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Stress and multiple memory systems: from 'thinking' to 'doing'

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Although it has been known for decades that stress influences memory performance, it was only recently shown that stress may alter the contribution of multiple, anatomically and functionally distinct memory systems to behavior. Here, we review recent animal and human studies demonstrating that stress promotes a shift from flexible 'cognitive' to rather rigid 'habit' memory systems and discuss, based on recent neuroimaging data in humans, the underlying brain mechanisms. We argue that, despite being generally adaptive, this stress-induced shift towards 'habit' memory may, in vulnerable individuals, be a risk factor for psychopathology.

Stress responses and adaptation to stress

Stress can be caused by a number of diverse events, ranging from the pressures of daily life familiar to everybody to life-threatening experiences, such as war or natural disasters. The appraisal of a situation as stressful is highly subjective and made by the prefrontal cortex and limbic structures, in particular the hippocampus and the amygdala, which link the current situation to experiences from the individuals' past. These brain regions are connected with the hypothalamus, a central hub in the coordination of the physiological response to stress. Within seconds after a stressful event, the hypothalamus activates the autonomic nervous system, which triggers the release of adrenaline and noradrenaline (see Glossary) from the adrenal medulla. At the same time, the hypothalamus initiates a slower hormone cascade, the hypothalamus-pituitary-adrenal axis. This cascade leads via intermediate steps to the release of glucocorticoids from the adrenal cortex. In addition to adrenaline, noradrenaline, and glucocorticoids, numerous other hormones, neuropeptides, and neurotransmitters are released in response to a stressor. Together these stress mediators help the organism to adapt to the stressor and to restore homeostasis [1,2].

One important way by which stress mediators facilitate adaptation to stressful environments is by shaping cognition and behavior. For example, glucocorticoids desensitize and decouple the amygdala from other structures involved in the stress response, thus preventing overactivation of stress systems and promoting recovery [3,4]. Glucocorticoids also act in concert with noradrenaline to shift the hippocampus to a 'memory formation mode', during which lasting memories of the stressful experience are created (Box 1). These strong memories enable the individual to avoid or prepare for similar situations in the future. Cognitive processes unrelated to the stressor, however, are suppressed, which reduces ambiguity, interference, and distraction in the ongoing stress situation (as discussed in [5–8]).

Below we will review recent evidence from animal and human studies showing that stress mediators may also alter the engagement of multiple memory systems during learning in a manner that favors rather rigid, but simple 'habit' memory, at the expense of flexible, but cognitively demanding 'cognitive' memory. This shift from 'cognitive' to 'habit' memory after stress constitutes another important mechanism by which stress mediators promote adaptation.

Stress and the engagement of multiple memory systems

First experimental evidence for the notion of multiple, anatomically and functionally distinct memory systems came from seminal work in amnesic patients and lesion studies in rodents [9–12]. More recently, neuroimaging studies confirmed the existence of separate memory systems in the human brain [13–15]. These memory systems interact in the course of learning in a cooperative or competitive manner [16]. In addition to other influences, such as practice, distraction or feedback timing [13,14,17], stress is a critical factor that orchestrates the engagement of multiple memory systems to optimize learning.

Glossary

Glucocorticoids: steroid hormones that are secreted from the adrenal cortex. The main glucocorticoid in humans is cortisol; in rodents it is corticosterone. Through binding to membrane-bound and intracellular glucocorticoid and mineralocorticoid receptors (GR and MR, respectively), glucocorticoids exert rapid, non-genomic and slow, genomic effects [2,63,64].
Goal-directed learning: encoding of the (causal) relationship between an action and the motivational value of an outcome.
Habit learning: encoding of the association between a response and preceding stimuli, without any link to the outcome that follows the response.
Instrumental learning: learning how to achieve pleasant and how to avoid unpleasant states.
Noradrenaline: catecholamine that acts both as a hormone and as a neurotransmitter. In the brain, noradrenaline is released mainly from the locus coeruleus and brainstem sites. Upon binding to α- and β-adrenoceptors, noradrenaline induces rapid changes in membrane potential.
Spatial learning: using the relationship between two or more stimuli in the environment in order to learn a route or the location of a target item.
Stimulus-response learning: learning of the association between a single stimulus and a behavioral response.
Stressor: physical or psychological stimulus or event that threatens the homeostasis of the organism.

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Box 1. Stress and hippocampal memory: how much do we remember?

