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Review

Memory formation under stress: Quantity and quality

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ABSTRACT

Stress shapes memory. Depending on the timing of the stress exposure facilitating and impairing effects of stress are reported on how much is learned and remembered. Beyond such stress-induced changes in the quantity of memory, recent research suggests that stress also affects the contribution of multiple memory systems to performance. Under stress, rigid 'habit' memory gets favored over more flexible 'cognitive' memory. Thus, stress has an impact on *the way* we learn and remember, that is the quality of memory. This shift between different behavioral strategies on "environmental demands" may facilitate adaptive responses. Here, we review stress effects on both quantity and quality of memory and address possible implications of these effects for the understanding of stress-related psychiatric disorders.

Contents

1. Introduction

"If any one faculty of our nature may be called more wonderful than the rest, I do think it is memory. There seems something more speakingly incomprehensible in the powers, the failures, the inequalities of memory, than in any other of our intelligences. The memory is sometimes so retentive, so serviceable, so obedient; at others, so bewildered and so weak; and at others again, so tyrannic, so beyond control! We are, to be sure, a miracle every way; but our powers of recollecting and of forgetting do seem peculiarly past finding out."

Jane Austen (1814), *Mansfield Park*.

Even two centuries after Jane Austen wrote *Mansfield Park* it is hard to describe the fascination that memory evokes better than she did. Though, while she portrays memory as a rather

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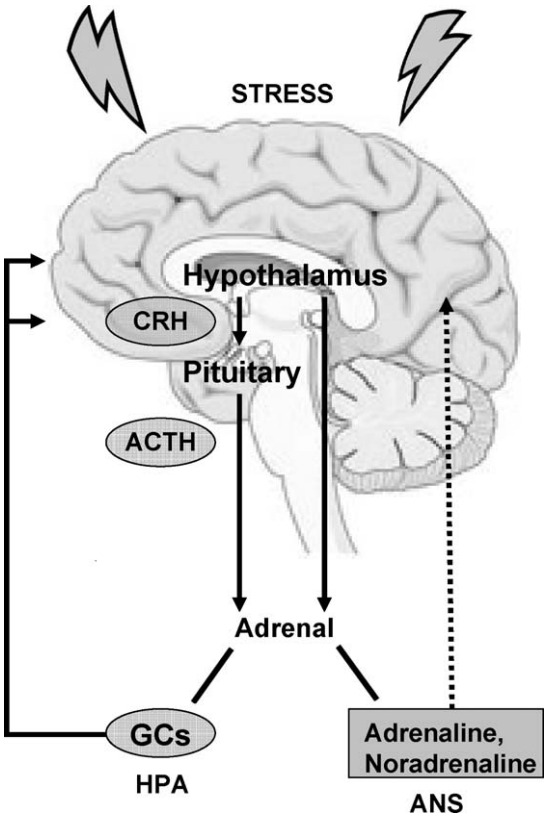

Fig. 1. Circuits activated by stress. If a situation is perceived as a threat for the physiological or psychological integrity of the organism, the brain activates two lines of defense systems that serve to adapt to the demand and to restore balance: the rapidly acting autonomic nervous system (ANS) and the slower hypothalamic–pituitary–adrenal (HPA) axis. Comparison of the ongoing event with previous experiences will stimulate arousal, alertness, vigilance and focused attention, all requiring memory processes. The first line of defense sets in immediately after the stressor occurs. The amygdala activates the hypothalamus; the head ganglion of the ANS. Activation of the hypothalamus in turn stimulates the sympathetic arm of the ANS which secretes noradrenaline at its postganglionic nerve endings. Among the effector organs of the ANS is the adrenal medulla which releases a hormone cocktail consisting of 80% adrenaline and 20% noradrenaline. These stress hormones exert a number of central and peripheral actions enabling the organism to fight, flight or freeze responses. Autonomic activation can indirectly (via the vagal nerve, solitary tract nucleus and locus coeruleus) lead to release of noradrenaline in the brain. The second line of defense is initiated by the secretion of corticotrophin releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus. CRH causes the secretion of β-endorphin and adrenocorticotrophic hormone (ACTH) from the anterior pituitary, which is transported in the blood stream to the cortex of the adrenal glands, inducing the secretion of glucocorticoids (GCs). The most abundant GC in humans is cortisol, in rodents it is corticosterone. GCs enter the brain where they bind to two types of receptors: (i) the broadly distributed, low affinity glucocorticoids receptors (GR) which become substantially activated when hormone levels rise after stress and (ii) the high affinity mineralocorticoid receptors (MR) which are extensively occupied when hormone levels are low and are primarily found in limbic regions. GCs exert negative feedback via GR at the pituitary and hypothalamus thereby reducing the enhanced activity of the HPA axis. Corticosteroids and noradrenaline – as well as transmitters and peptides not mentioned in this review, such as acetylcholine, glutamate, GABA, CRH, ACTH, vasopressin and opioids (McGaugh, 2004) – act together, not only helping to face imminent threats but also to prepare the organism for similar challenging situations in the future.

