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REVIEW
Memory under stress: from single systems to network changes

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Abstract

Stressful events have profound effects on learning and memory. These effects are mainly mediated by catecholamines and glucocorticoid hormones released from the adrenals during stressful encounters. It has been known for long that both catecholamines and glucocorticoids influence the functioning of the hippocampus, a critical hub for episodic memory. However, areas implicated in other forms of memory, such as the insula or the dorsal striatum, can be affected by stress as well. Beyond changes in single memory systems, acute stress triggers the reconfiguration of large scale neural networks which sets the stage for a shift from thoughtful, 'cognitive' control of learning and memory toward more reflexive, 'habitual' processes. Stress-related alterations in amygdala connectivity with the hippocampus, dorsal striatum, and prefrontal cortex seem to play a key role in this shift. The bias toward systems proficient in threat processing and the implementation of well-established routines may facilitate coping with an acute stressor. Overreliance on these reflexive systems or the inability to shift flexibly between them, however, may represent a risk factor for psychopathology in the long-run.

Introduction

Stress is ubiquitous in our daily life and has a major impact on how we feel, think, and behave. In particular, stress may alter cognitive processes such as learning and remembering (Joëls *et al.*, 2006; Diamond *et al.*, 2007; Roozendaal *et al.*, 2009a; Schwabe *et al.*, 2012a). These effects are mainly driven by the numerous hormones, peptides and neurotransmitters that are released during stressful encounters. Two stress response systems that are known to play a key role in the modulation of learning and memory are the rapidly acting autonomic nervous system (ANS) and the slower hypothalamus-pituitary-adrenal (HPA) axis. Within seconds after the exposure to a stressful event, the ANS, activated by the hypothalamus, stimulates the release of adrenaline and noradrenaline from the adrenal medulla. Although adrenaline and noradrenaline cannot cross the blood-brain barrier, they exert indirect effects on the brain via the vagus nerve, resulting in the activation of noradrenergic brain stem nuclei (Williams & Clayton, 2001). Parallel to the activation of the ANS, the hypothalamus triggers the HPA axis, leading, via intermediate steps and within 15–20 min after the onset of a stressful event, to the secretion of glucocorticoids (mainly corticosterone in rodents and cortisol in humans) from the adrenal cortex. Glucocorticoids cross the blood-brain barrier and exert their actions through glucocorticoid and mineralocorticoid receptors (GR and MR, respectively). Traditionally, these receptor types were thought to be only intracellular receptors mediating relatively slow, genomic actions. However, more recent evidence points to membrane-bound MR (and presumably GR) that can induce rapid, non-genomic changes in neural excitability and cognition (Joëls *et al.*, 2008, 2012; Barsegyan *et al.*, 2010). MRs and GRs are colocalized and densely expressed in prefrontal and medial temporal areas (Reul & de Kloet, 1985; McEwen *et al.*, 1986), those areas that are pivotal for learning and memory (Buckner & Wheeler, 2001).

Stress-induced changes in learning and memory have crucial implications for educational settings (Vogel & Schwabe, 2016a) as well as for understanding stress-related mental disorders, such as depression, addiction or posttraumatic stress disorder (PTSD; de Quervain & Margraf, 2008; de Quervain *et al.*, 2009; Schwabe *et al.*, 2011a). In particular, the clinical relevance of stress effects on learning and memory motivated a number of studies targeting the neuroendocrine mechanisms underlying the impact of stress on memory. For decades, these studies have focused mainly on how stress changes neuroplasticity and memory processes in the hippocampus (for reviews, see Lupien & Lepage, 2001; Kim & Diamond, 2002). In the first part of this review, I will therefore provide a concise summary of what is known about the impact of stress on hippocampus-based learning and memory.

However, although the hippocampus is certainly a key structure for (episodic and spatial) memory (Scoville & Milner, 1957;

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O'Keefe & Speakman, 1987; Burgess *et al.*, 2002), other brain regions are critically involved in memory processes and these non-hippocampal forms of memory may also be affected by stress. In particular, there is accumulating evidence suggesting that stress may affect dorsal striatum-dependent memory and this evidence will be highlighted in the second part of this review. Even more importantly, it is by now widely accepted that different memory systems, including the hippocampus and the dorsal striatum, are not acting in isolation but that complex cognitive process, such as memory, rely on highly distributed networks involving many interacting brain areas (Bressler & Menon, 2010; Spreng *et al.*, 2013). How stress affects the recruitment and crosstalk of distinct memory networks will be discussed in the third and final part of this review. I will also briefly address implications of stress-induced changes in memory networks for future research on the impact of stress on learning and memory.

Focus on single memory systems

It has been known for more than half a century that stress and stress hormones affect learning and memory processes (Lazarus *et al.*, 1952; McGaugh, 1966). Since then, a plethora of studies has demonstrated that stress can have both enhancing and impairing effects on memory and technical progress, such as the development of neuroimaging techniques in humans, has helped to shed light on the mechanisms involved in these effects. Most of this research focused on how stress alters the functioning of single, memory-relevant brain areas. The area that received most attention was the hippocampus, yet evidence for stress effects on other, non-hippocampal memory systems is accumulating.

Stress, memory, and the hippocampus

Stress effects on hippocampus-dependent memory processes have been extensively studied, most likely because of the outstanding role of the hippocampus in episodic memory (Scoville & Milner, 1957; Burgess *et al.*, 2002), the type of memory that is usually meant by 'memory' in day-to-day usage, and because this area expresses MR and GR at a high density (Reul & de Kloet, 1985; McEwen *et al.*, 1986). How does stress impact hippocampal memory? The answer to this question depends largely on the memory stage affected by stress. For memory encoding, studies yielded heterogeneous results. Whereas some studies reported enhanced memory (Smeets *et al.*, 2007; Schwabe *et al.*, 2008), others found impaired memory (Kirschbaum *et al.*, 1996; Elzinga *et al.*, 2005; Diamond *et al.*, 2006), when individuals experienced stress before learning. In addition to specific methodological differences between studies, the emotionality of the learning material (Payne *et al.*, 2007) and the interval between stress exposure and learning experience (Joëls *et al.*, 2006) are only two of several variables that were discussed as possible explanations for the heterogeneous findings on the influence of stress before learning on subsequent memory. Yet, to what extent these factors may account for the conflicting data on the effect of stress on encoding is still debated. For instance, stress about 30 minutes before encoding has been found to impair subsequent memory in two studies (Zoladz *et al.*, 2011, 2013) but to enhance memory in another study (Vogel & Schwabe, 2016b). Thus, the stress-learning interval alone cannot fully explain conflicting findings in the literature. The studies reporting different effects of stress 30 minutes before learning, however, differed in the extent to which the material learned was meaningful to the participants (encoding in a laboratory vs. a naturalistic context) and to what extent encoding was related to the stress experience, which might result in a different impact of stress (Joëls *et al.*, 2006).

