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Modulatory mechanisms of cortisol effects on emotional learning and memory: Novel perspectives

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Summary It has long been known that cortisol affects learning and memory processes. Despite a wealth of research dedicated to cortisol effects on learning and memory, the strength or even directionality of the effects often vary. A number of the factors that alter cortisol's effects on learning and memory are well-known. For instance, effects of cortisol can be modulated by emotional arousal and 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 is to disseminate knowledge regarding less well-known modulators of cortisol effects on learning and memory. Since several models for the etiology of anxiety, such as post-traumatic stress disorder (PTSD), incorporate stress and the concomitant release of cortisol as important vulnerability factors, enhanced understanding of mechanisms by which cortisol exerts beneficial as opposed to detrimental effects on memory is very important. Further elucidation of the factors that modulate (or alter) cortisol's effects on memory will allow

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reconciliation of seemingly inconsistent findings in the basic and clinical literatures. The present review is based on a symposium as part of the 42nd International Society of Psychoneuroendocrinology Conference, New York, USA, that highlighted some of those modulators and their underlying mechanisms.

1. Introduction

In response to stress the hypothalamus-pituitary-adrenal (HPA) axis is activated, resulting in the secretion of corticosteroid hormones from the adrenal glands. These hormones (mainly corticosterone in rodents and cortisol in humans) exert their effects by binding to two different receptors: the high affinity mineralocorticoid receptor (MR) and the lower affinity glucocorticoid receptor (GR). GRs are ubiquitously present in the brain, and MRs are observed most predominantly in limbic structures (de Kloet et al., 2005; Reul and de Kloet, 1985). The hippocampus, amygdala and prefrontal cortex are among the structures where both receptors are co-localized (e.g., McEwen et al., 1986; de Kloet et al., 2005; Joëls and Baram, 2009). These brain regions play a fundamental role in emotional learning and memory processes and alterations in these networks have repeatedly been related to anxiety and affective disorders (Elzinga and Bremner, 2002; Shin and Liberzon, 2010). For instance, several models for the etiology of anxiety disorders, such as post-traumatic stress disorder (PTSD), incorporate stress and the concomitant release of cortisol on learning and memory as important vulnerability factors. Thus, insights gained from studies investigating the effects of stress hormones on memory are of particular interest with regard to our understanding of psychopathology.

A longstanding history of basic experimental research has demonstrated that cortisol robustly affects learning and memory processes. For instance, it has been widely acknowledged that cortisol generally impairs memory performance when administered before retrieval (de Quervain et al., 2009; Wolf, 2009). However, though animal studies show that memory consolidation is typically enhanced by cortisol, the effects of cortisol on encoding and/or consolidation in humans are more variable, with both enhancing, impairing, or even null effects (de Quervain et al., 2009; Wolf, 2009). An explanation for this variability is that the effects of cortisol on memory are modulated by several factors. For instance, emotional arousal, the magnitude of cortisol elevation, and the memory phase under study are critical in determining the direction of cortisol effects on memory (Lupien and McEwen, 1997; de Quervain et al., 2009; Roozendaal et al., 2009; Wolf, 2009). But even when these factors are taken into account findings often vary, suggesting that additional factors (i.e., modulators) exist that influence cortisol effects on memory. Additionally, if we are to truly understand the nature of these modulators, individual differences should be taken into account (Kosslyn et al., 2002). Thus, it becomes increasingly clear that there is a need to progress from describing average memory effects between experimental groups toward characterizing individual differences in susceptibility to cortisol effects on memory, and identifying their determinants as well as underlying mechanisms.

The present review is based on a symposium as part of the 42nd International Society of Psychoneuroendocrinology Conference, New York, USA. We would like to emphasize that this minireview is by no means intended to be exhaustive; rather, we intend to draw attention to a number of important modulatory factors on cortisol effects on memory and their underlying mechanisms that have not been previously emphasized in the literature. These novel factors may pose promising directions for future research. The review commences with a discussion of the role of corticosteroid receptors in determining cortisol's effects on memory, including discussion of molecular genetic findings related to genes for corticosteroid receptors. We will continue describing personal characteristics, including dispositional and experiential variation of individuals, which have been shown to act as moderators of the relationship between cortisol effects and memory. Next, we focus on the moderating role of situational factors, including context and timing of cortisol elevations relative to memory formation. Further, cortisol's effects on brain mechanisms underlying learning and memory are discussed. In addition, we will review studies showing that cortisol may alter memories that already have been established by acting upon the process of reconsolidation. Finally, we will discuss the importance of these novel perspectives regarding modulatory factors of cortisol effects on memory formation and possible implications for understanding the etiological mechanisms of PTSD.

