Time your stress if you aim for success: the influence of stress on memory for different memory phases

Review

In the field of memory research, the influence of stress on memory is still unclear. The aim was therefore to review existing literature on the topic and to determine whether memory is facilitated or impaired by stress. A model is reviewed that hypothesizes that stress improves learning when it is experienced in the context and around the time of the stressful event. This is achieved via catecholamine and non-genomic glucocorticoid actions. Conceptually, the hormones shift the brain into a memory formation mode that facilitates encoding and suppresses the retrieval of irrelevant information. When catecholamine levels have returned to baseline, slow genomic glucocorticoid actions subsequently shift the brain into a memory storage mode where encoding of new irrelevant information will be suppressed to allow successful consolidation of information regarding the stressful event. It was concluded that stress can both enhance and impair memory depending on the timing of the stressful event.

Keywords: Stress, glucocorticoid actions, memory formation, memory storage.

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INTRODUCTION

Stress has become a popular topic in our society, both judging by the articles that appear frequently in the media about its negative impact on human health, and by the many stress management therapies that are offered these days. Chronic stress is a risk for physical health problems: stress hormones such as glucocorticoids antagonize insulin and increase blood pressure, which increases the risk for developing diabetes and cardiovascular disease (Hjortskov et al., 2004; Kivimäki et al., 2002) Furthermore, stress impairs tissue growth and repair and suppresses immune functions which in turn increases the risk of infection (Chrousos, 2009). In addition, prolonged stress can lead to mental health problems such as burnout, which is mainly characterized by feelings of emotional exhaustion (Hooftman, 2011). Burnout is a major and still growing cause of work disability. In the Netherlands in 2010, about 13 percent of the working population experienced burn out problems (Hooftman, 2011).

Although it has become clear that (chronic) stress could have detrimental effects on human health, also positive effects of stress have been demonstrated in the field of memory research (Buchanan & Lovallo, 2001). An emotionally arousing experience can have an enhancing effect on memory. For example, when a boy is attacked by a dog in his childhood, it is likely that he still remembers this experience vividly years later. An extreme case of the enhancing effect of emotions on memory is a flashbulb memory. This is a highly vivid memory for an intense, emotionally engaging event (Hamann, 2001). Most people for instance will still remember vividly what they were doing on the day the Twin Towers were attacked. From an evolutionary perspective, the memory enhancing effect of emotional experiences is understandable since a highly emotionally arousing event is likely to have an effect on immediate or future survival, and therefore it will be important to be remembered for future occasions (Hamann, 2001). Even though the enhancing effects of acute stress on memory are clearly documented, stress or emotional arousal can also impair memory (Schwabe & Wolf, 2010). A typical example is when a person forgets a doctor’s appointment as a consequence of being under a lot of pressure at work. In sum, research studies provide mixed results on the effect of stress on memory. Both enhancing and impairing effects of stress on learning are reported. It is still unclear how stress influences memory processes and what factors determine the performance outcome.

In sum, stress is a frequently occurring and increasing phenomenon in the working environment, therefore it is relevant to investigate to which degree experienced stress can be either harmful or beneficial. The aim of this paper is to review existing literature on this topic and to investigate which factors determine whether stress causes an enhancing or an inhibiting effect on memory. First, the nature of the stress response in the human body including involved brain areas and released stress hormones is explained. Second, the effects of stress on different memory stages are discussed while the influence of the valence of the learned material will be taken into account. Third, theories that can explain the opposing effects of stress on memory are described. Finally, this paper discusses possible effects of daily stressors on job performance and implications for everyday life.
THE STRESS RESPONSE

When confronted with a stressful event, the body reacts by activating two biological systems: the rapidly acting autonomic nervous system (ANS) and the slower hypothalamic-pituitary-adrenal (HPA) axis (Schwabe, Wolf, & Oitzl, 2010). Important organs of the ANS are the adrenal glands, located above the kidneys. The inner portion of the adrenal glands, the adrenal medulla, releases a combination of hormones named catecholamines consisting of adrenaline and noradrenaline (Schwabe et al., 2010). These stress hormones act on the body to prepare an organism to a fight, flight or freeze response, for example by increasing heart rate and blood pressure (Lupien, Maheu, Tu, Fiocco, & Schramek, 2007). Adrenaline cannot enter the brain directly, but exerts its influence by activating the sensory vagus outside the brain and sending information via the nucleus of the solitary tract and the locus coeruleus into the brain. An important brain structure containing adrenergic receptors is the amygdala, which plays a role in fear processing and memory for emotionally relevant information (Adolphs, Tranel, & Damasio, 1998; Davis, 1992).