The impact of stress during learning depends also critically on the contextual relatedness of stress and learning experience. Learning under stress may facilitate memory when stress is directly related to the learning experience (Sandi *et al.*, 1997; Smeets *et al.*, 2007; Vogel & Schwabe, 2016b), presumably through the action of glucocorticoids (Akirav *et al.*, 2004). However, stress during learning that is unrelated to the learned information may act as a distractor and can disrupt subsequent recall (Schwabe & Wolf, 2010a). Stress shortly after learning, in turn, strengthens memory, in particular for emotionally arousing information (Cahill *et al.*, 2003; Smeets *et al.*, 2008; Zoladz *et al.*, 2015). In contrast to these enhancing effects on memory consolidation, stress often impairs memory retrieval (de Quervain *et al.*, 1998; Kuhlmann *et al.*, 2005; Buchanan *et al.*, 2006; Smeets *et al.*, 2008; Schwabe & Wolf, 2009a; Zoladz *et al.*, 2012; but see Schwabe *et al.*, 2009b; Schilling *et al.*, 2013). Same as stress effects on consolidation, the stress-induced retrieval deficit is typically most pronounced for emotional material (Kuhlmann *et al.*, 2005; Buchanan *et al.*, 2006). Moreover, stress may affect subsequent memory even when experienced after retrieval. Memory reactivation during retrieval is thought to render memories labile, requiring another period of stabilization called 'reconsolidation' (Nader *et al.*, 2000; Nader & Hardt, 2009). Because reconsolidation manipulations have potentially far-reaching clinical implications (Brunet *et al.*, 2008; Schwabe *et al.*, 2014), some studies investigated also the impact of stress after retrieval on subsequent remembering. The findings of these studies, however, were inconclusive, with some studies reporting enhancing (Coccoz *et al.*, 2011; Bos *et al.*, 2014) and others impairing effects of stress (Maroun & Akirav, 2008; Zhao *et al.*, 2009; Schwabe & Wolf, 2010c). Further research on this important topic is needed.

The modulatory effects of stress on different stages of hippocampal memory are critically mediated by the many hormones and neurotransmitters that are released during stress. In particular, adrenaline, noradrenaline, and glucocorticoids play a key role in stress effects on hippocampus-dependent memory. Enhancing effects of catecholamines on memory formation were reported early on by the pioneers of the scientific inquiry of memory modulation (Gold & van Buskirk, 1975, 1978; Introini-Collison & McGaugh, 1986). Interestingly, subsequent research showed that noradrenaline enhances not only memory formation but might also boost retrieval processes (Sara & Devauges, 1989; Murchison *et al.*, 2004). Neurophysiological studies confirmed that noradrenaline may promote synaptic plasticity in the hippocampus (Stanton & Sarvey, 1985; Gray & Johnston, 1987). Likewise, corticosterone administration has been shown to directly alter hippocampal plasticity. Whereas most studies reported impairing effects of corticosterone on plasticity in the hippocampus (for a review see Kim & Diamond, 2002), subsequent evidence suggested that corticosterone may also enhance hippocampal plasticity when high hormone levels and high-frequency stimulation coincide in time (Wiegert *et al.*, 2006; see below). On a behavioral level, pharmacological glucocorticoid elevations largely resembled the effects of stress on memory consolidation and retrieval. Both in rodents and humans, glucocorticoid administration enhanced memory formation but impaired retrieval (de Quervain *et al.*, 1998, 2000; Roozendaal *et al.*, 2006b, 2009b; de Quervain *et al.*, 2007; Buchanan & Lovallo, 2001). Administration of the glucocorticoid synthesis inhibitor metyrapone or GR antagonists, in turn, blocked the effects of stress on hippocampus-dependent memory processes (de Quervain *et al.*, 1998; Liu *et al.*, 1999; Maheu

et al., 2005; Tronche *et al.*, 2010). Human neuroimaging studies further showed that glucocorticoid administration reduces the activity of the hippocampus and adjacent cortices at rest (Lovallo *et al.*, 2010) as well as during retrieval (de Quervain *et al.*, 2003).

Importantly, the effects of catecholamines and glucocorticoids are not independent of each other but intimately linked. Specifically, glucocorticoids are thought to require simultaneous noradrenergic activity to exert their effects on consolidation and retrieval. Compelling evidence for this idea comes from a series of elegant experiments in rodents (for reviews, see Roozendaal *et al.*, 2006a, 2009a; Roozendaal & McGaugh, 2011). For example, the injection of the β-adrenergic receptor antagonist atenolol blocked the enhancing effect of intra-hippocampal corticosterone infusions on the consolidation of an inhibitory avoidance task (Roozendaal *et al.*, 1999). Similarly, the β-adrenergic receptor antagonist propranolol abolished the retrieval deficit induced by intra-hippocampal infusion of a GR agonist (Roozendaal *et al.*, 2004). These findings were later translated to humans. Same as in the rodent studies, propranolol administered concurrently with glucocorticoids prevented the glucocorticoid-induced impairment of hippocampus-based memory retrieval (de Quervain *et al.*, 2007). Furthermore, the repeatedly observed finding that stress and glucocorticoid effects are most pronounced for emotionally arousing information (Buchanan & Lovallo, 2001; Cahill *et al.*, 2003; Schwabe *et al.*, 2008) is well in line with the idea that glucocorticoid effects on memory necessitate simultaneous noradrenergic activation. Notably, the hippocampus itself seems not to be the locus of the critical interaction of noradrenaline and glucocorticoids. This interaction is thought to take place in the basolateral nucleus of the amygdala, which then modulates memory processes in the hippocampus (Roozendaal & McGaugh, 1997; Roozendaal *et al.*, 2006b, 2009a). Thus, although neurophysiological studies indicate that catecholamines and glucocorticoids may act directly on hippocampal functioning, there is also striking evidence that stress and glucocorticoid effects on hippocampus-dependent memory are critically shaped by interactions of the hippocampus with other brain areas, in particular the basolateral amygdala.