2. The role of MR and GR in cortisol's effects on memory

As mentioned in the previous section, corticosteroids exert their effects via the glucocorticoid (GR) and mineralocorticoid receptor (MR). Both GRs and MRs are present in limbic brain regions, which are known to be important for learning and memory and the processing of emotionally arousing information (e.g., McEwen et al., 1986; Joëls and Baram, 2009). GRs are thought to play a role in the normalization of stress-induced effects and storage of stress-related information for future events, while MRs have been implicated in fast effects on cognitive processes, such as appraisal and attention processes needed for encoding of new stimuli (de Kloet et al., 2005). Dysregulation and altered sensitivity of GRs and MRs are related to variation in behavioral adaption to stress and HPA axis reactivity (e.g., DeRijk and de Kloet, 2005). Altered sensitivity of GRs and MRs has been related to several naturally occurring polymorphisms within the GR and MR genes (DeRijk and de Kloet, 2005). Given the location of GRs and MRs in the brain, their role in memory, and the possible influence of GR and MR gene polymorphisms on corticosteroid sensitivity, variations in these genes may modulate emotional memory processes and sensitivity of these processes to cortisol.

Indeed, a well-known intronic single nucleotide polymorphism (SNP) of the GR-gene, the *Bcl*I polymorphism (*C* to *G* nucleotide change) has been implicated in emotional memory in healthy individuals (Ackermann et al., 2012) as well as in heart surgery patients (Hauer et al., 2011). Specifically, in a large sample of healthy young individuals, subjects homozygous for the *G*-allele of the *Bcl*I, as compared to *GC*- and *CC*-carriers, had better memory for emotional pictures than for neutral pictures in a short delay recall condition of a picture memory task (Ackermann et al., 2012). Additionally, a study in patients that underwent cardiac surgery revealed that homozygous *Bcl*I *G*-allele carriers had more traumatic memories from intensive care unit (ICU) therapy at 6 months after heart surgery than the other two genotype groups (Hauer et al., 2011). In the latter study, the *Bcl*I polymorphism was not only related to emotional memory per se, but also to PTSD symptoms. Homozygous *Bcl*I *G*-allele carriers had more stress-related PTSD symptoms after their stay at the ICU. Bachmann et al. (2005) investigated whether two common polymorphisms of the GR-gene (N363N and *Bcl*I) are related to the risk for the development of PTSD. They showed that variation in the two GR-polymorphisms (i.e., N363N and *Bcl*I) did not significantly differ between PTSD patients and healthy controls. However, within the PTSD-group, individuals homozygous for the *G*-allele of the *Bcl*I variation displayed lower basal cortisol levels and scored higher on a PTSD-symptoms scale. Together these studies suggest that homozygous *Bcl*I G allele carriers are at risk for developing enhanced emotional memories and PTSD symptoms.

To our knowledge there are no studies in humans considering genetic variations in the MR-gene and emotional memory processing. However, studies in rodents have shown that in addition to the GR, the MR is also implicated in fear memory. For instance, mice lacking forebrain-specific MRs show deficits in the formation of fear memories (Zhou et al., 2010). Other evidence suggests that a common polymorphism of the MR gene, MR180V, modulates cortisol responses to a stressful event (Derijk, 2009). One recent study suggests that changes in the MR/GR balance can modulate stress effects on memory (Cornelisse et al., 2011). In this study the MR antagonist spironolactone was administered, presumably causing a shift in the balance from MR toward GR activation, before subjects were exposed to a social stress task followed by memory tasks. Results showed that the consolidation of long-term memory was enhanced in subjects that received spironolactone in combination with the stress tasks, resulting in highly elevated cortisol levels while MRs were blocked. Future studies are needed to determine whether naturally occurring genetic variations in the MR and GR-genes may modulate cortisol actions on memory.