The hippocampus, a key structure for memories of episodes from the past, is one of the brain regions with the highest density of receptors for glucocorticoids, suggesting that this area is particularly sensitive to stress. Indeed, effects of stress and stress hormones on hippocampal activity and hippocampus-dependent memory processes are well documented. The nature of these stress effects, that is, whether stress enhances or impairs hippocampal functioning, depends on the timing of the stressor. Neurophysiological studies show that glucocorticoids at the time of long-term potentiation (LTP) induction lead to a rapid enhancement of hippocampal LTP, yet after approximately 60 minutes, when genomic glucocorticoid actions have developed, this effect is reversed and glucocorticoids impair LTP in the hippocampus [25,65,66]. This biphasic influence of glucocorticoids on the hippocampus is confirmed by recent neuroimaging data [67] and reflected in time-dependent changes in the influence of stress on hippocampus-dependent memory. Stress before learning may enhance memory when it occurs within the context of a learning experience (for example, shortly before or during learning), whereas stress out of the learning context (for example, relatively long before learning) impairs memory [8,68,69]. Stress shortly after learning strengthens subsequent memory, particularly for emotionally arousing information [38,70]. Conversely, stress before retention testing typically reduces retrieval performance, again particularly for emotionally arousing information [71–74]. In addition, stress may also interfere with the re-stabilization ('reconsolidation') of memories after retrieval ([75,76]; Figure I). All in all, the unifying principle in the time-dependent effects of stress and stress hormones on hippocampus-dependent memory seems to be that strong memories are formed for information that is present around the time of the stress experience and directly related to the stressor. This memory enhancement for stress-related information, however, may come at the cost of impaired memory for events unrelated to the stressor.

Although, the hippocampus is the structure that has been associated most often with memory processes over the past century and for which the impact of stress is particularly well-established, it has become increasingly clear that stress influences also memory processes beyond the hippocampus [6,77]. Moreover, as discussed in this review, stress may not only affect the performance of a single memory system, but also the contribution of multiple memory systems to behavior.
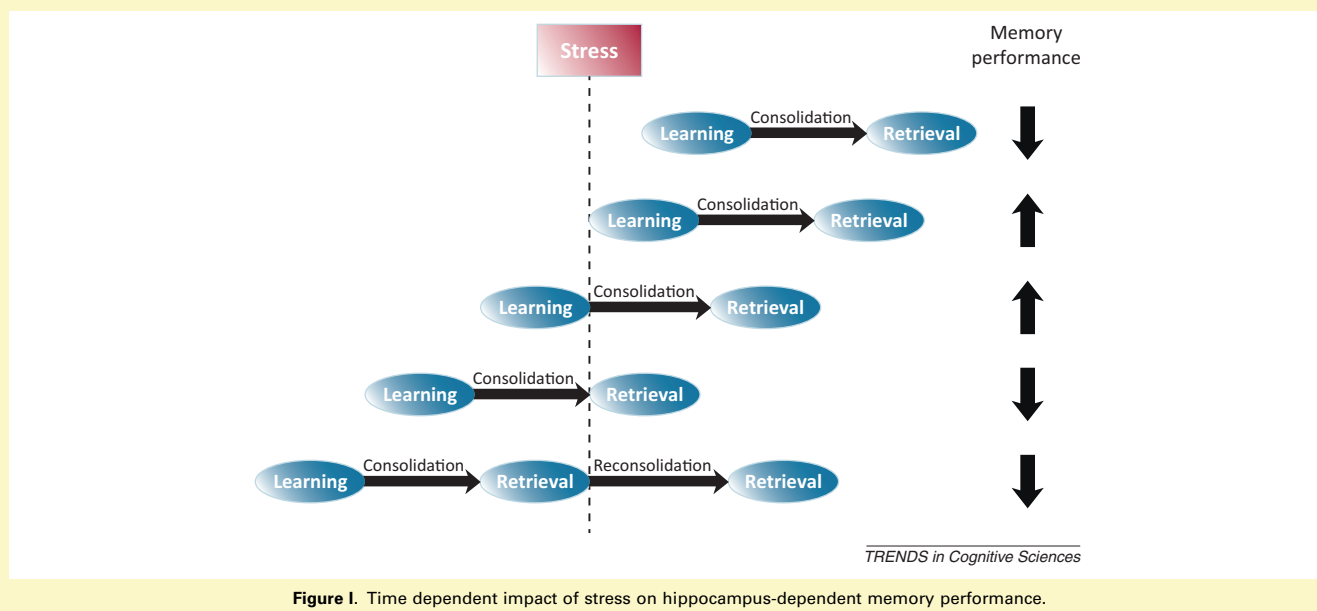

Figure I. Time dependent impact of stress on hippocampus-dependent memory performance.