Noradrenaline appears to be primarily responsible for stress-related changes in the activation of the amygdala, leading to memory modulation in other areas including the hippocampus. These noradrenergic actions are facilitated by glucocorticoids, presumably in interaction with the endocannabinoid system (Campolongo *et al.*, 2009; Atsak *et al.*, 2015), reaching the amygdala shortly after noradrenaline (Joëls *et al.*, 2011). Glucocorticoids, however, may act on different time scales. Intracellular GRs and MRs mediate rather slow, genomic actions, whereas membrane-bound receptors allow rapid, non-genomic glucocorticoid actions (Joëls *et al.*, 2012). Critically, these two modes of glucocorticoid actions may have distinct, perhaps even opposite, effects on the brain. For instance, corticosterone may facilitate hippocampal long-term potentiation (LTP), when present around the time of LTP induction and non-genomic actions prevail (Korz & Frey, 2003; Wiegert *et al.*, 2006). Delayed, genomic glucocorticoid actions, however, were consistently found to suppress hippocampal LTP (Kim & Diamond, 2002). Based on these neurophysiological data, a number of behavioral studies in humans started to vary the time interval between stress exposure and memory task. In one study, individuals underwent a stressor either shortly or 30 minutes before learning a list of words and it was found that stress shortly before learning enhanced subsequent memory, whereas stress 30 minutes before the task had the opposite effect (Zoladz *et al.*, 2011). This finding points to distinct effects of noradrenergic arousal and cortisol on memory encoding but does not speak to potential differences between rapid and slow glucocorticoid effects. A very recent study aimed to distinguish also between rapid and slow stress-induced cortisol effects and therefore tracked the development of stress (hormone) effects on memory formation in a real-life setting (i.e., during a zoo tour) over more than 2 hours (Vogel & Schwabe, 2016b). This study obtained enhanced memory for information encoded during the stressful encounter and this enhancement was directly related to the stress-induced activation of the ANS. Facilitation of memory was also found for material that was encoded about 30 minutes after the stressor, when cortisol was elevated, and this memory enhancement was directly linked to the cortisol elevation. However, no stress effect was found for the memory of events encoded about 2 h after the stressful encounter, when genomic cortisol actions should have developed; although it cannot be ruled out that genomic glucocorticoid actions need even more than 2 hours to fully develop in humans. Time-dependent effects of stress that were closely linked to the temporal profiles of the ANS and HPA axis were also found for memory retrieval. Whereas stress-related ANS activity appeared to facilitate memory retrieval during the stressful experience, impaired retrieval was found as soon as cortisol levels peaked and this retrieval effect lasted for at least 90 min, when cortisol levels had returned to baseline and non-genomic cortisol actions were rather unlikely (Schönfeld *et al.*, 2014; Schwabe & Wolf, 2014).

Neuroimaging studies began recently to test the proposed opposite effects of rapid and delayed glucocorticoid effects on the human brain. Pharmacological elevations of glucocorticoids led indeed to decreased task-related activity in the amygdala and hippocampus, when administered several hours before imaging (Henckens *et al.*, 2010, 2012), i.e., when genomic actions had most likely developed and information processing in these areas should be suppressed. However, glucocorticoid administration shortly before imaging was not found to increase brain activity in these studies and the status of the noradrenergic system remained unclear.

Thus, although it remains, at least in humans, difficult to target the proposed different modes of glucocorticoid actions, there is accumulating evidence that stress and glucocorticoid effects on hippocampal memory processes (as well as amygdala processing) are time-dependent. A recent model aimed to integrate these time-dependent effects of stress and glucocorticoids with the known noradrenaline-glucocorticoid interactions to explain how stress affects memory processes in the hippocampus and other memory systems (Schwabe *et al.*, 2012a; see Joëls *et al.*, 2011 for a related model). This model postulates that rapid catecholamines and non-genomic glucocorticoid actions interact in the basolateral amygdala which then shifts memory systems such as the hippocampus into a 'memory formation mode' (Fig. 1). Direct effects of stress hormones on the hippocampus further promote the memory formation mode. In this mode, encoding and early consolidation of the stressful experience is enhanced. Competitive cognitive processes, such as the encoding or retrieval of information that are unrelated to the stressor, however, are suppressed. As time after the stressful encounter proceeds and genomic glucocorticoid actions set in, the hippocampus is changed to a 'memory storage mode' during which the threshold for the processing of new material is increased to bring the organism back to baseline and to protect the consolidation of stressful episode from distraction.

Stress and memory beyond the hippocampus

In addition to stress-induced changes in hippocampal memory, stress effects on prefrontal cortex-dependent working memory processes have been recognized for decades (Lupien *et al.*, 1999; Arnsten,