3. Personal characteristics alter cortisol's effects on learning and memory

It is well established that transient psychological states moderate the effects of cortisol on learning (Abercrombie et al., 2006; Okuda et al., 2004). However, only recently has research focused on how traits or lasting qualities (e.g., due to past experiences) moderate the effects of cortisol on learning (Abercrombie et al., 2012a; Bagot et al., 2009; Champagne et al., 2008). Evidence is emerging showing that lasting inter-individual differences due to variation in early life experiences and/or dispositional ("trait") emotional arousal moderate cortisol's effects on neuroplasticity and learning.

3.1. Dispositional emotional arousal

Animal research has shown that arousal-related activation of noradrenergic circuitry within the amygdala is a necessary prerequisite for corticosteroid effects on memory formation; if the basolateral amygdala is not activated, corticosteroids do not alter learning and memory formation (Roozendaal et al., 2006). Thus, it has been hypothesized that humans who are dispositionally prone to higher levels of emotional arousal (i.e., higher "trait" emotional arousal) would be more sensitive to the effects of cortisol on memory (Abercrombie et al., 2012a). Data consistent with this hypothesis have been observed in women; Abercrombie et al. (2012a) found that cortisol elevation was related to facilitation of memory formation only in women who endorsed greater levels of "trait" negative emotion. Cortisol levels were not related to memory performance in women with lower levels of trait negative emotional arousal. Thus, both emotional states and emotional traits (i.e., affective style; emotional disposition) have the potential to moderate the relation between cortisol and memory formation.

It should be noted that Abercrombie et al. (2012a) found for men (compared to women) that trait emotional arousal operated differently as a moderator. In two studies, they found that cortisol elevation was related to memory facilitation in men who reported experiencing *lower* (not higher as in women) levels of trait emotional arousal. It is difficult to draw any firm conclusions regarding these sex differences, which could be attributable to a number of confounding factors (e.g., different cortisol levels in men vs. women). Nonetheless, these findings are intriguing; rather than null results for trait emotional arousal, men with lower (rather than higher) trait emotional arousal showed a strengthening of the relation between cortisol and memory formation. In summary, trait emotional arousal was found to robustly moderate the relation between cortisol and memory formation, but the findings paint a more complex picture than the original hypothesis that higher levels of trait emotion arousal would invariably strengthen the relation between cortisol and memory. Possibly, the moderating role of trait emotional arousal varies by sex and/or magnitude of cortisol elevation.

3.2. Variation in past experiences

Past experiences can dramatically alter the effects of corticosteroids on learning and hippocampal plasticity (Alfarez et al., 2003; Pavlides et al., 2002). For instance, early life stress in rodents, such as lower levels of maternal care, causes alterations into adulthood in levels of glucocorticoid receptor (GR) gene expression (Weaver et al., 2004) and in the effects of corticosteroids on learning (Champagne et al., 2008). For instance, adult rats with a history of low levels of maternal care have a bias toward learning during threatening contexts with corticosteroid elevation, whereas adult rats with a history of high levels of maternal care have a bias

toward learning when corticosteroids are not elevated (Champagne et al., 2008). These effects of early maternal care on learning are associated with effects of corticosteroids on hippocampal plasticity measured in vitro. Corticosterone enhances LTP in hippocampal CA1 and dentate gyrus slices from adult rodents with a history of low maternal care, whereas previous experience of higher rates of maternal care is associated with a reduction in LTP in the presence of corticosterone (Bagot et al., 2009; Champagne et al., 2008). In a preliminary study in humans, Abercrombie et al. (2012b) found that childhood loss due to parental divorce moderated the effects of cortisol (vs. placebo) on negative memory bias in mildly depressed adults (none of whom experienced abuse as children). The findings showed that cortisol administration biased memory in a negative direction only in subjects whose parents divorced. Cortisol administration had no effect on memory bias in depressed subjects who did not experience parental divorce. Thus, human and animal data suggest that past experiences, including mildly adverse early experiences, moderate the effects of corticosteroids on learning.

3.3. Potential mechanisms through which dispositional emotional arousal and/or past experience of adversity alter corticosteroid's effects on learning

It has been hypothesized that a history of even mild early life stress (e.g., relatively lower levels of parental care) "prepares" the organism for functioning under conditions of adversity and enhances cognitive performance under corticosteroid elevation and threatening conditions (Champagne et al., 2008). A variety of mechanisms may link early life stress with lasting alterations in stress hormone effects on learning.