Hippocampal and striatal memory systems

Interactions between memory systems have often been studied in spatial navigation tasks, which can be acquired both by a hippocampus-dependent spatial memory system that learns the relationship between multiple cues in the environment and by a dorsal striatum-dependent stimulus-response (S-R) memory system that encodes the association between a single cue and a certain response (Box 2). Rodent studies indicate that stress before training in such a dual-solution navigation task promotes a shift from hippocampal spatial to dorsal striatal S-R learning [18]. Similar effects are observed after injections of anxiogenic drugs or reactivation of aversive memories [19,20]. Glucocorticoids play a key role in the stress-induced shift towards dorsal striatum-based memory. Corticosterone injections mimic the stress effect in mice and, more importantly, the effects of stress or corticosterone injection on the engagement of hippocampus-dependent and dorsal striatum-dependent memory disappear after pharmacological blockade of the mineralocorticoid receptor (MR) [21].

In humans, stress may affect the engagement of hippocampus-dependent and dorsal striatum-dependent memory, as well. Healthy participants that undergo a psychosocial stressor before they are trained to locate a 'win-card' in a 3D model of a room use significantly more often S-R learning strategies and less often spatial learning strategies compared to non-stressed controls [22]. Interestingly, stressed participants that shift towards an S-R strategy have higher cortisol concentrations before training than those participants who keep using a spatial strategy after stress. High basal cortisol concentrations and pharmacologically elevated cortisol concentrations, however, favor spatial over S-R learning strategies [23,24]. Although these findings provide further evidence for a crucial role of glucocorticoids in the coordination of hippocampus-dependent and dorsal striatum-dependent memory systems, they challenge the idea of a linear association between glucocorticoids and the shift towards S-R learning. Instead, the finding that both low and (very) high glucocorticoid concentrations are associated with more

Box 2. Separating multiple memory systems

Learning and memory can be supported by multiple memory systems that process information simultaneously and in parallel. These memory systems may contribute to 'quantitative' learning performance (in terms of latencies or number of errors) equally well. Thus, pure learning performance is not very informative with respect to which memory system controls behavior. In order to dissociate the contributions of multiple memory systems, several elegant behavioral tests have been developed.

Spatial navigation
Spatial navigation can be based on a hippocampus-dependent spatial memory system that uses the relationship between multiple cues to create a 'cognitive map' and on a dorsal striatum-dependent S-R memory system that learns the association between a stimulus and a response. To separate these systems, subjects are trained in a spatial task in which the location of the target is constant across trials and a single intra-maze cue and multiple extra-maze cues allow spatial and S-R learning (Figure Ia). In a test trial, the single intra-maze cue is relocated. Going to the location where the target had been during training indicates spatial learning, whereas going to the novel location of the intra-maze cue indicates S-R learning.

Probabilistic classification learning
Learning how to categorize stimuli can also be supported by a hippocampus-based 'declarative' and a striatum-based 'procedural'

system. For example, in the weather-prediction task, a widely used classification task, participants see one to three (out of four) cards per trial and learn based on trial-by-trial feedback how to predict from these cards one of two weather outcomes ('rain' or 'sunshine'; Figure Ib). The amount of explicit task knowledge, which should be higher if learning is controlled by the hippocampus, indicates which system controls learning. Furthermore, hippocampus-based and striatum-based learning strategies can be dissociated by means of mathematical models (for details, see [42,78,79]).