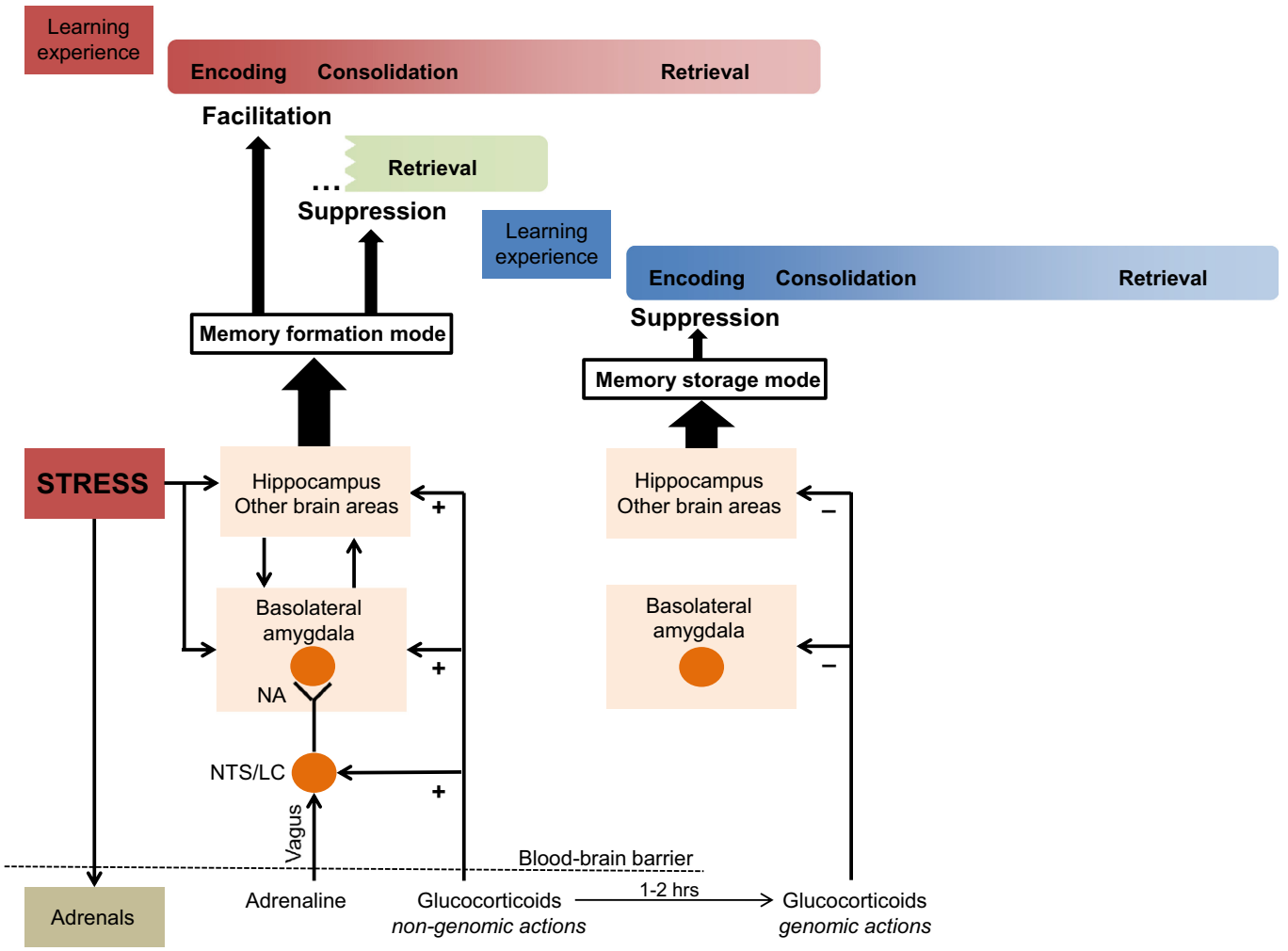

FIG. 1. Integrative model of the impact of stress on memory process in the hippocampus (and other brain areas). Rapid catecholamine and non-genomic glucocorticoid effects interact in the basolateral amygdala to shift the hippocampus (and, presumably, other areas such as the dorsal striatum) into a 'memory formation' mode. During this memory formation, the processing of events present around the time of the stressful experience is facilitated, whereas other cognitive operations such as memory retrieval or the encoding of events that are unrelated to the stressor are suppressed. With time, non-genomic glucocorticoid actions become active which promote a 'memory storage mode' that reduces interference with memory consolidation by suppressing the encoding of new information. NA – Noradrenaline; NTS – Nucleus tractus solitaries; LC – Locus coeruleus. Modified, with permission, from Schwabe *et al.* (2012a).

2009). Both the hippocampus and prefrontal cortex (PFC) are key structures of 'declarative' or 'explicit' memory (Eichenbaum, 2000). Non-declarative memory, which includes very diverse memory processes ranging from priming and conditioning to procedural skills or habits (Squire, 2009), received far less attention in the stress literature. Some authors suggested that non-declarative memory would be more or less insensitive to stress (Kirschbaum *et al.*, 1996; Lupien *et al.*, 1997; Lupien & Lepage, 2001). Yet, this view is challenged by several more recent studies showing that also non-declarative memory processes can be affected by stress and stress hormones. For instance, injections of corticosterone or a selective GR agonist into the insular cortex enhanced the consolidation of object recognition, taste aversion or inhibitory avoidance tasks which do not depend, or depend to a lesser extent, on the hippocampus (Miranda *et al.*, 2008; Roozendaal *et al.*, 2010; Fornari *et al.*, 2012). Moreover, accumulating evidence indicates that stress and glucocorticoids may also impact memory processes in the dorsal striatum, which is implicated in habit memory and stimulus-response (S-R) learning (Packard & Knowlton, 2002). Rodent studies showed that corticosterone injections directly into the dorsal striatum dose-dependently enhanced the consolidation of cued water maze and inhibitory avoidance tasks (Medina *et al.*, 2007; Quirarte *et al.*, 2009). Furthermore, systemic corticosterone injections impaired the retrieval of dorsal striatum-based S-R memory. Injection stress had a very similar effect on S-R memory retrieval and this effect was blocked by the glucocorticoid synthesis inhibitor metyrapone (Atsak *et al.*, 2016). In humans, the acquisition of an S-R memory task was affected by both stress (in men) and glucocorticoid administration (Guenzel *et al.*, 2014a, b). Moreover, irrespective of participants' gender, stress impaired S-R memory retrieval (Guenzel *et al.*, 2013), thus mirroring the findings in rodents.

Most interestingly, there is first evidence that stress effects on dorsal striatum-dependent memory may necessitate simultaneous glucocorticoid and noradrenergic activity as well. Specifically, a recent study showed that corticosterone injections shortly after training in a cued water maze task or a response-based version of the water plus maze task enhanced subsequent memory and this memory enhancement disappeared after concurrent administration of

propranolol (Goodman *et al.*, 2015). Although this study administered the drugs systemically and therefore allows no conclusions regarding the site of the glucocorticoid-noradrenaline interactions, it is well-known that the amygdala projects directly to the caudate nucleus (Pikänen, 2000), making it tempting to speculate that also stress (hormone) effects on dorsal striatal memory are mediated by the stress-related noradrenergic activation of the amygdala. Together, these findings show clearly that stress and glucocorticoids may also influence memory processes in other regions than the hippocampus. The mechanisms involved in these stress effects on non-hippocampal memory may resemble those on hippocampus-dependent memory: stress enhances memory consolidation but impairs memory retrieval, presumably through glucocorticoids, interacting with noradrenergic arousal.