Effects of the early environment on HPA function in rodents are due at least in part to influences of maternal care on epigenetic programming of glucocorticoid receptor (GR) expression (i.e., modification of methylation at the exon 1_7 GR promoter) in the hippocampus (Weaver et al., 2004). Hypermethylation of the promoter region of the GR gene (which is related to reduced expression of the gene and reduced GR protein) may alter neural signaling of cortisol in hippocampal tissue. Epigenetic modification of expression of a variety of cortisol-related genes may be a mechanism through which early life stress alters corticosteroids' effects on learning.

In addition, early life stress likely causes lasting changes in thresholds for activation in neural circuitry supporting emotional learning. Humans with a history of adversity tend to exhibit amygdalar sensitization (Tottenham and Sheridan, 2009). Furthermore, individuals with history of trauma show enhanced adrenergic or catecholaminergic activation (Geracioti et al., 2001; Otte et al., 2005). Even healthy individuals with a history of childhood trauma show heightened catecholaminergic responses to highly negatively arousing stimuli (measured with salivary 3-methoxy-4-hydroxy-phenylglycol; MHPG) (Otte et al., 2005). As mentioned above, corticosteroid effects on memory require noradrenergic activation of the amygdala (Roozendaal et al., 2006). Possibly, individuals with higher levels of dispositional emotional arousal or a history of adversity are more likely to exhibit the neural milieu that supports cortisol enhancement of memory for stress- and emotion-related material.

4. Situational factors moderate cortisol's effects on memory

As outlined in the previous sections, effects of cortisol on learning and memory may depend on inter-individual differences in a number of factors (ranging from variation in genetic make-up to variation in past experiences). In addition to inter-individual differences in genetic and personal characteristics, *situational* moderators of cortisol effects on memory exist as well. The most well-known and extensively studied situational factor that can determine the direction of cortisol effects on memory is emotional arousal, an important prerequisite for the occurrence of cortisol effects on memory processes (Roozendaal et al., 2006). Here, we will discuss recent theories and findings on two less extensively studied situational factors: context and the timing between cortisol elevations and memory formation.

4.1. Context

Memories are more likely to be remembered when the retrieval context resembles the encoding context (Goddon and Baddeley, 1975). Such contextual dependency of memories is highly adaptive as it can enhance retrieval of memories that are appropriate in that specific context. The hippocampus likely subserves context effects on memory (Chun and Phelps, 1999) and is highly sensitive to cortisol, as mentioned above (Joëls and Baram, 2009; McEwen et al., 1986). Thus, through its effects on the hippocampus, cortisol may alter the contextual dependency of memories.

One study investigated whether stress can alter contextual dependency of memories by subjecting participants to a stress task or a control procedure after which they performed an object-location task (Schwabe and Wolf, 2009). The next day, memory performance was assessed in congruent or incongruent contexts as compared to the encoding context. The results indicated that stress prior to memory encoding eliminated the beneficial effects of context on memory performance for neutral material. Another study (van Ast et al., submitted) manipulated cortisol levels during memory encoding of emotional and neutral words presented in unique background contexts, and tested subsequent contextual dependency of emotional versus neutral memories the following day. Recognition data revealed that elevated cortisol levels during encoding abolished subsequent contextual dependency of emotional memories, pointing to a role of cortisol (perhaps in interaction with emotional arousal, see Roozendaal et al., 2006) in altering contextual dependencies of memory. A recent study in mice corroborates the idea that corticosteroid effects on the hippocampus indeed may alter contextual modulation of memory; corticosteroids, injected after fear conditioning, reduced context-bound fear responses the next day (Kaouane et al., 2012), causing fear to generalize to cues that did not originally predict danger. In summary, there is increasing experimental evidence that cortisol may alter the contextual dependency of memories. Specifically, stress and/or cortisol elevation may alter the

magnitude of the contextual dependency effect. However, as discussed below, timing may moderate these effects.