Instrumental learning
Instrumental learning can be controlled by a prefrontal cortex-dependent goal-directed system that encodes the action-outcome relationship and by a dorsolateral striatum-dependent habit system that encodes S-R associations. The gold standard to separate these systems is outcome devaluation, which consists of three stages. First, subjects are trained in two instrumental actions leading to two food outcomes. Next, one of the food outcomes is devalued. A final extinction test reveals whether learning is under goal-directed or habitual control. If learning is goal-directed, this should be reflected in a reduced frequency of the now devalued action. The absence of this behavioral sensitivity indicates habit learning (Figure Ic).
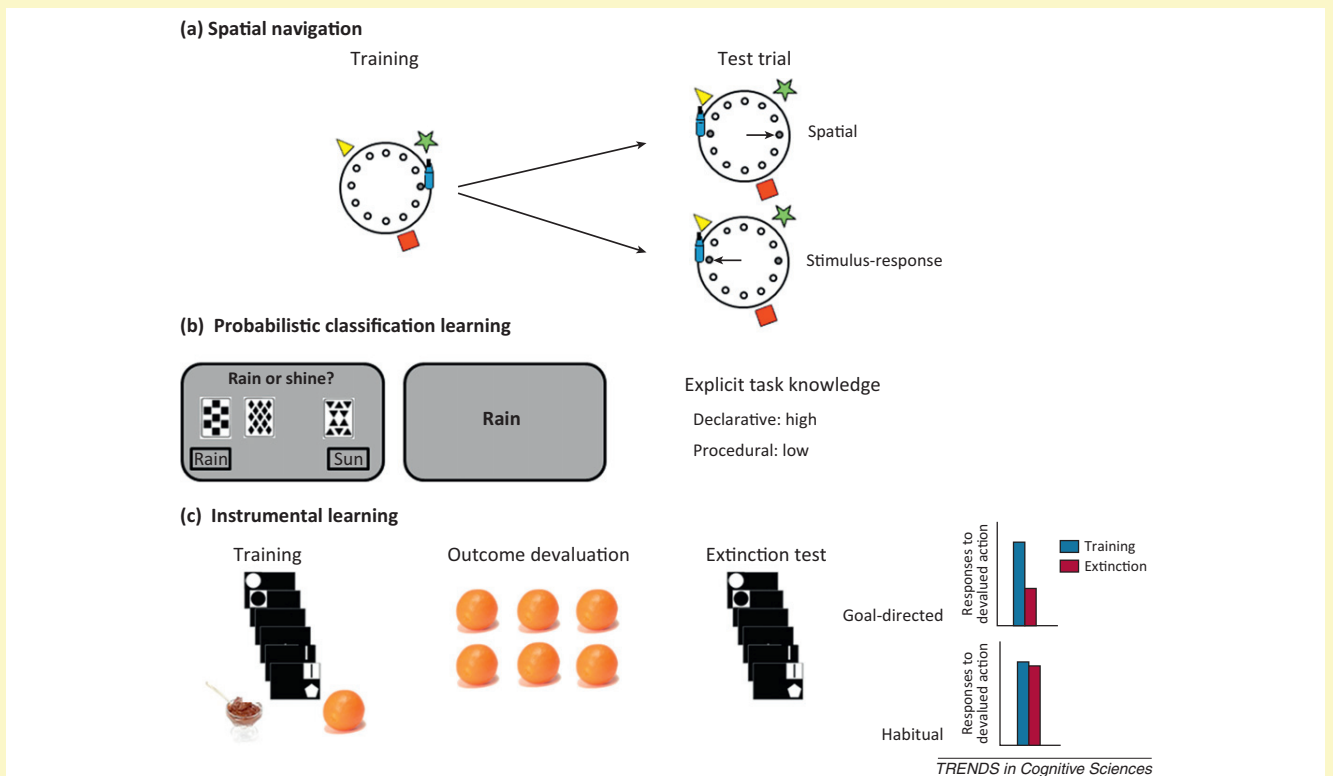

(a) Spatial navigation
Training   Test trial
Spatial
Stimulus-response

(b) Probabilistic classification learning
Rain or shine?
Rain   Sun
Rain
Explicit task knowledge
Declarative: high
Procedural: low

(c) Instrumental learning
Training   Outcome devaluation   Extinction test
Training   Extinction
Goal-directed
Responses to devalued action
Habitual
Responses to devalued action

TRENDS in Cognitive Sciences

Figure I. Examples of paradigms used to separate the contributions of multiple memory systems. **(a)** Spatial navigation. **(b)** Probabilistic classification learning. **(c)** Instrumental learning.

spatial learning, whereas moderate cortisol elevations after stress promote a shift towards more S-R learning might suggest that the relationship between glucocorticoids and the bias towards S-R learning exhibits an inverted u-shaped function, as has been suggested for stress and other memory processes [25,26]. This possibility should be addressed more directly in future experiments.

In addition to acute stress, prolonged or repeated stress may also favor striatum-dependent memory at the expense

of hippocampus-dependent memory [27]. Moreover, recent data suggest that stress experiences during critical periods of brain development can have a significant impact on which brain system controls learning and memory [28,29]. For example, adults whose mothers experienced major stressful life events during their pregnancy used in a virtual navigation task caudate nucleus-dependent learning strategies more often than hippocampus-dependent learning strategies, compared to adults whose mothers had no such adverse

experiences during their pregnancy [28]. In summary, over the past few years evidence has accumulated showing that stress, whether acute, chronic, or present in early life, may promote a shift from hippocampus-based spatial to dorsal striatum-based S-R memory processes.

Prefrontal cortical and striatal memory systems
Is the modulatory effect of stress specific to the engagement of hippocampus-dependent versus dorsal striatum-dependent memory? Or, is there a more general mechanism, that is, does stress generally promote a shift from 'cognitive' to 'habitual' learning and memory? If there is such a general mechanism, then stress should also affect the coordination of other 'cognitive' and 'habitual' memory systems.