Focus on changes in memory networks

Memory processes are not localized to specific centers but distributed throughout the brain, in large networks of interconnected areas (Eichenbaum & Cohen, 2001). However, memory is not distributed throughout the brain homogeneously. Instead, different networks or systems subserve distinct memory functions. Which of these systems predominates has considerable implications for the nature of learning and memory, for instance, with respect to the flexibility of the acquired memories. Efficient learning and memory requires an intricate balance of distinct memory systems and networks. Acute stress is thought to transiently tilt the balance of multiple memory systems in favor of rather reflexive processing, presumably to optimize coping with the stressful event.

Stress and the balance of distinct memory networks

During the encoding of a complex episode, multiple memory networks with distinct functions are active in parallel. For instance, when watching your favorite TV show with friends, one network will encode this specific episode, i.e., what is happening when and where. At the same time, another more semantic system is recruited to aid understanding the plot of the show and to extract information across episodic events to build more abstract representations. Furthermore, some habitual responses may develop such as the consumption of certain snack foods while watching the show. And even more automatic processes may evolve, such as bodily responses to the show's theme or a specific tone signaling an upcoming event. Indeed, there is a number of studies showing that numerous brain areas with very diverse functions are simultaneously active during learning (Wagner *et al.*, 1998; Poldrack *et al.*, 2001; Bassett *et al.*, 2011; Schwabe & Wolf, 2012).

First evidence that stress may have a critical impact on which of these many brain areas may guide learning came from a rodent study about 15 years ago (Kim *et al.*, 2001). This study used a cued water maze task that could be solved by hippocampus-based learning of the spatial relation between multiple extra maze cues or by learning the association with a single proximal cue, a form of S-R learning that is known to rely on the dorsal striatum (McDonald & White, 1994; White & McDonald, 2002). Relocating the proximal cue after training revealed the predominating memory system. Compared to non-stressed control rats, rats that had been exposed to foot-shock stress before training used significantly more often the S-R strategy, suggesting a stress-induced shift from hippocampus-dependent spatial to dorsal striatum-dependent S-R learning. In a follow-up study, a similar effect was obtained after intra-amygdala injection of a α2-adrenoceptor antagonist, pointing to an important role of noradrenergic activation and the amygdala in the modulation of multiple memory systems (Packard & Wingard, 2004). Later, these findings were translated to humans. Specifically, it was shown that acute stress before learning a dual-solution task favored S-R learning over spatial learning also in humans (Schwabe *et al.*, 2007). Whereas these data showed a shift in learning strategies at the behavioral level, fMRI data further revealed that stress may indeed induce a shift from hippocampal to dorsal striatal control of learning in the human brain (Schwabe & Wolf, 2012; Schwabe *et al.*, 2013b). Similar to the stress-induced modulation of hippocampal and dorsal striatal learning, stress has been shown to bias instrumental learning in favor of dorsal striatum-dependent habit behavior and at the expense of PFC-dependent goal-directed action (Schwabe & Wolf, 2009b, 2010b; Seehagen *et al.*, 2015). Together, these findings suggest that stress biases memory networks during learning toward simple but rather rigid memory processes.

How may stress induce such a bias in learning? What are the underlying neuroendocrine mechanisms? And which network changes are involved in the stress-induced bias toward habit memory? One model that aims to answer these questions focusses on the critical role of the PFC in cognition and emotion regulation (Arnsten, 2009). Under no-stress conditions and moderate levels of arousal, prefrontal functioning would be optimal. Via direct and indirect connections to dopaminergic and noradrenergic brain stem nuclei, the PFC can control its own catecholamine input (Arnsten & Goldman-Rakic, 1984; Carr & Sesack, 2000). Optimal catecholamine levels in the PFC facilitate the PFCs capacity to inhibit inappropriate habitual responding, to exert top-down control of attention, and to prevent overshooting of emotional responding in the amygdala. Under stress, however, high levels of noradrenaline and dopamine would disrupt PFC functioning and enhance amygdala processing, resulting in a shift from thoughtful PFC control of cognition and behavior toward rapid, reflexive responding of the amygdala and related areas (Arnsten, 2009). This model was recently further elaborated by taking larger neurocognitive networks into account (Hermans *et al.*, 2014). One of these networks, the 'salience network', consist mainly of the amygdala, the hypothalamus, the dorsal anterior cingulate cortex, and inferotemporal regions, and is specialized for processing salient, threat-related cues (Seeley *et al.*, 2007; Menon, 2011). Another network, the 'executive control network', in turn, consisting of the dorsomedial and dorsolateral PFC as well as dorsal parietal regions, is implicated in cognitive control processes, cognitive flexibility and rational decision-making (Seeley *et al.*, 2007; Menon, 2011). Acute stress has been suggested to result in an upregulation of the salience network, paralleled by a downregulation of the executive control network (Hermans *et al.*, 2014). These opposite changes in large scale networks were demonstrated nicely in human neuroimaging studies. One of these studies reported increased activation and interconnectivity within the salience network while participants were watching highly stressful movie clips (Hermans *et al.*, 2011). This stress-related activation of the salience network disappeared after the administration of the β-adrenergic receptor antagonist propranolol, suggesting a critical role of noradrenaline in this network activation. In line with these findings, pharmacological increases in noradrenergic stimulation after yohimbine intake resulted (in women) in amygdala activation during processing of fear-related material (Schwabe *et al.*, 2013a). Administration of the glucocorticoid synthesis inhibitor metyrapone, however, did not alter the neural changes in response to stress, indicating that glucocorticoids are not involved in the rapid activation of the salience network after stress (Hermans *et al.*, 2011). Whereas the salience network was activated under stress, key structures of

the executive control network, such as the dorsolateral PFC, showed reduced activation after stress (Qin *et al.*, 2009). Corroborating earlier findings in rodents (Arnsten, 1998), this stress-induced decrease in PFC activity was most pronounced in individuals with increased catecholamine activity (Qin *et al.*, 2012a). These findings from rodents and humans strongly suggest that acute stress promotes the recruitment of a network centered on the amygdala, at the cost of a network centered on the PFC, and that these network changes are mainly driven by catecholamines.