independent, self-determined entity, today we know that memory is subjected to a variety of modulating factors. Emotionally arousing experiences together with a lack of control and predictability, either acute or chronic, ranging from the multitude of daily hassles to life-threatening situations, are potent modulators of memory. These homeostasis threatening situations are generally referred to as "stress" (McEwen, 2000).

Stress elicits a number of physiological responses directed at reinstating homeostasis. Two biological systems mediate these stress responses: the autonomic nervous system (ANS) and the hypothalamic–pituitary–adrenal (HPA) axis (Fig. 1). These systems exert their action primarily via catecholamines (i.e. adrenaline and noradrenaline) and glucocorticoids (GCs; cortisol in humans, corticosterone in rodents). It has been known for more than 40 years that stress and stress hormones influence memory (de Kloet et al., 1999; McGaugh, 1966). Since then, a large body of literature demonstrates that stress has an impact on *how much* we remember, i.e. on the *quantity* of memory (Joels et al., 2006; Kim and Diamond, 2002; Lupien and McEwen, 1997). In the first part of this review, we will give a brief overview of the stress effects on these quantitative aspects of memory.

In the past few years it has been shown that stress affects not just how much or how fast but also the way we learn and remember, i.e. the *quality* of memory (Kim et al., 2001; Schwabe et al., 2007). In the second part of this review, we will introduce the multiple memory systems theory and present evidence that stress affects the quality of memory by modulating the contribution of multiple memory systems. Stress and glucocorticoid hormones operate as switch between flexible "cognitive" memory and "habit" memory, a form of implicit memory that may be altered by priming and conditioning processes (Mishkin et al., 1984; Squire, 1992). Finally, we will highlight the relevance of stress effects on quantity and quality of memory for psychopathology.

2. Stress effects on the quantity of learning and memory

Stress effects on quantitative memory parameters depend critically on the timing of the stressor relative to the memory phases of encoding, consolidation and retrieval (Joels et al., 2006; Roozendaal, 2002). Here, we will address the influence of stress on these memory stages separately. We will focus primarily on the impact of stress on memory that relies on the hippocampus and adjacent cortical areas, because most studies investigated stress-induced quantitative changes in this kind of memory (for studies investigating stress effects on procedural memory and priming see, e.g. Domes et al., 2002; Kirschbaum et al., 1996; Lupien et al., 1997; Schwabe et al., 2009c; for studies on the effect of stress on fear conditioning and avoidance learning see, e.g. Jackson et al., 2006; Merz et al., in press; Roozendaal and McGaugh, 1996; Stark et al., 2006; Zorawski et al., 2006).

2.1. Stress effects on memory encoding

To estimate how stress affects solely memory encoding is a challenging task. This is primarily due to the fact that such studies face a virtually unsolvable problem: they have to stress individuals before learning which implicates that possible stress effects on encoding are inevitably confounded with effects on consolidation processes and memory retrieval. Indeed, the findings of those studies are highly inconsistent. Some authors reported enhancing effects of stress (Nater et al., 2007; Schwabe et al., 2008a); others found impairing effects (Elzinga et al., 2005; Kim et al., 2001; Kirschbaum et al., 1996; Lupien et al., 1997). One critical factor appears to be the emotionality of the presented material with memory for emotional information being preserved or even enhanced by stress or GC administration whereas memory for non-emotional information is impaired (Payne et al., 2006; Tops et al., 2003). Another factor might be the stressor intensity and the GC dose, respectively, with memory impairments being particularly severe following intense stressors or very high GC doses (Abercrombie et al., 2003; Diamond et al., 1992). Probably more important, however, is the fact that studies which administer stress before learning are particularly sensitive for variations in experimental procedures. For example, if memory is tested shortly after learning, effects on memory retrieval may be pronounced. If,

however, the interval between learning and testing is prolonged, effects on memory consolidation are prominent.