'Cognitive' and 'habitual' systems may also be involved in instrumental learning, which can be controlled by (i) a goal-directed system that is based mainly on the orbitofrontal cortex and dorsomedial striatum and (ii) a habit system that is primarily supported by the dorsolateral striatum [30–32]. The key difference between these two systems is that the goal-directed system encodes the relationship between an action and the motivational value of the outcome, whereas the habit system learns the association between a response and preceding stimuli, without any link to the outcome that is engendered by the response [31,33]. Accordingly, the two systems can be dissociated by changing the action-outcome contingency or the value of the outcome (Box 2). Using these experimental approaches, recent studies demonstrate that stress may prompt a shift from prefrontal cortex- and dorsomedial striatum-based goal-directed learning to dorsolateral striatum-based habit learning.

Chronic unpredictable stress biases instrumental behavior towards habitual responding in rats [34]. In humans, acute stress renders behavior insensitive to outcome devaluation and thus habitual, both when participants are stressed before learning and when they are stressed after the outcome devaluation [35,36]. This stress effect can be mimicked by the simultaneous administration of the synthetic glucocorticoid hydrocortisone and the α2-adrenoceptor antagonist yohimbine, which leads to increased noradrenergic stimulation [37]. Hydrocortisone or yohimbine alone, however, do not affect the nature of instrumental behavior, indicating that concurrent glucocorticoid and noradrenergic activity is needed to shift learning from goal-directed to habitual control, same as for stress (hormone) effects on hippocampus-dependent memory [7,38]. This conclusion is supported by findings showing that the shift towards habit learning correlates with stress-induced elevations in cortisol and that this shift can be prevented by administering the β-adrenergic antagonist propranolol prior to the stress exposure [39]. Together, these studies illustrate that the modulatory effect of stress is not limited to the engagement of hippocampus-dependent and dorsal striatum-dependent memory systems and that stress coordinates, at least, also prefrontal cortical and dorsolateral striatal systems in instrumental learning.

Stress-induced modulation of multiple memory systems: looking into the human brain
Theoretically, the shift from 'cognitive' (declarative, spatial, or goal-directed) to 'habit' (procedural or S-R) memory

systems after stress may be owing to an impairment of 'cognitive' systems, to an enhancement of 'habit' systems, or to both impaired 'cognitive' systems and enhanced 'habit' systems. Data from rodent studies suggest that stress can indeed affect 'cognitive' and 'habit' systems at the same time and in opposite directions. For instance, noradrenergic stimulation impair hippocampus-dependent spatial learning but enhance dorsal striatum-dependent S-R learning [40]. Moreover, stress and noradrenergic arousal increase impulsivity and 'exploitation' at the expense of 'exploration' [41]. Most interestingly, the bias towards habitual responding after repeated stress is paralleled by opposite structural changes in the systems that underlie goal-directed and habit learning, with hypertrophy in the dorsolateral striatum and atrophy in the medial prefrontal cortex [34].

How stress modulates multiple memory systems in the human brain was examined in two very recent neuroimaging studies. In one of these studies, healthy participants underwent a stressor before they performed a probabilistic classification learning task in the scanner [42]. Similar to navigation learning, probabilistic classification learning can be supported by a 'declarative' hippocampus-dependent memory system and by a 'procedural' striatum-dependent memory system (Box 2; [10,13,14]). Stress before training in the classification task did not alter classification performance. However, stress reduced explicit task knowledge (Figure 1a-b) and changed learning strategies from declarative to more procedural strategies thus suggesting that stress shifted learning from hippocampal to striatal control. This conclusion was confirmed by the neuroimaging data showing that learning performance correlated with activity in striatal regions in participants that were exposed to the stressor before learning, whereas learning performance correlated with hippocampus activity in non-stressed control participants (Figure 1c-d). These findings provide the first direct evidence that acute stress may indeed modulate the engagement of multiple memory systems in the human brain. In addition, to this shift form hippocampal to striatal control of learning, hippocampal activity was also reduced during learning after stress (Figure 1e), whereas striatal activity remained unaffected by stress, suggesting that stress impaired primarily the hippocampal memory system. Interestingly, a negative correlation between hippocampal activity and learning performance in stressed participants indicated that the attempt to recruit the hippocampal system, which supported successful learning in controls, was associated with disrupted performance after a stress.

