E. H., Berger, S., Oitzl, M., Joëls, M., & Krugers, H. J. (2010). Both mineralocorticoid and glucocorticoid receptors regulate emotional memory in mice. *Neurobiology of Learning and Memory*, *94*(4), 530–537. https://doi.org/10.1016/J.NLM.2010.09.005