The activation of the slower HPA system starts in the brain, in the paraventricular nucleus of the hypothalamus where corticotrophin releasing hormone (CRH) is secreted. CRH causes secretion of adrenocorticotrophic hormone (ACTH) from the anterior pituitary, a gland connected to and located beneath the hypothalamus. ACTH is then transported in the blood stream until it reaches the cortex of the adrenal glands where it induces the secretion of glucocorticoids (GCs).

In humans, the most abundant glucocorticoid is cortisol (called corticosterone in rodents). In response to a stressor, glucocorticoids trigger a chain of hormonal events that prepare the body for action, and lead for instance to an increase in heart rate and blood pressure. Glucocorticoids trigger different effects in the body that increase the availability of energy substrates in an organism and allow the organism to adapt to the changing environment and restore homeostasis. Since glucocorticoids are liposoluble, they can cross the blood-brain barrier to bind with receptors located in different parts of the brain. Three of the most important brain structures containing glucocorticoid receptors are the hippocampus, amygdala and frontal lobes; all areas known to be involved in learning and memory (Lupien et al., 2007).

STRESS EFFECTS ON MEMORY: A MATTER OF TIMING?

Both memory enhancement (Cahill, Gorski, & Le, 2003) and impairment (Buchanan, Tranel, & Adolphs, 2006; Kirschbaum, Wolf, May, Wippich, & Hellhammer, 1996) due to stress have been reported. To explain how stress can lead to these opposing effects, a theory was proposed stating that the timing of the stressor relative to the memory phase determines the memory outcome (Joels, Pu, Wiegert, Oitzl, & Krugers, 2006; Roozendaal, 2002).
Stress effects on encoding

Encoding is the first step in the process of creating a new memory. In one of the early human studies investigating the effect of stress on encoding, the effects of a psychological stressor as well as a physical stressor on learning were investigated (Kirschbaum et al., 1996). To induce psychosocial stress the Trier Social Stress Test (TSST) was used, which requires participants to deliver a speech in front of an audience. It reliably elicits moderate stress in laboratory settings and has shown to increase cortisol levels from 8.46 ± 1.02 (SE) nmol/l before the test to 17.65 ± 2.17 nmol/l after the stress induction (Kirschbaum et al., 1996).

In the second part of Kirschbaum’s experiment, 10mg cortisol was administered to investigate the effect of physical stress independent of psychological stress. Participants had to learn a list of 26 nouns and recall the words after a short distraction task. The increase in cortisol level in the blood induced by the psychosocial stress task was inversely correlated with the number of remembered words from the list. The same memory-impairing effect was found for the group that received the synthetic cortisol. From this research, it can be concluded that stress and elevated cortisol levels has the potential to impair learning.

In a different study, participants underwent a cold pressure test (a test where participants are instructed to hold their hand in ice water as long as possible) ten minutes before positive, negative, and neutral words were presented (Schwabe, Bohringer, Chatterjee, & Schachinger, 2008). During the subsequent 1-h delayed free recall test, memory enhancement was found for the group that experienced pre-learning stress. The subjects who experienced a stress-induced cortisol elevation showed enhanced memory for negative terms but not for neutral words. The authors argue that this difference is due to the amygdala, which has a role in mediating the effects of stress on memory, and only processes emotionally valent material.

The facilitating effect of emotionally arousing material was confirmed in research that used a more complex memory task designed to resemble a real life situation instead of a simple word list (Payne et al., 2006). After stress induction using the TSST, the participants were shown a detailed slide show containing 9 neutral and 3 emotionally arousing slides combined with a narrative. This study found that stress led to an impaired memory for neutral information, while memory for emotional information was preserved (Payne et al., 2006).

From these studies, it is not entirely clear whether stress impairs or enhances encoding of memories. It seems that stress impairs memory for neutral material, but that it can protect or even enhance memory for emotionally arousing stimuli. However, it is not certain that these reported effects on memory are entirely attributable to the encoding phase. It is likely that stress induced shortly before a training session not only influences encoding during the learning phase, but also subsequent stabilization of the memory, i.e. memory consolidation.