2.2. Stress effects on memory consolidation

Remembering emotionally arousing experiences is critical for survival. In line with this view, considerable evidence suggests that adrenal hormones, released by emotional arousal, play a crucial role in enabling the significance of an experience to regulate the strength of memory (McGaugh, 2000). In rodents, adrenaline, GCs as well as drugs that activate stress hormone receptors facilitate memory consolidation (de Kloet et al., 1999; Gold and van Buskirk, 1975; Lupien and McEwen, 1997). The enhancing effects of GCs on memory consolidation appear to require a co-occurrence of noradrenergic activity in the basolateral amygdala (BLA) mediated at least partly by neurons of the nucleus of the solitary tract which receives input from the periphery via the vagus nerve (Roozendaal, 2000). This model received compelling evidence from studies in rats showing that the consolidation enhancing effect of GCs is abolished by BLA lesion or administration of beta-adrenoceptor antagonists in the BLA (Roozendaal and McGaugh, 1997; Roozendaal et al., 2006). Additionally, the blockade of glucocorticoid receptors (GR), the low affinity corticosteroid receptors that are distributed throughout the brain, impaired memory consolidation (Oitzl and de Kloet, 1992; Sandi and Rose, 1994), whereas the infusion of GR agonists enhanced memory consolidation (Roozendaal and McGaugh, 1996). Thus, GR activation seems to be a prerequisite for the enhanced consolidation of relevant information.

The stress (hormone)-induced enhancement of memory consolidation is well supported by human studies. Memory performance was enhanced by stress or pharmacologically elevated GC concentrations after learning (Abercrombie et al., 2003; Cahill et al., 2003; Smeets et al., 2008). Importantly, this effect was most pronounced for emotionally arousing material activating the BLA. In addition, GCs facilitated memory consolidation only in individuals that were emotionally aroused (Abercrombie et al., 2006), thus corroborating the proposed interaction of noradrenergic and GC activity in enhancement of memory consolidation (Roozendaal, 2000).

2.3. Stress effects on memory retrieval

Stress effects on memory retrieval appear to be opposite to those on memory consolidation. Rodents stressed before retention testing in the Morris water maze showed impaired spatial memory retrieval (de Quervain et al., 1998; Diamond et al., 2006). Similar effects were observed when GCs were administered before spatial memory testing (de Quervain et al., 1998). There is ample evidence that the effects of stress on memory retrieval necessitate, same as stress effects on memory consolidation, co-occurring GC and noradrenergic activity in the BLA. Blockade of beta-adrenergic receptors as well as lesioning the BLA prevented the impairing effects of GCs on spatial memory retrieval (Roozendaal et al., 2003, 2004).

Several studies indicate that stress or GC administration disrupt declarative memory retrieval in humans as well (Buchanan et al., 2006; Coluccia et al., 2008; Kuhlmann et al., 2005a,b). Again, the effect was most pronounced for emotionally arousing material pointing to the importance of interacting GC and noradrenergic activity. Corroborating this assumption, administration of beta blockers abolished the effects of stress or pharmacological GC elevations on memory retrieval (de Quervain et al., 2007; Schwabe et al., 2009b). In the same line, GCs did not impair retrieval performance when declarative memory was assessed in a non-arousing testing environment (Kuhlmann and Wolf, 2006). Though, stress and GCs seem to have generally impairing effects on declarative memory retrieval, there are some studies suggesting that stress or elevated GC levels may also enhance retrieval performance (Buchanan and Tranel, 2008; Domes et al., 2005; Schwabe et al., 2009c). These studies deserve attention and future research is required to identify factors that mediate possible enhancing effects of stress on memory retrieval, particularly in the face of first studies that aim to treat psychiatric disorders with GCs and rely critically on the assumption of stress-induced retrieval impairments (Aerni et al., 2004; see below).

In summary, the modulating influence of stress on memory depends on the context and convergence of stress hormone action (de Kloet et al., 1999; Diamond et al., 2007; Joels et al., 2006). Memory is facilitated when stress and GCs are experienced within the context of the learning episode, i.e. when the stress hormones exert their actions on the same neural circuits as those activated by the learning experience, and around the time of the event that needs to be remembered. However, if the hormones and transmitters released by stress exert their action out of the learning context (e.g. when they are present during memory retrieval), they are mainly interrupting memory performance.