Another recent fMRI study addressed the neural signature of the interactive effect of glucocorticoids and noradrenaline on instrumental learning in the human brain ([40]; Figure 2). In this study, participants ingested a placebo, hydrocortisone or yohimbine alone, or a combination of the two drugs before they were trained in the scanner in two instrumental actions leading to two distinct food outcomes. After training, one of the two outcomes was devalued by feeding subjects to satiety with this food before an extinction test was given. The behavioral data confirmed that only the combined administration of hydrocortisone and yohimbine shifts behavior towards habits.
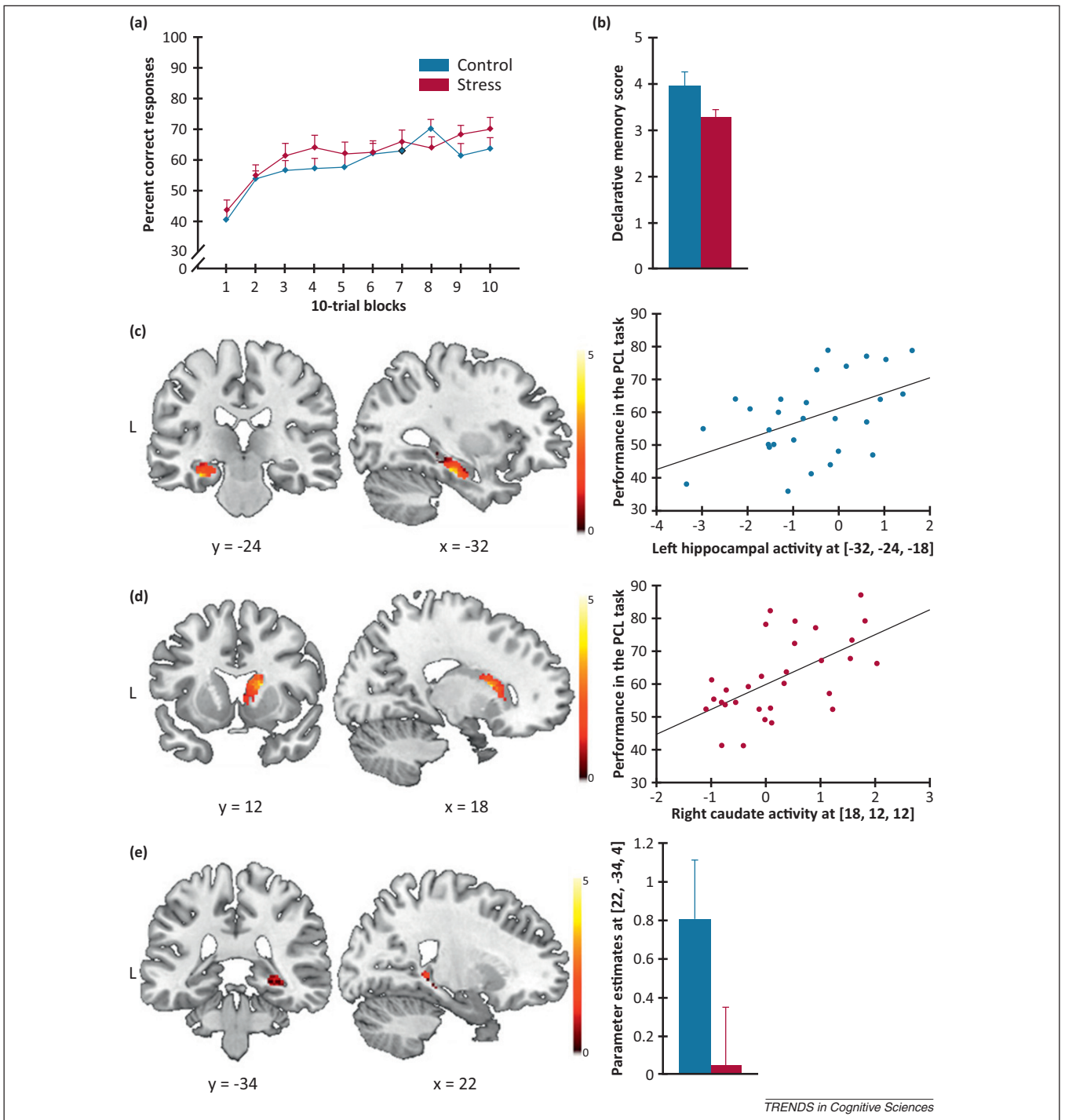
Figure 1. Impact of stress on the engagement of hippocampal and striatal systems during classification learning. Healthy participants underwent a stress or control procedure before they performed a classification task that can be solved by hippocampus-dependent 'declarative' and striatum-dependent 'procedural' learning during fMRI scanning. **(a)** The results showed that learning performance was comparable in the stress and control groups but that **(b)** declarative task knowledge was impaired in stressed participants. **(c)** At the neural level, classification performance was correlated with activity of the hippocampus in the control condition, **(d)** whereas caudate activity was associated with performance in the stress condition. **(e)** Moreover, stress reduced hippocampal activity during classification learning. Error bars represent Standard Error of the Mean. Adapted, with permission, from [42].