Also, differences in design of the afore-mentioned studies may be responsible for diverging results. Furthermore, in the study of Kirschbaum et al. (1996), subjects were instructed to learn the word list, while in other research protocols participants were given instructions that kept them oblivious to the true purpose of the task. It is therefore possible that subjects in the Kirschbaum study used the delay period to rehearse the learning material which may have interfered with the results.
Stress effects on consolidation

After the initial acquisition, a new memory trace is stabilized during the consolidation phase. The enhancing effects of stress on consolidation are mediated by the release of adrenal hormones like adrenaline and GCs that are released by emotional arousal. The brain contains two types of glucocorticoid receptors: the high-affinity mineralocorticoid receptors (MRs) and the low-affinity glucocorticoid receptors (GRs). A striking difference between the two receptor types is that the MRs bind glucocorticoids with an affinity that is 6–10 times higher than the GRs (Lupien et al., 2005; Reul & de Kloet, 1985). Under normal conditions, the glucocorticoid secretion has a 24-h circadian rhythm with a maximum concentration in the morning which slowly declines during the day until it reaches the circadian trough in the evening (Lupien et al., 2005).

It was hypothesized that activation of GRs and not MRs are involved in memory consolidation, since GRs become mainly occupied during stress when levels of glucocorticoids are high, while MRs are almost fully occupied under basal conditions (Reul & de Kloet, 1985; Roozendaal, 2000). Because it is therefore likely that GRs alone mediate the stress effects on memory consolidation, this was investigated by intracerebroventricular administration of specific antagonists of GRs or MRs in rats before or immediately after a training session in a Morris water maze task (De Kloet, Oitzl, & Joëls, 1999). In the experiment, only infusions of a GR antagonist impaired retention of the task 24h later. Treating the rats with the GR antagonist before the retrieval session was ineffective, which leads to the conclusion that GR inhibition interferes with the consolidation phase and not the retrieval of the learned spatial information (De Kloet et al., 1999). When the MRs were inhibited, the rats did not need more time to find the platform, but in a free swim trial their search pattern changed. They still swam directly to the former location of the platform, which shows their retention was still intact, but different from the controls that remained searching in the vicinity of the platform, they subsequently explored other areas of the pool. This distinct behavior was explained by the authors as MR activation induced increase in behavioral reactivity (approaching and investigating a stimulus) which depends on the hippocampus (De Kloet et al., 1999). A similar increase in reactivity was found in the absence of corticosteroids after adrenalectomy and with a high occupation of both MR and GR following high doses of corticosterone. This line of research confirms the hypothesis that GRs are involved in regulating glucocorticoid effects on memory consolidation, while MR activation is important for the interpretation of environmental stimuli and is involved in the selection of a behavioral response (De Kloet et al., 1999).

To explain the effects of glucocorticoids on cognitive performance, the MR/GR ratio hypothesis was developed, which suggests that the proportion of occupied GR and MR receptors rather than separate receptor activation determines memory performance. This can be described as an inverted u-shaped function (De Kloet et al., 1999). When most of the MR and only a part of the GR receptors are activated, cognitive functioning is optimal (top of the curve). However, when the MR/GR ratio is low as a result of a decrease or increase of circulating glucocorticoid levels (both extremes of the function), memory performance will be impaired.

The MR/GR ratio hypothesis was investigated in humans using a hormone
removal–replacement protocol (Lupien et al., 2002). In the experiment of Lupien et al. (2002), glucocorticoid levels were pharmacologically lowered using metyrapone, a glucocorticoid synthesis inhibitor, and subsequently restored by infusing hydrocortisone, a synthetic glucocorticoid. The results showed that when circulating glucocorticoid levels were lowered, memory performance significantly decreased. Memory impairment was completely reversed when glucocorticoid levels were restored after hydrocortisone replacement. This experiment proves that the absence of glucocorticoids impairs memory.

A few years earlier, an experiment had been performed to investigate the influence of high circulating levels of GCs on memory, which would match the right extreme of the function (Lupien, Gillin, & Hauger, 1999). The researchers infused a dose of glucocorticoids in the morning at the time of the circadian peak to create a very high glucocorticoid concentration, and indeed found a severely impaired memory function. This research shows that the time of testing should be chosen carefully since it could influence the outcome of the experiment. Applying a stressor in the morning can impair memory performance while the same stressor experienced in the afternoon could increase memory function (Lupien et al., 2005). Together, these studies show that glucocorticoids can have different behavioral effects. This can be attributed to the distinct functions of the MRs and GRs and the proportion of receptor occupation as explained by the MR/GR ratio hypothesis. As for the influence of stress on memory: stress during the consolidation phase seems to enhance memory by stimulating the formation of a stable memory trace. The memory enhancing effects are attributed to the activation of the glucocorticoid receptors by the stress hormone cortisol. There is evidence that this memory enhancement applies especially to emotionally arousing stimuli due to a mediating role of adrenal hormones.