3. Stress effects on the quality of learning and memory

The studies discussed above showed that stress may cause a quantitative decline or boost in memory performance. Individuals remembered more or less words or pictures following stress or GC administration. Rodents exposed to stress showed higher or lower escape latencies in spatial memory tasks or an altered exploration time in object recognition tasks. In these studies, the focus was on stress-induced changes in the performance of a single (mostly hippocampus-dependent) memory system. Although these studies on stress and quantitative memory performance yielded important findings that may have implications for educational and clinical settings, stress-memory researchers have rather neglected that our memory consists of multiple systems processing information in parallel (Squire, 2004).

3.1. Multiple memory systems

The idea that memory is no single entity but composed of distinct systems goes back to the writings of 19th century philosophers and psychologist, such as Maine de Biran (1804/1929) and James (1890). This idea became topic of experimental research in the second half of the past century after reports of amnesic patients who could acquire rule-based knowledge (“knowing how”) in the absence of any memory for the learning episodes (“knowing that”) (Cohen and Squire, 1980; Knowlton et al., 1996; Milner, 1962). Nowadays, the assumption of multiple anatomically and functionally distinct memory systems is well supported by converging lines of evidence, including neuroimaging studies in humans (Bohbot et al., 2004; Iaria et al., 2003) and animal studies using brain lesion techniques (Kesner et al., 1993; Packard et al., 1989; White and McDonald, 2002), and widely accepted among memory researchers (Squire, 2004).

Most views on multiple memory systems have been dualistic, opposing a taxon and a locale system (O’Keefe and Nadel, 1978), a simple and a configural association system (Sutherland and Rudy, 1989), an explicit or implicit memory system (Graf and Schacter, 1985) or a declarative and a non-declarative system (Squire, 1982). Common to most of these dualisms is the distinction between a flexible, representational memory system that allows conscious recollection and a rather rigid, dispositional form of memory that is expressed in performance (Squire, 2004). In line with early proponents of this multiple memory systems view (James, 1890; Tolman, 1948) we refer to these systems as “cognitive”

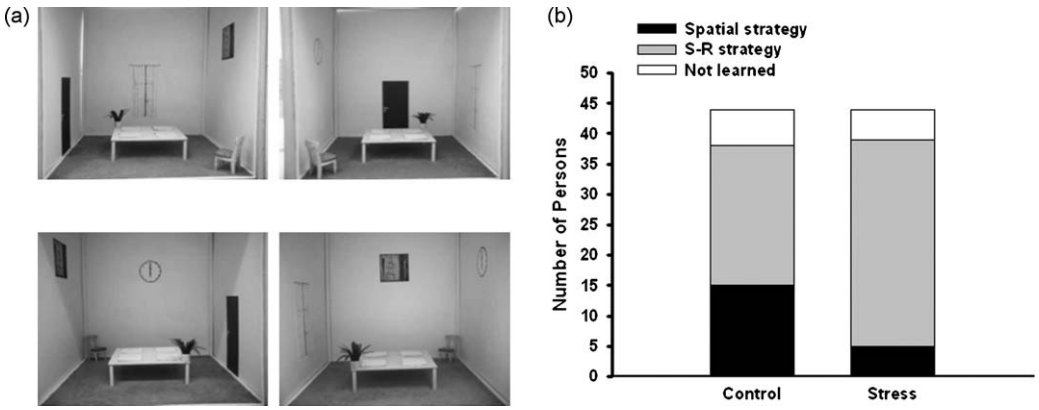

Fig. 2. Stress effects on spatial and stimulus-response (S-R) learning and memory in humans. (a) Participants were presented a 3D model of a room (removable walls; perspectives changed during training) and trained to identify a "win-card" out of four cards placed on the table. The "win-card" could be located by using the relation between multiple distal cues in the room model (spatial strategy) or by using a single proximal cue (the plant; S-R strategy). The used strategy was revealed in a test trial in which the proximal cue was relocated. (b) Stress before training in the learning task increased the use of a S-R strategy.Parts of this figure are reprinted from Schwabe et al. (2007) with permission from Cold Spring Harbor Laboratory Press©.

and "habit" memory, respectively (see also Mishkin and Appenzeller, 1987; Mishkin et al., 1984). Although such a distinction is in our view helpful, it is important to note that reality appears to be more complex than suggested by such a dualism and that "cognitive" and "habit" memory systems consist of subsystems and subfunctions (Eichenbaum and Cohen, 2001; Squire, 2004).