4.2. Timing

For many years it has been known that the direction of cortisol effects on memory depends on the memory phase under study. While retrieval processes are typically impaired by cortisol, its effects on encoding and consolidation are more variable (de Quervain et al., 2009; Wolf, 2009). But even on a smaller scale, it has become evident in recent years that corticosteroids differentially influence neurobiological processes depending on the time between peak cortisol elevation and the task at hand (Joëls et al., 2011). Shortly after stress, corticosteroids interact with noradrenaline and are thought to promote immediate reflex-like responses to the stressor, such as fight-or-flight reactions and focused attention. This may help the organism to focus and subsequently remember the most significant aspects of an event and the most habitual (or reflex-like) responses (Roozendaal et al., 2006), at the expense of the more complex, cognitive aspects. By contrast, after some delay, gene-mediated corticosteroid actions are thought to facilitate restorative processes, thereby aiding in the consolidation of certain events in a more cognitively controlled manner.

Although this theory (Joëls et al., 2011, 2012) and several other models predict differential effects by corticosteroids or stress in the time-domain shortly vs. several hours after stress, not many experimental studies have manipulated the timing of cortisol administration relative to a memory encoding task. Instead, the majority of studies have typically tested the effects of corticosteroids on learning or memory encoding at a single time point varying from 30 to 120 min after cortisol administration. Since gene-mediated transcriptional changes are discernible already 1 h after cortisol exposure, the majority of studies targeted either rapid non-genomic corticosteroid actions alone or both genomic and non-genomic processes, complicating a straightforward interpretation of results.

One recent study directly tested rapid versus slow corticosteroid effects on neural processing associated with memory formation in men (Henckens et al., 2012). Although no behavioral effects of cortisol were found, cortisol's slow effects reduced prefrontal and hippocampal responses, while no significant rapid effects of cortisol were observed. These results provide initial evidence for time-dependent changes of corticosteroid effects on brain regions involved in memory formation. Another clue comes from a study from the same group that demonstrated that cortisol's slow effects improved working memory performance, in the absence of any rapid effects (Henckens et al., 2011). As mentioned above, van Ast et al. (submitted) demonstrated that rapid effects of cortisol, administered shortly before memory encoding, impaired contextual dependency of emotional memories in a recognition test the next day. In the same study however, an opposite effect was found when the memory task was given 3.5 h after cortisol administration, thus, cortisol's slow effects enhanced contextual dependency of emotional memory the next day. Together, this initial evidence emphasizes the importance for future studies to take into account the time lag between cortisol elevations and administration of the task.

5. Cortisol has robust but variable effects on the neural circuitry of memory

It is well established that the medial temporal lobe (MTL) is a region integral to memory function. It incorporates the hippocampus and amygdala, key areas involved in learning and memory. Studies in humans using neuroimaging methods have only begun to elucidate the neural circuitry involved in the effects of stress and/or stress hormones on memory. Most commonly, alterations in hippocampal activation are found in studies examining effects of corticosteroids on neural function. However, the direction of stress hormone effects on hippocampal activation vary, which may be related to the well-known biphasic effects of cortisol on hippocampal function (Lupien and McEwen, 1997), or possibly to factors that have been discussed earlier in this review.

In one study, an emotional response was induced by exposure to stressful videos. Here, memory facilitation was predicted by *reduced* hippocampal activation during viewing of stressful videos, both within and between participants (Henckens et al., 2009). In another study, administration of hydrocortisone was found to enhance memory and, in contrast to the previous study, activity in the right hippocampus was *increased* (van Stegeren et al., 2010). Interestingly, within the same study, combined administration of yohimbine and cortisol did not have distinct behavioral effects on memory (relative to placebo). However, together they induced a marked shift in brain activation, resulting in *deactivation* of the hippocampus, prefrontal cortex and BA47. The study of van Stegeren et al. (2010) demonstrates the potential complexity of interacting systems to modulate cortisol effects on memory and underlying brain activity. A third study investigated cortisol effects on emotional memory in depressed participants compared with healthy matched controls. Alterations in hippocampal response to cortisol during encoding were found in depressed women, but not in depressed men. Nonetheless, in both depressed men and women, cortisol's effects on hippocampal function were correlated with its effects on recall performance. This study shows that cortisol is related to hippocampal activation and emotional memory, and that these relationships may be moderated by depression and/or sex (Abercrombie et al., 2011). A final study manipulated timing of cortisol relative to memory encoding. Though cortisol did not affect behavioral measures of memory, results revealed that cortisol's slow effects (presumably genomic) reduced both prefrontal and hippocampal responses, but no significant rapid actions of corticosteroids were observed (Henckens et al., 2012). This latter study and other studies (Lovallo et al., 2010) provide evidence that cortisol timing can moderate the way cortisol affects brain regions involved in memory formation in humans.