**Stress effects on retrieval**

Retrieval refers to the process of accessing information that has been saved in memory. Several studies investigated the effect of stress on retrieval (Buchanan et al., 2006; De Quervain et al., 2003; De Quervain, Rozendaal, Nitsch, McGaugh, & Hock, 2000; Kuhlmann, Kirschbaum, & Wolf, 2005; Tollenaar, Elzinga, Spinovoden, & Everaerd, 2009).

The impairing effect of cortisol on delayed free recall was demonstrated in a research using only neutral words (De Quervain et al., 2000). In a different study, both neutral and negative words were used to assess the effect of the valence of the material on memory (Kuhlmann, Kirschbaum, et al., 2005). The effect of cortisol administration was measured 5h after an intentional learning session. Performance on free recall, cued recall and working memory (using a digit span task) was compared between a cortisol and placebo group. Cortisol significantly impaired retrieval of negative words while having no significant effect on neutral words. Another research using both emotional and neutral words used a delay period of an entire week before assessing retrieval performance. This study demonstrated that cortisol administration before recall lead to a significant decrease in memory performance compared to a placebo group. This memory impairment caused by cortisol remained even when recall was tested again after a washout period of one
week. Furthermore, emotional words were recalled better compared to neutral words, but no interaction with treatment group was demonstrated (Tollenaar et al., 2009).

These studies successively show that (i) cortisol can impair recall of (neutral) material, (ii) cortisol impairs memory but only for negative words and (iii) cortisol leads to a decrease in memory performance but that emotional material is remembered better than neutral items. These contradicting findings could be a consequence of different research designs, but mainly show that research is still inconclusive about the effects of stress on retrieval and possible interacting effects of valence of the learning material.

Besides valence of the learned material, research has focused on revealing what type of memory is affected by cortisol. Cortisol treatment has shown to impair free delayed recall, while cued recall and recognition memory were preserved (Kuhlmann, Kirschbaum, et al., 2005; Wolf et al., 2001). However, different research has shown impaired cued recall as well (De Quervain et al., 2003). While the type of recall method leads to different results, researchers agree that cortisol seems to influence declarative memory specifically, and does not affect working memory, attention, verbal executive function or vigilance (De Quervain et al., 2000; Kuhlmann, Kirschbaum, et al., 2005; Tollenaar et al., 2009; Wolf et al., 2001). It was hypothesized that the hippocampus mediates the negative effects of cortisol on recall (Wolf et al., 2001), since it has been demonstrated that hippocampal activation is important for successful memory retrieval (Schacter & Wagner, 1999). In order to investigate this theory, a PET study was conducted which tested the 24h delayed recall of a word list (De Quervain et al., 2003). Cortisone administration before recall significantly impaired cued recall and induced a decrease in regional cerebral blood flow in the right posterior medial temporal lobe, with a maximal decrease in the parahippocampal gyrus. This latter brain area is associated with successful verbal memory retrieval (Schacter & Wagner, 1999), which suggests that elevated glucocorticoid levels can disturb medial temporal lobe function and thereby impair declarative memory retrieval (De Quervain et al., 2003). This result is in line with earlier research that showed a cortisol-induced reduction in hippocampal glucose metabolism (De Leon et al., 1997).

THEORIES ON THE DIFFERENTIAL EFFECT OF STRESS ON MEMORY

The studies discussed in the previous section have shown that stress can have enhancing as well as detrimental effects on memory, depending on the memory phase during which the stress was experienced. Different theories have been developed in an attempt to explain this phenomenon.

In order to explain the seemingly paradoxical time-dependent effects of stress on memory, Joëls et al. (2006) state that learning will only be facilitated when stress is experienced in the context and around the time of the event that needs to be remembered. Stress will enhance memory when neurotransmitters and hormones that are released in reaction to a stressful situation act upon the same neuronal circuits that are involved in the processing of the information (convergence in
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space). Also, the increase of circulating stress hormones has to take place at about the same time that these circuits are activated by the event (convergence in time), and the stress has to be experienced within the learning context (convergence in context).