How do these multiple memory systems relate to each other? Although each memory system makes distinct contributions to the optimization of behavior, recent evidence indicates complex interactions between memory systems (Kim and Baxter, 2001). For instance, it is now well established that the amygdala, a structure involved in emotional memory (Cahill et al., 1995), is able to modulate other memory systems (McGaugh, 2000; Packard and Teather, 1998). Beyond such direct modulation, evidence accumulates that the memory system involved in a task may be determined by the proportion of involvement of another system. Some authors suggest cooperative interactions between memory systems in which one system can compensate for the functional degradation of another (McIntyre et al., 2003; Voermans et al., 2004), whereas other studies indicate rather competitive interactions (Matthews and Best, 1995; Poldrack et al., 2001; Schroeder et al., 2002). Which factors and underlying mechanisms modulate the use of memory systems? Extensive training and distraction favor neostriatum-based "habit" memory over hippocampus-based "cognitive" memory (Foerde et al., 2006; Iaria et al., 2003). Given that memory-related limbic structures, such as the hippocampus, are highly sensitive to stress and stress hormones (de Kloet et al., 1999), it has been hypothesized that stress might also modulate the contribution of multiple memory systems and thus affect the way *how* we learn, i.e. the quality of learning and memory. Below we present recent evidence supporting this hypothesis.

3.2. Acute stress effects on the use of multiple memory systems

Interactions between memory systems are most evident in situations in which multiple memory systems can support behavioral performance. For instance, in a fixed-location visible platform water maze task performance can rely on both hippocampus-dependent spatial ("cognitive") and neostriatum-dependent stimulus-response (S-R; "habit") memory. The contribution of either system can be elegantly tested by relocating the platform (marked by a salient pole) to a novel position. Swimming to the original platform location could be interpreted as hippocampus-dependent spatial memory while swimming to the pole in the novel location would indicate neostriatum-dependent S-R memory. Stress prior to training facilitated the use of a S-R strategy and reduced the use of a spatial strategy to find the platform in rats (Kim et al., 2001). Injections of anxiogenic drugs which do not necessarily lead to stress but to some sort of emotional arousal had similar effects (Packard and Wingard, 2004). Interestingly, injections of anxiogenic drugs directly into the basolateral amygdala appeared to be sufficient to bias rats towards neostriatum-based S-R memory suggesting a critical role of the amygdala in the "emotional" modulation of multiple memory systems (Packard and Wingard, 2004). Recently, these findings were translated to humans. Participants were trained to locate a "win-card" in a 3D model of a room which could be identified by using multiple distal cues, i.e. spatial memory, or a single proximal cue, i.e. S-R memory (Fig. 2). Similar as in rodents, stress prior to training in this task favored the use of neostriatum-based S-R memory at the expense of hippocampus-based spatial memory (Schwabe et al., 2007). Pharmacological studies in mice and humans identified the corticosteroid stress hormones as key players in the switch between memory systems (Schwabe et al., 2009b, in press). Using a spatial learning task in mice (Fig. 3) revealed that the stress-induced transition from hippocampus-dependent to neostriatum-dependent memory was prevented by blockade of the mineralocorticoid receptor (MR). This high affinity corticosteroid receptor in the brain is relevant for the initial appraisal of novel environments (Oitzl et al., 1994). We conclude that stress modulates the use of multiple memory systems via a corticosteroid mechanism involving the MR (Schwabe et al., in press). Moreover, we showed in this study for the first time that the stress-induced switch from spatial to S-R learning rescued quantitative performance. This addresses the interesting but so far not well understood interaction of memory quantity and memory quality.