Catecholamine activity alone, however, appears not to be sufficient to induce a stress-related shift from cognitive toward habit memory, which has been demonstrated across species and tasks (Goodman *et al.*, 2012; Schwabe, 2013; Schwabe & Wolf, 2013). For this shift to occur, glucocorticoids are crucial, most likely acting via the MR (Vogel *et al.*, 2016; but see Gourley *et al.*, 2012 for evidence for a role of the GR). Mice that were exposed to stress or injected corticosterone before training in a dual-solution task showed the expected shift from spatial toward S-R learning and this shift was abolished by the parallel administration of the MR antagonist spironolactone (Schwabe *et al.*, 2010a). Similar findings were obtained in human participants who underwent a stressor before learning a dual-solution task in a MRI scanner. Also in humans, spironolactone blocked the stress-induced shift from hippocampal to dorsal striatal control of learning (Schwabe *et al.*, 2013b). Most interestingly, the fMRI data provided insights into the neural mechanism underlying the stress-related change in the predominating memory system. Specifically, stress reduced hippocampal activity during learning, decreased amygdala connectivity with the hippocampus and increased amygdala connectivity with the putamen. MR blockade by spironolactone did not prevent the decrease in hippocampal activation after stress but blocked the opposite effects of stress on amygdala connectivity with the hippocampus and dorsal striatum. A subsequent study using a vigilance processing task confirmed that stress may increase the crosstalk between the amygdala and dorsal striatum and that this increase is MR-dependent (Vogel *et al.*, 2014). Thus, the amygdala appears to be critically involved in the orchestration of multiple memory systems and glucocorticoid actions via the MR may be necessary to accomplish the shift from hippocampal to dorsal striatal learning and memory.

Although the amygdala may play a pivotal role in the bias of memory networks toward habit memory after stress, there might be additional changes in network interactions that contribute to this shift. In particular, the hippocampus and dorsal striatum have been suggested to compete for control over learning (Poldrack *et al.*, 2001; Poldrack & Packard, 2003). Indeed, inhibitory connections between these areas are well known. Inactivation of the hippocampus enhanced dorsal striatum-dependent learning (Packard *et al.*, 1989; Schroeder *et al.*, 2002). Conversely, disruption of the dorsal striatum facilitates hippocampus-based learning (Mitchell & Hall, 1988). Moreover, intra-hippocampal injections of glutamate prevented the practice-related shift toward dorsal striatal learning, whereas intra-caudate glutamate injections accelerated this shift (Packard, 1999), indicating that strengthening one system hinders the other. If acute stress reduces hippocampal activation, as shown repeatedly (Pruessner *et al.*, 2008; Henckens *et al.*, 2009; Schwabe & Wolf, 2012), this may release the dorsal striatum from inhibitory hippocampal control, which in turn increases the suppression of the hippocampus by the dorsal striatum. However, although such stress-induced changes in the interplay of the hippocampus and dorsal striatum appear likely, they are still somewhat speculative as direct empirical evidence for such interactions is still missing.

In sum, there is good evidence that stress leads, via increased catecholamine activity, to large scale network changes, in particular to a shift from an executive control network to a salience network. This shift includes stronger activation of the amygdala, which then orchestrates the shift from cognitive to habit memory (Fig. 2). The latter, however, requires glucocorticoid activity. Thus, the stress-induced shift from cognitive to habitual control of learning and memory may be implemented in two steps and require the concerted action of catecholamines and glucocorticoids. First, increased catecholamine activity recruits the salience network and thus brings the amygdala in the position to modulate other memory systems. The shift toward habit memory, however, necessitates additional glucocorticoid activity (or at least an intact MR, in the face of increase noradrenergic stimulation, Packard & Wingard, 2004). Indeed, stress effects on the control of instrumental learning have been shown to require simultaneous glucocorticoid and noradrenergic activity. A low cortisol increase after stress or the reduction in noradrenergic arousal by propranolol prevented the stress-induced shift toward habit learning (Schwabe *et al.*, 2011b). Likewise, only the parallel pharmacological elevation of glucocorticoid and noradrenergic activity induced a shift toward dorsal striatal habit learning, whereas the activation of only one of the two systems did not (Schwabe *et al.*, 2010b, 2012b). In line with these findings, only the simultaneous administration of hydrocortisone and yohimbine reduced the activity of prefrontal areas that are key nodes of the executive control network and critical for goal-directed learning (Schwabe *et al.*, 2012b). Although pharmacological manipulations may result in a rather artificial pattern of stress system activation, shortly after stress rapid, non-genomic glucocorticoid actions may interact with noradrenergic activity to promote the described changes in memory network activity and connectivity. The slower, genomic glucocorticoid effects, acting outside of the time-window of catecholamine actions, may have opposite effects on the memory networks. Specifically, slow glucocorticoid actions appear to dampen the salience network and to boost the executive control network (Henckens *et al.*, 2010, 2011, 2012; Hermans *et al.*, 2014), thus helping to restore homeostasis after a stressful event.

Stress and altered network configurations

The stress-induced bias toward networks supporting habitual forms of memory is paralleled by several other changes in the nature of memory. Memories created under stress or elevated glucocorticoid levels often lack contextual details (Schwabe *et al.*, 2009a; van Ast *et al.*, 2013) and are less precise; although these effects may also depend on the exact timing of the stress exposure relative to encoding (Zoladz *et al.*, 2014). The latter, for instance, is reflected in an impaired ability to distinguish between information that were indeed encoded under stress and those that were semantically closely related but not presented (Payne *et al.*, 2002). Under stress, memory is focused on the core aspects of an emotional event, it becomes more semanticized or gist-like and processing of peripheral details is reduced (Christianson & Loftus, 1987). More liberal responding after stress, indicative of a lack of memory precision, was found to correlate with ANS activation (Qin *et al.*, 2012b). Neuroimaging data further showed that stress abolished the association of hippocampal and midbrain activity with subsequent recall. Instead, memory performance was linked to parahippocampal activity in stressed individuals (Qin *et al.*, 2012b). These data suggest that stress shifts the memory network from areas involved in detailed episodic encoding, such as the hippocampus (Burgess *et al.*, 2002; Addis & Schacter, 2008), to cortical areas such as the