**Memory formation mode model**

Schwabe et al. (2012) combined and expanded the model of Joëls et al. (2006) with an earlier developed model that described stress-hormone induced interaction of brain systems (McGaugh, 2000) to form an integrated model (fig. 1). A stressful event stimulates the secretion of adrenaline and glucocorticoids. The rapid adrenaline and non-genomic glucocorticoid effects interact in the basolateral amygdala, which causes other brain areas including the hippocampus and the prefrontal cortex to shift into a ‘memory formation mode’. In this memory formation mode the processing of the stressful event will be stimulated by facilitating the encoding of information about the situation and environment and by suppressing other cognitive processes, which might interfere with the consolidation process. Over time, the slower genomic glucocorticoid actions become active leading to a ‘memory storage mode’. In this mode, encoding of new information will be suppressed to reduce interference with memory consolidation. Possibly, the retrieval of old information will also be impaired. By suppressing encoding of new material, the storage mode promotes consolidation and long-term storage of relevant information about the stressful experience (Schwabe, Joels, Roozendaal, Wolf, & Oitzl, 2012).

![Figure 1. Memory formation mode model of stress effects on memory. NA: noradrenaline; NTS: nucleus tractus solitarius; LC: locus coeruleus. Reprinted with permission from Schwabe et al. (2012).](image-url)
DISCUSSION

The aim of this paper was to investigate the effects of stress on memory. A large body of research studies suggests that stress has opposing effects for each of the memory stages, because timing determines whether stress enhances or impairs memory. The differential effects of stress can be explained by the immediate actions of catecholamines and non-genomic glucocorticoids that shift the brain into a memory formation mode, and the slower genomic glucocorticoid actions that cause a memory storage mode. These different brain modes facilitate encoding and consolidation of relevant information about the stressful event and, at the same time, increase the threshold for information unrelated to the stressor. This system ensures efficient information processing and storage of threatening events, which may be important for future survival. The different effects of stress on memory performance can thus partially be explained by differences in timing of stress relative to the training phase. However, when studies are categorized by timing of the stressor, results are still incomprehensive.

The MR/GR ratio hypothesis could further clarify these opposing findings. As suggested by the inverted u-shaped function, the proportion mineralocorticoid and glucocorticoid receptors rather than the separate receptor activation determines memory performance. When most of the MR and only a part of the GR receptors are activated, cognitive functioning is optimal but if the MR/GR ratio is low as a result of a decrease or increase of circulating glucocorticoid levels memory performance will be impaired.

Since human circulating glucocorticoid levels follow a 24-h circadian rhythm with a peak in the morning and a trough in the afternoon, the time of day at which the experiment is carried out is essential for the results. Glucocorticoid intake when internal levels are low could improve memory while a dose of cortisol when circulating hormone levels are high could be detrimental for learning. Additionally, the ingested dosage could make the difference between memory impairment and stimulation. Every study used different doses of glucocorticoids, which could partially explain differing results, since it has been shown that only optimal glucocorticoid levels in the blood enhance performance while higher or lower levels could impair learning and memory (Lupien et al., 1999; Lupien et al., 2002).

In most studies on the influence of stress on memory a single event was used to invoke a short-lasting stress response in the participants. It is therefore still unknown how (chronic) daily life stressors affect memory and whether, for example, work stress would have impairing or stimulating effects on job performance. Based on the before discussed studies (De Quervain et al., 2000; Kuhlmann, Piel, & Wolf, 2005; Tollenaar et al., 2009), it seems probable that under stressful circumstances like examinations or approaching deadlines, elevated stress hormones could induce problems with remembering information. On the other hand, experiencing stress could cause a person to shift his cognitive resources to the important situation in question for efficient information processing and consolidation without distraction from irrelevant stimuli. Furthermore, prolonged exposure to stress may induce changes in hormone and neurotransmitter systems and could cause functional and structural changes in the hippocampus that would lead to impaired memory.
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storage (De Quervain et al., 2000).

Intuitively, it seems likely that trying to remember information is harder when feeling stressed or aroused. However, participants usually report no side effects or strange feelings after cortisol treatment (De Quervain et al., 2003; Tollenaar et al., 2009). Although participants thus seem unaware of the artificially induced stress, research clearly shows impairing effects of stress on memory performance. This could mean that in daily life, elevated stress levels could go unnoticed by an individual, while still having detrimental effects on his memory and performance.

Finally, it can be stated that stress not only influences how much is learned, but also affects how information is learned and what aspects of the information will be remembered. In other words, besides the quantity, also the quality of memory is influenced by stress. Stress could influence which (mal)adaptive learning strategies people use in their daily lives, and can affect how people behave in response to work-related dilemma’s (Schwabe et al., 2007).

To conclude, the literature shows that stress can have both a stimulating and impairing influence on memory, depending on the context and timing of the stressful event. Whether these stress effects are similar in daily life situations still needs to be determined.

REFERENCES