Most studies on the influence of stress on the use of multiple memory systems focused on hippocampus-dependent spatial and caudate nucleus-dependent S-R memory. There is however recent evidence demonstrating that stress modulates the use of multiple memory systems not only in spatial navigation but also in instrumental learning (Schwabe and Wolf, 2009). Instrumental learning can be controlled by goal-directed action-outcome and habitual S-R processes (Dickinson, 1985). Goal-directed instrumental learning is mediated by the prefrontal cortex whereas habitual goal-directed learning relies on the dorsolateral striatum (Balleine and Dickinson, 1998; Tricomi et al., 2009; Valentin et al., 2007; Yin et al., 2004). These two forms of instrumental learning can be separated in a so-called devaluation paradigm (Balleine and Dickinson, 1998; Valentin et al., 2007). In this paradigm,

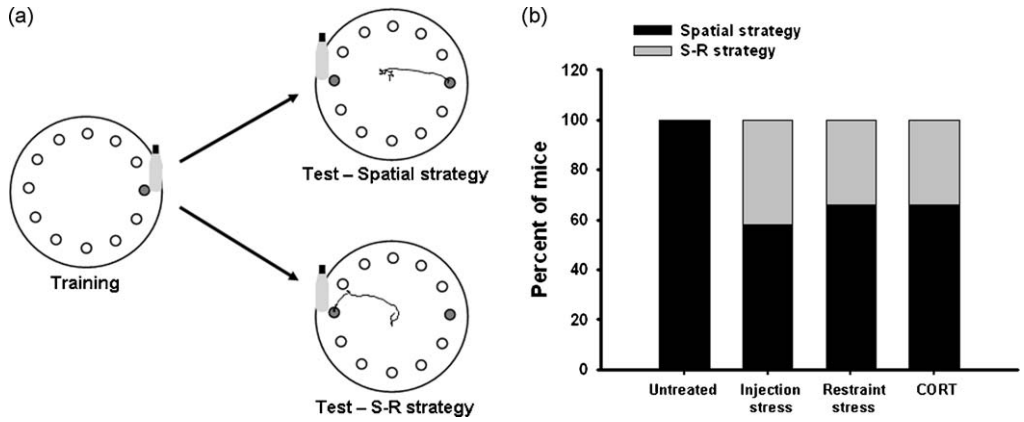

Fig. 3. Stress and glucocorticoid effects on spatial and stimulus-response (S-R) learning and memory in mice. (a) Mice were trained on a circular hole board to find the open hole providing access to the homecage (marked grey in the drawing). The position of the open hole could be located via the relation between multiple room cues (spatial strategy) or via a single, proximal cue (the bottle; S-R strategy). Relocating the proximal cue in a test trial revealed the applied strategy. (b) Injection stress, restraint stress and corticosterone (CORT) injection before training in the circular hole board task changed learning strategies towards more S-R learning. Parts of this figure are reprinted from Schwabe et al. (in press) with permission from MIT Press©.

individuals are first trained in two instrumental responses that are associated with the delivery of different food rewards. After training, one of the food outcomes is devalued by feeding individuals to satiety with that food. Whether behavior is ruled by goal-directed or habitual processes can be assessed in a subsequent extinction test, in which the two learned instrumental actions are presented again but this time they are never followed by the food rewards. Decreased responding to the action associated with the devalued outcome indicates goal-directed performance whereas the continued selection of the devalued instrumental action reflects habitual performance. Interestingly, acute stress before instrumental learning rendered participants' behavior insensitive to changes in the value of the outcome, made participants' behavior habitual (Schwabe and Wolf, 2009). In other words: stress favored the dorsolateral striatum-dependent habit learning system over the prefrontal cortex-dependent goal-directed learning system.

Taken together, these studies provide convincing evidence that stress affects not only how much and how fast individuals learn but also the way we learn depending on the distinct contribution of multiple memory systems. Importantly, none of the above mentioned studies that showed stress effects on the used learning strategy (i.e. memory quality) found significant changes in quantitative parameters, such as escape latencies or number of holes visited in rodents and learning curves in humans. We propose that depending on the nature and severity of the stressor, the quality of learning and memory will switch while quantitative performance might remain unchanged.

3.3. Are stress effects on the quality of memory timing-dependent?

Stress effects on quantitative aspects of memory depend critically on the timing of the stress exposure (or GC administration). Is there a comparable time-dependency for stress (hormone) effects on qualitative aspects of memory? The above cited studies administered stress and drugs, respectively, before learning and the test trial that revealed the used memory system either immediately after learning (Schwabe et al., 2007, 2009b, in press; Schwabe and Wolf, 2009) or 24 h later (Kim et al., 2001; Packard and Wingard, 2004). The similar pattern of results in these studies can be taken as evidence that the observed memory-modulating effect of stress is primarily due to stress effects on encoding. Two very recent studies showed that anxiogenic drugs favored S-R over spatial memory also if they were administered immediately after learning or immediately before retention testing (Elliott and Packard, 2008; Wingard and Packard, 2008). Moreover, there is first evidence that stress favors habitual instrumental behavior even when stress occurs before the extinction test, i.e. without any effect on instrumental learning (Schwabe and Wolf, unpublished data). Thus, the available data suggest that stress or stress hormones bias rodents and humans towards neostriatum-based "habit" memory irrespective of the memory phase addressed.