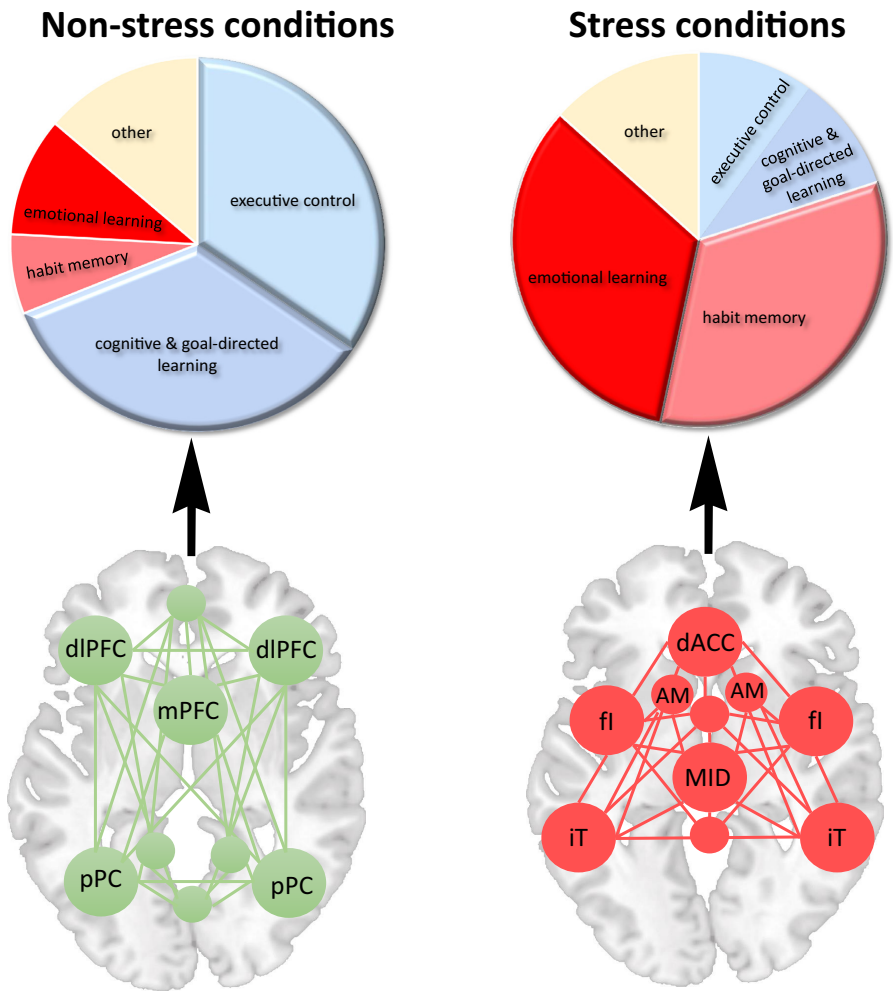

FIG. 2. Stress-related network changes promoting habit memory, at the cost of cognitive memory. Under no-stress conditions, an executive control network which supports cognitive control processes as well as 'cognitive' or goal-directed forms of learning. Key nodes of this executive control network are the dorsolateral prefrontal cortex (dlPFC), the medial prefrantal cortex (mPFC), and the posterior parietal cortex (pPC). Acute stress downregulates the executive control network and upregulates a salience network, consisting mainly of the dorsal anterior cingulate cortex (dACC), the amygdala (AM), frontoinsular cortex (fI), midbrain areas (MID), and inferotemporal areas (iT). This salience network promotes, mainly via the recruitment of the amygdala, which, may then orchestrate hippocampal and dorsal striatal learning, a shift toward habit-based memory. Partly modified, with permission from Hermans *et al.* (2014) and Vogel *et al.* (2016).

parahippocampal cortex that are implicated in more abstract, semantic representations (Binder *et al.*, 2009). The idea that stress results in more cortical and less hippocampal processing, leading to less specific, more gist-like memories is supported by recent rodent studies. Stressful training conditions reduced memory precision and rendered memories independent of the hippocampus (Pedraza *et al.*, 2016). Both of these effects were dependent on the stress-induced release of glucocorticoids and noradrenaline. A similar glucocorticoid-dependent shift from hippocampal to cortical memory was observed when rats were stressed before retention testing (Dominguez *et al.*, 2014). All in all, this switch from detailed processing to more gist-like processing that focusses on the essential parts of a stressful or emotionally arousing experience is well in line with the recruitment of the salience network under stress (Hermans *et al.*, 2014). And indeed the observed shift from specific hippocampal to more gist-like parahippocampal memory came along with increased salience network activation (Qin *et al.*, 2012a).

Whereas the hippocampus is required for the specific encoding of novel events, it should be less involved in processing material that relates to prior knowledge (Tse *et al.*, 2007; van Kesteren *et al.*, 2012). Pre-existing knowledge, represented as a schema, is assumed to be detected by the mPFC, which then coordinates memory processes in other cortical areas, including the angular gyrus and precuneus (van Kesteren *et al.*, 2010a, b, 2012; Tse *et al.*, 2011). The hippocampus, however, should be less activated when encoding information for which a relevant schema exists. Very recent evidence from our lab shows that stress interferes with the adequate network configuration depending on the existence of prior knowledge. In two independent tasks, stress reduced the activity of the mPFC while processing schema-related information (Vogel, Kluen, Fernandez, & Schwabe, unpublished-a and –b). Moreover, stress led to an incorporation of the hippocampus into the schema-network. Conversely, the medial PFC, relevant for the detection of schema-congruence, was more active in stressed individuals when learning entirely novel material. These findings suggest that stress may disrupt the selection of neural networks enabling the efficient use of prior knowledge. Together with the known recruitment of the salience network and enhanced memory formation under stress, these data suggest that stress facilitates highly focused processing of ongoing, directly threat-related events,

thereby hampering the integration of contextual details and links to prior experiences.