6. Modulating established memories: effects of cortisol on reactivation and reconsolidation

Recently, it has become clear that memory traces are not permanent after they have initially been established, as was assumed in the classical view of memory. In fact, it has been demonstrated that memory retrieval could act by

reactivating the already consolidated memory trace. Once reactivated, the memory trace is labile again, as it was following its initial encoding. This short time window of instability is followed by the reconsolidation of the memory trace in the long-term memory system. This suggests that memory reactivation opens a window of opportunity during which the already consolidated memory trace could be modulated before it stabilizes again in the long-term memory system (Nader et al., 2000).

Given the known impact of stress on the initial process of memory consolidation, recent studies have investigated the impact of stress and cortisol on memory reconsolidation. Tollenaar et al. (2009) performed a study where they administered cortisol, propranolol or placebo to healthy young men before the retrieval of a word-list containing neutral and emotional material. Consistent with prior research (de Quervain et al., 2009; Wolf, 2009), memory retrieval was impaired in the group that received cortisol. Interestingly, this lower memory performance was still present one week later, after the drug washout. The results suggested that the impact of cortisol might last beyond the time of memory retrieval, possibly affecting reconsolidation of the material (Tollenaar et al., 2009).

Schwabe and Wolf (2010) tested the impact of a stressor on the reconsolidation of autobiographical memories (positive, neutral and negative). Their results demonstrated that stress following reactivation of autobiographical memories decreased the reconsolidation of neutral (but not emotional) autobiographical memories. Similarly, Zhao et al. (2009) tested, in a sample of heroin addicts, the impact of stress on a reactivated wordlist (negative and positive words associated with heroin and neutral words). Their results showed that stress decreased the reconsolidation of both the positive and negative words.

On the other hand, Coccoz et al. (2011) exposed participants to a physical stressor following memory reactivation of cue-syllables association. Their results demonstrated an enhancing effect of stress on memory reconsolidation. In the same line, Marin et al. (2010) tested the impact of a psychosocial stressor following memory reactivation of a slideshow depicting neutral and emotional segments. The results showed that immediately following the stressor, the stress-exposed group had greater memory for the emotional material and this effect was still present five days later. Memory for the neutral material was left unaffected (Marin et al., 2010). In addition, the same group investigated whether reduction of emotional memories could be achieved by reducing cortisol levels at the time of memory reactivation. If stress increases reactivated emotional memories, it was hypothesized that decreasing cortisol levels would have the reverse effect. They randomly exposed participants to placebo, one dose or two doses of Metyrapone (a potent cortisol synthesis inhibitor). As in their previous study (Marin et al., 2010), participants reactivated the memory trace of the slideshow. Memory performance was assessed again four days later, once the drug was cleared out. The group that received an adequate dose (i.e., double dose) of Metyrapone had significantly poorer memory performance for the emotional material, at the time of memory reactivation as well as four days later. Once again, the neutral memory was left unaffected (Marin et al., 2011).

These studies in humans show that memory reconsolidation is sensitive to variation in cortisol levels within a timeframe proximal to memory reactivation. As with the research on cortisol's effects on memory formation, the direction of cortisol effects on memory reconsolidation varies. Clearly, further research is needed to better understand the exact parameters by which cortisol can impact memory reactivation and reconsolidation in humans.

7. Conclusions and future directions

It is clear that the effects of cortisol on memory depend on a range of factors, many of which already have been well described elsewhere (e.g., de Quervain et al., 2009; Roozendaal et al., 2009; Wolf, 2009). In this review we aimed to highlight novel findings regarding moderators of cortisol's effects on memory formation and reconsolidation (for an overview of plausible modulators see Fig. 1). Further knowledge regarding factors that modulate stress hormone effects on memory may aid in directing future research, and further our understanding of disorders that are characterized by alterations in memory such as PTSD.