So far, we were referring to effects of acute stress on the use of multiple memory systems. There is, however, also some first evidence that chronic stress influences the quality of learning and memory in a similar manner. The use of a "habit" strategy in a spatial task was favored in mice that were repeatedly exposed to an environmental stressor and in healthy humans that reported high stress levels in the months before testing (Schwabe et al., 2008b). Similarly, chronic stress rendered instrumental responding habitual in rats (Dias-Ferreira et al., 2009). Interestingly, the switch to more habitual instrumental performance after chronic stress was accompanied by opposing structural changes in the neural structures underlying goal-directed and habit learning. Chronic stress caused an atrophy of the medial prefrontal cortex but a hypertrophy of the dorsolateral striatum (Dias-Ferreira et al., 2009). In addition, chronic stress leads to a hypertrophy of the amygdala (Vyas et al., 2002) which may further contribute to the change in memory quality following repeated or long-lasting stress. These findings might have important implications for psychopathology as chronic stress has been linked to various psychiatric disorders (McEwen, 2004; Wolf, 2008). Given that a flexible use of acquired information and the transfer of knowledge to novel situations are mainly associated with hippocampal and prefrontal cortex-dependent memory (Eichenbaum et al., 1990; Squire and Zola, 1996), the stress-induced shift in memory systems at the expense of these "cognitive" systems appears also highly relevant for educational and working environments.

4. Stress effects on quantity and quality of learning and memory: implications for psychopathology

While learning and memory are critical for a successful adaptation to the environment, not all learning is beneficial. Learning can produce dysfunctional patterns of thinking and emotional responding which, in the extreme, may constitute psychiatric disorders. In several disorders such maladaptive learning and memory processes are paralleled by abnormalities of the stress system. Below, we will focus on the implications the

stress effects on quantity and quality of memory have for three of these disorders: post-traumatic stress disorder, major depression and specific phobia.

Post-traumatic stress disorder (PTSD) is characterized by avoidance behavior, hyperarousal and re-experiencing of the traumatic event (American Psychiatric Association, 1994). Typically, PTSD patients show an increased activity of the noradrenergic system (O'Donnell et al., 2004) and reduced GC levels most likely due to enhanced negative feedback mechanisms and increased GC sensitivity of immunologic tissues (Rohleder et al., 2004; Yehuda, 2002, 2006). Based on the evidence of improved memory consolidation by stress, it has been postulated that the extreme arousal associated with the traumatic event leads to exceptionally strong, "over-consolidated", trauma (fear) memories that lack contextual specificity and are not adequately integrated in autobiographical memory (Ehlers and Clark, 2000; Pitman, 1989). This "over-consolidation" hypothesis stimulated the development of several approaches for the pharmacological treatment of the trauma memory in PTSD patients. Beta blockers were administered shortly after the traumatic experience to prevent the emotional arousal necessary for memory consolidation (Pitman et al., 2002). Furthermore, low doses of GCs were applied to inhibit the retrieval of the traumatic memory and to facilitate the integration of the trauma in autobiographic memory (Aerni et al., 2004; Schelling et al., 2006). Very recently, beta blockers were given following trauma-script driven reactivation of the traumatic event to disrupt the reconsolidation of the trauma memory (Brunet et al., 2008). Though these strategies have been tested in rather small patient groups so far, the first results are promising.

A further hypothesis about the pathogenesis of PTSD may be derived from the stress-induced modulation of multiple memory systems. We propose that the extreme stress experienced during a traumatic event affects not only the strength of consolidation but also which memory systems are involved in the encoding and consolidation of the traumatic experience. In healthy individuals, stress favors the use of neostriatum-dependent "habit" (S-R) memory at the expense of hippocampus-dependent "cognitive" or prefrontal cortex-dependent goal-directed memory (Schwabe et al., 2007; Schwabe and Wolf, 2009). It is tempting to speculate that there is a common mechanism in PTSD patients resulting in strong stimulus-response like associations linking single trauma-related cues to the emotionality experienced during the trauma. In line with this view, trauma reactivation decreases hippocampal activation (Bremner et al., 1999) and single trauma relevant stimuli, such as combat sounds, are capable to provoke strong emotional responses in PTSD patients (Liberzon et al., 1999; Pissiota et al., 2002). Moreover, healthy subjects exposed to stress before learning tended to restrict the range of cues they attend to and failed to integrate contextual cues in the memory for the learning episode (Schwabe et al., 2009a). Given that "habit" memory is less sensitive to extinction than "cognitive" memory (Valentin et al., 2007), the stress-induced facilitation of "habit" memory could also account for the persistence of trauma memories.