Implications of stress-induced network changes and conclusion

The past decades have seen considerable progress in our understanding of how stress and stress hormones shape memory processes. Stress has been shown to affect hippocampal memory and neuroplasticity in a time-dependent manner, closely related to the temporal profiles of action of catecholamines and glucocorticoids (Joëls *et al.*, 2006, 2011; Schwabe *et al.*, 2012a). These major stress mediators interact in the basolateral amygdala which then modulates hippocampal memory (Roozendaal *et al.*, 2009a; Roozendaal & McGaugh, 2011). Further elaborations of this model, in particular with respect to the role of the endocannabinoid system, are on the way (Atsak *et al.*, 2012). Another important factor that should be taken into account are potential gender differences in the impact of stress on hippocampal memories. Differences between men and women in the influence of stress and glucocorticoids on encoding, consolidation or retrieval have been repeatedly observed (Andreano & Cahill, 2006; Buchanan & Tranel, 2008; Zoladz *et al.*, 2013; Guenzel *et al.*, 2014b). Although the literature on sex differences in stress effects on memory is not very consistent and several studies did not obtain different effects in men and women (Buchanan *et al.*, 2006; Schwabe *et al.*, 2008; Zoladz *et al.*, 2011; Schilling *et al.*, 2013), potential sex differences should be taken into account when building models of how stress changes memory and also with respect to potential clinical implications.

More and more studies further indicate that other areas than the hippocampus, such as the insula or the dorsal striatum, are sensitive to stress and that the mechanisms underlying stress effects on non-hippocampal memory strongly resemble those that have been identified for the hippocampus (Guenzel *et al.*, 2013, 2014a; Goodman *et al.*, 2015; Atsak *et al.*, 2016). Beyond stress-induced changes in single systems, recent evidence indicates that acute stress triggers changes in large scale networks, enhancing rather reflexive systems such as the amygdala, at the expense of more reflective systems such as the PFC (Arnsten, 2009; Hermans *et al.*, 2014). These network reconfigurations are not independent of but most likely directly due to stress-induced changes in single systems. Moreover, these large scale network changes then set the stage for a shift in the control of memory, from cognitive to habitual processing (Schwabe, 2013; Schwabe & Wolf, 2013). This shift is reflected in less flexible and less specific memories that are difficult to integrate with existing memory representations (Payne *et al.*, 2002; Schmidt *et al.*, 2014; Dandolo & Schwabe, 2016).

The evolutionary benefit of the stress-related recruitment of rather crude but highly efficient systems, proficient in threat processing and the implementation of established routines, is fairly obvious. Relying on automatized behaviors grounded in past experience is likely to be highly adaptive in demanding situations. Indeed, both rodent and human studies found that the bias toward habit memory may rescue performance under stress. Blocking this shift with a MR antagonist, forcing the individual to rely on the cognitive memory network, resulted in severely impaired performance after stress (Schwabe *et al.*, 2010a, 2013b).

Overreliance on the habit system, however, and the inability to switch flexibly between different memory networks may be maladaptive and might promote psychopathologies in vulnerable individuals. Addictive disorders, for instance, have been interpreted as the endpoint of a number of transitions from initially goal-directed to habitual and ultimately compulsive behaviors (Everitt & Robbins, 2005, 2016). As stress is a known risk factor for addiction and relapse to addictive behaviors (Piazza & LeMoal, 1998; Koob & Kreek, 2007; Sinha, 2007), the reported stress-induced shift from cognitive to habit memory processes might represent a neurocognitive mechanism through which stress promotes addictive behaviors (Schwabe *et al.*, 2011a). In addition, the balance of cognitive and habitual memory processes is most likely highly relevant in the context of anxiety disorders and PTSD (Everitt & Robbins, 2005; Schwabe *et al.*, 2010c, 2011a; Goodman *et al.*, 2012). Classically, the overly strong emotional memory in PTSD has been attributed to an overconsolidation process as a consequence of the extreme stress during the traumatic event (Pitman, 1989; Ehlers & Clark, 2000). This strong emotional memory, however, might also result from an inability to shift to another memory system. At the same time, an aberrant reliance on the habitual system due to the extreme stress could account for the strong responses of patients to single trauma-related cues as well as patients' difficulties to integrate the traumatic experience into their autobiographical memory (Liberzon *et al.*, 1999; Dalgleish, 2004; Kleim *et al.*, 2008). Elucidating the mechanisms involved in the impact of stress on memory and the systems controlling memory could help to identify new targets for novel intervention strategies in stress-related disorders, such as PTSD, anxiety or addiction (de Quervain & Margraf, 2008; de Quervain *et al.*, in press).

Taking the stress-related network changes, which were highlighted above, into account makes it clear that any theory on the impact of stress on memory that focuses only on a single memory system is most likely over-simplistic. The fact that multiple, interconnected areas are active at the same time during learning may further point to the possibility that one system may stand in for another. Neuropsychological data provide clear evidence for such compensations (Knowlton *et al.*, 1996; Voermans *et al.*, 2004). Compensations between different parts of a memory network may have relevant implications for our interpretations of how stress alters memory. More specifically, stress may leave learning performance intact and this might be taken as evidence that stress did not affect learning. However, performance under stress might be carried by a different system than under rest that is equally well able to support learning but processes information in a very different way. Thus the conclusion that stress did not influence learning may be premature and the critical impact of stress on what has been learned may become apparent only after changes in the environment or when forced to transfer the memories to novel situations.

Understanding the network interactions underlying the impact of stress on memory (or cognition in general) may further help to identify potential targets for the modulation of these stress effects. The stimulation or inhibition of central nodes in the network may allow the strengthening of desired or weakening of adverse influences of stress on memory. For instance, a recent study showed that transcranial direct current stimulation over the dorsolateral PFC may attenuate stress-induced working memory deficits (Bogdanov & Schwabe, 2016). Yet, despite these promising data and the advances made in our understanding of how stress changes learning and memory, we are still rather at the beginning and many open questions remain. For instance, related to the exact neuroendocrine mechanisms involved in stress-induced network reconfigurations or to potential individual and gender differences in the sensitivity to these changes after stress. Answering these and related questions will aid our understanding of how stressful encounters affect our memory and could have far-reaching

implications, in particular, but not exclusively, for stress-related mental disorders.

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