Instrumental learning-related brain activity was not modulated by hydrocortisone and/or yohimbine. In the critical extinction test after outcome devaluation, however, activity in prefrontal regions was decreased after simultaneous hydrocortisone and yohimbine intake (but not after hydrocortisone and yohimbine alone). In particular, simultaneous glucocorticoid and noradrenergic activation reduced the sensitivity of brain areas implicated in goal-directed control, that is, the orbitofrontal and medial prefrontal cortex, to changes in outcome value. Hydrocortisone or yohimbine effects on neural correlates of habit behavior were not observed.
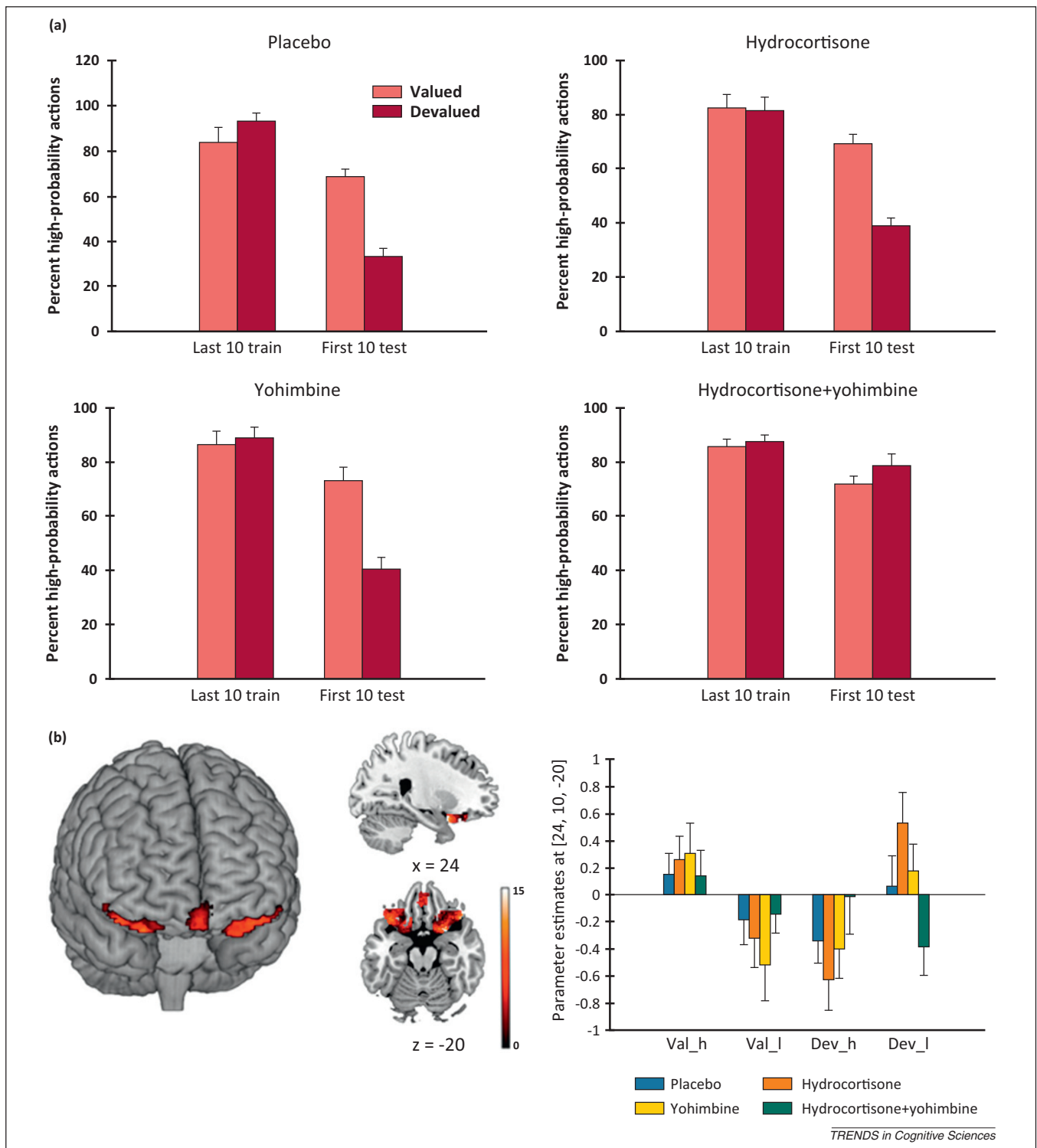
Figure 2. Interactive influence of glucocorticoids and noradrenaline on the systems controlling instrumental learning. Participants received placebo, hydrocortisone, the alpha2-adrenoceptor antagonist yohimbine, or a combination of hydrocortisone and yohimbine before they were trained in two instrumental actions leading to two food outcomes. After training, one of the actions was devalued by feeding participants to satiety with the corresponding food, whereas the value of the other action remained intact (valued). A subsequent extinction test revealed whether learning was goal-directed or habitual: goal-directed behavior is reflected in a decrease in the choice of the action previously associated with the now devalued outcome from the last 10 training trials (last 10 train) to the first 10 extinction trials (first 10 test); habitual learning is indicated by participants' insensitivity to the change in the value of the outcome. **(a)** The results showed that participants that received hydrocortisone or yohimbine alone performed in a goal-directed manner, same as participants that had received a placebo. However, if participants received both hydrocortisone and yohimbine, this rendered behavior habitual. **(b)** This shift from goal-directed to habitual behavior after simultaneous hydrocortisone and yohimbine administration was paralleled by a decrease in activity in orbitofrontal and medial prefrontal areas [shown is the hydrocortisone × yohimbine × trial type (valued vs devalued) × action type (high vs low probability) interaction]. Parameter estimates suggest that the combined hydrocortisone and yohimbine administration affected particularly the representation of the devalued action. Error bars represent SEM. Val_h – action that led during training with a high-probability to the outcome that was not devalued; Val_l - action alternative on valued trials that was, however, never paired with the valued outcome; Dev_h - action that led during training with a high-probability to the outcome that was devalued after the training session; Dev_l - action alternative on devalued trials that was, however, never paired with the later devalued outcome. Adapted, with permission, from [80].