In major depression, affective disturbances such as the inability to experience pleasure from pleasurable events (anhedonia) are the core of the disorder (American Psychiatric Association, 1994). In addition to these affective symptoms there is however a number of cognitive symptoms such as rumination, i.e. persistent focusing on negative themes, or negatively biased memory encoding and retrieval (Leppanen, 2006) which are closely related to the depressive mood. With respect to HPA axis functioning depressive disorders are characterized by excessive circulating cortisol levels (Holsboer, 2000; Van Praag et al., 2004). This hypercortisolaemia is related to dysfunctions of limbic brain regions which most likely contribute to the cognitive disturbances observed in depression (Herbert et al., 2006). As studies in healthy individuals show elevated GC levels may lead to the negative memory bias and the lack of specificity of autobiographic memory characteristic for depressed patients (Buss et al., 2004; Tops et al., 2003; Williams et al., 2007). Moreover, the GC elevations and associated hippocampal dysfunctions (MacQueen et al., 2003) may favor the use of rather rigid "habit" memory expressed as reduced cognitive flexibility and impaired mental set shifting capabilities often found in depressive disorders (Airaksinen et al., 2004; Austin et al., 2001). Note that while we argued above that the severe stress during the traumatic experience may result in a rigid, habitual memory for the traumatic event (i.e. a single event or episode) in PTSD, we propose here that the chronically elevated GC levels in major depression may lead to a more general proneness to habit learning and memory.

Irrational and persistent fear of specific objects or situations accompanied by pronounced avoidance behavior is the hallmark of phobic disorders (American Psychiatric Association, 1994). Exposure to phobic stimuli provokes retrieval of innate or conditioned fear memories. Such confrontation elicits exceptionally strong GC responses (Furlan et al., 2001) which could explain the well consolidated fear memory (Cordero and Sandi, 1998). In addition, the strong HPA axis activation might facilitate the establishment of inflexible "habit" memories which substantially contribute to the pattern of anticipatory fear and avoidance behavior. A recent study suggested that GCs may have a therapeutic value for treating phobia. Cortisol administration before the presentation of phobic stimuli reduced phobic fear in humans with social or spider phobia presumably due to impairing effects on fear memory retrieval (Soravia et al., 2006).

Taken together, stress effects on the quantity and quality of memory may have important implications for the pathogenesis of several psychiatric disorders. A better understanding of these effects could promote the development and advancement of novel treatment strategies.

5. Concluding statements

A vast amount of evidence shows that stress and GCs affect learning and memory processes. These influences are characterized by a remarkable diversity. Stress and GCs affect how much we remember, yet these effects on the quantity of memory depend critically on the timing of stress or pharmacologically induced GC elevations, whether within or out of the learning context. Moreover, stress and GCs affect how we learn (i.e. the quality of memory) by modulating the use of "cognitive" and "habit" memory. Both, the effects on quantity and quality of memory may improve our understanding of several psychiatric disorders. Considering the mechanism underlying these effects could open the door to novel therapeutic approaches.

From the many examples above one might be prone to divide the consequences of stress on memory in "good", such as enhanced memory consolidation, and "bad", such as reduced memory retrieval and the bias towards rigid "habit" memory. In stressful situations, however, interference, ambiguity and distraction have to be reduced; fast reactions are required. Extensive cognitive reflections cause hesitations, delays that might endanger the organism. We thus argue that even the putative misdeeds of stress on memory are part of a generally adaptive mechanism that allows focusing on coping with the current stress and to form a lasting, easily accessible memory of it. If the stress response, however, is excessive and inadequate like in depressive disorders or PTSD, the otherwise useful mechanism may overshoot. Then, memory may turn out, as Jane Austen wrote, "so tyrannic, so beyond control."

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