The described findings on the role of the GR and MR in emotional memory and cortisol reactivity point to a role of these receptors and their genetic variations in emotional memory processes. Future research should address the impact of the genetic variability of the entire GR- and MR-gene (haplotypes as opposed to single variations). Given the fact that corticosteroid effects take place through the transcriptional regulation of specific sets of MR and GR genes it is likely that these genes may be associated with strength and direction of cortisol effects on memory. However, to date, no human studies have directly tested whether certain genetic predispositions may alter cortisol effects on memory. Moreover, even with the same set of genes, epigenetic modification of expression of a variety of cortisol-related genes may take place. Findings especially point to early life stress as a plausible mechanism through which corticosteroid's effects on learning are altered. Thus, apart from gene x gene interactions, gene x environment interactions should be investigated. Not only GR- and MR-genes but also other genes related to the HPA axis and the noradrenergic system might contribute to variations in corticosteroid effects on emotional memory. Related to this, trait characteristics such as dispositional arousal are likely to play an important role in memory modulation by cortisol, but few studies have examined the relation between variability in cortisol effects on memory and inter-individual differences in lasting characteristics. The inclusion of relevant assessments of personal characteristics such as affective style or past experiences could be a good starting point in future research to explore the moderating role of dispositional characteristics in cortisol effects on memory. From a clinical perspective, such variables together might be able to explain, at least in part, why some individuals are more susceptible to develop psychiatric symptoms after adverse life events or trauma.

Recent data have also shown situational characteristics add to the variability in cortisol effects on memory. Findings that cortisol modulates the contextual dependency of memories have important implications for studies investigating stress and/or associated stress hormone effects on memory

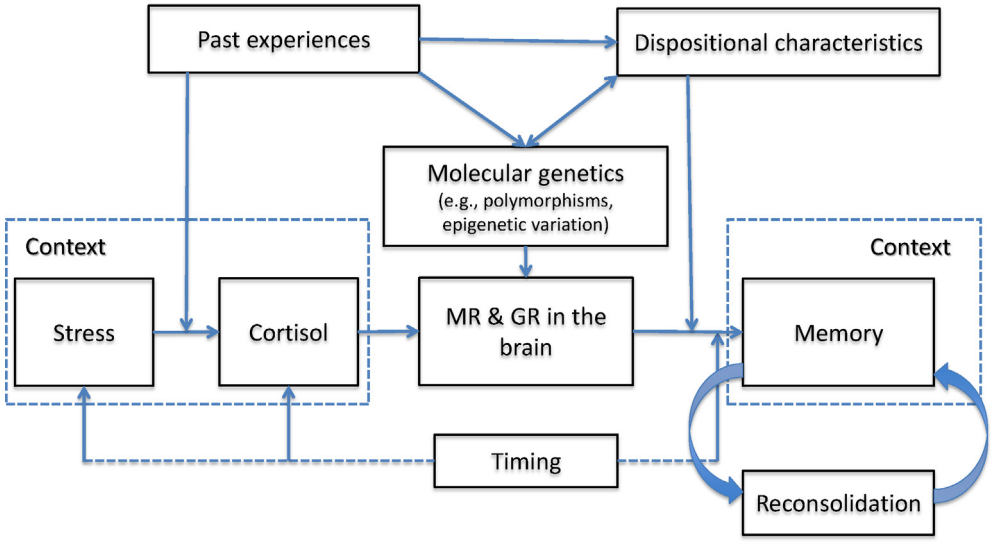

Figure 1 Summary of plausible modulators and their interactions with cortisol effects on memory. Genetic polymorphisms, past experiences, dispositional characteristics, situational characteristics (like context and timing) together contribute to the way cortisol affects the ultimate consolidation and/or reconsolidation of memories. The figure is merely illustrative of the wide variety of factors shown to moderate cortisol's effects on memory, rather than a systematic model. As mentioned in the text, multi-level analysis and/or structural equation modeling will be necessary to clearly specify the inter-relations among the variables shown in the figure.

consolidation. Possibly, stress alters the ability to use cues from the environment to retrieve the central memories, perhaps resulting in more gist-like memories (e.g., Nadel and Payne, 2002). On a broader level, stress hormone effects on the contextual dependency of memories may have implications for (etiological) mechanisms of PTSD. Patients suffering from post-traumatic stress disorder (PTSD) display enhanced memories for central cues, along with reduced memory for cues in the traumatic context (Elzinga and Bremner, 2002). Therefore, theories of PTSD emphasize impairment in the ability to store fearful memories into their original encoding context (e.g., Ehlers and Clark, 2008), or a more general impairment in the behavioral modulation by contextual cues (e.g., Liberzon and Sripada, 2008).

Another situational modulator may be the time lag in between cortisol elevation and a learning experience. Several theories (Diamond et al., 2007; Joëls et al., 2011, 2012; Richter-Levin and Akirav, 2003) predict differential effects by corticosteroids in the time-domain shortly after stress as opposed to several hours later. However, not many human studies have taken this factor into account. Several pioneering studies suggest that timing is an important factor to be aware of when designing future studies investigating stress effects on memory.

Studies investigating brain regions mediating cortisol effects on memory have suggested that the MTL, particularly the hippocampus, is involved. However, the hippocampus does not work alone, and action of amygdala and other structures in conjunction with the hippocampus may also take place. The behavioral effects of cortisol on memory are widespread and sensitive to a number of variables, such as interaction with arousal. It is thus plausible that, with increasing knowledge, this complexity is likely to be reflected in underlying and interacting brain regions, which are yet to be fully understood. Thus, research examining connectivity among structures during memory formation will be essential to determine the role of the hippocampus within the larger network of structures responsible for glucocorticoid effects on memory. In addition, future research must address potential moderating effects of variables enumerated above (e.g., personal characteristics, emotional arousal, timing, and context) on glucocorticoids' effects on the neural circuitry of memory.

As described in the final part of this review, it has become clear that memory traces are not permanent after they have initially been established, as was assumed in the classical view of memory. Recent studies have shown that when a memory is retrieved, the underlying memory trace is labile and can be modified. Cortisol is one of the agents able to modulate reactivated memories, but one must keep in mind that other pharmacological (i.e., propranolol) and environmental (i.e., a stressor or interference learning) agents have also been successfully used. Further research may aid in understanding processes that contribute to the maintenance of traumatic memories or reveal ways of disrupting an earlier acquired fear memory by (pharmacologically) blocking reconsolidation, that could have significant clinical implications (e.g., Kindt et al., 2009).

From the modulators of cortisol effects on memory as discussed in this review it becomes clear that many factors that have received relatively little attention in the scientific literature contribute to cortisol's role in memory consolidation. Furthermore, the modulators of cortisol's effects described herein undoubtedly interact with one another. As a consequence of our increasing understanding of many possible modulators, numerous interesting questions arise that can be addressed in future research. For instance, 'Are individuals who have suffered from childhood trauma more prone to store emotional memories in a decontextualized fashion due to cortisol?' and 'Is the interplay between cortisol, genetic susceptibility and certain personal characteristics associated with BOLD fMRI signal changes in the

hippocampus when storing a memory?' In order to answer such a wealth of complex questions, future research may profit from analysis techniques that can take into account several levels of variables, instead of focusing on just a few at the same time. For instance, multilevel approaches provide a powerful way to simultaneously assess the contribution of genetic background, individual differences in trait characteristics, hippocampal reactivity and childhood experience to predict memory. Further, cortisol timing and contextual variables can be added to such a model as well. Finally, it can be investigated whether first level relationships might be moderated by second level variables. Perhaps even more versatile, structural equation modeling (SEM) provides estimates, or path coefficients, which indicate the direction and significance of the association between constructs, as well as several fit indices which evaluate the fit of any proposed model.

In conclusion, the factors described herein may explain important variability in corticosteroid effects on memory. These factors should be taken into account in studies examining corticosteroid effects on memory. Many interesting questions remain to be answered that perhaps require sophisticated analytical techniques in order to provide a nuanced picture of the way stress and cortisol interact with several moderators to affect long-term memories, and how these again can be modulated once established. Knowledge regarding ways in which genetics, lasting characteristics, and other variables moderate cortisol's effects on memory consolidation and/or reconsolidation can serve as a foundation for treatment research, which could further elucidate the potential therapeutic benefits of manipulating neural signaling of corticosteroids.

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Conflicts of interest

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