Box 3. Outstanding questions

- Exactly how do stress mediators alter the contributions of multiple memory systems to behavior?
- Is the modulatory effect of stress on 'cognitive' and 'habit' systems mediated by other brain structures (such as the amygdala)?
- Is there, in addition to the role of the MR, also a role of the GR in the stress-induced shift from 'cognitive' to 'habit' memory?
- What is the role of hormones and transmitters other than glucocorticoids and noradrenaline (for example, dopamine or serotonin) in the shift towards 'habit' memory?
- Are the effects of stress mediators on the engagement of multiple memory systems time-dependent, that is, dependent on the interval between the stressor and the learning experience?
- Does stress modulate the predominance of 'cognitive' vs 'habit' memory systems during encoding, consolidation, and retrieval?
- Why do some individuals shift from 'cognitive' to 'habit' memory, whereas others do not?
- Could the prevention of the shift towards 'habit' memory be an effective therapeutic strategy in clinical settings?

These findings are in line with previous evidence showing that the hippocampus and prefrontal cortex are particularly sensitive to stress and stress hormones [43–45] and suggest that stress disrupts these 'cognitive' systems whereas 'habit' systems remain unchanged by stress, thus allowing the latter systems to control learning and memory. Although a positive correlation between cortisol concentrations and striatal activity was observed during classification learning [42], evidence for enhanced 'habit' learning after stress in humans is scarce. Whether stress may, same as in rodents, have opposite effects on 'cognitive' and 'habit' systems in humans is one of the questions that need to be addressed by future research in order to better understand how stress modulates the contribution of multiple 'cognitive' and 'habit' memory systems to behavior (Box 3).

Stress-induced modulation of multiple memory systems: adaptation and risk factor

Shifting from 'cognitive' to 'habit' memory systems may be adaptive during stressful situations. Compared to 'cognitive' memory, 'habit' memory is cognitively less demanding and more efficient. Apparently, the shift towards 'habit' memory may help to avoid hesitation and delays and to save cognitive resources that are needed for coping with the ongoing stressor. Beyond these considerations, there is also direct empirical evidence suggesting that the shift towards 'habit' memory after stress may be adaptive, at least with respect to current performance. For example, stress before learning of a spatial task that is typically acquired by the hippocampus reduced memory in some rats but not in others. Interestingly, stressed rats with good memory exhibited significantly greater c-fos mRNA expression in the dorsal striatum compared to stressed rats with bad memory [46], suggesting that the recruitment of a 'habit' system enabled successful learning despite stress. Preventing the stress-induced shift towards 'habit' memory by an MR antagonist, however, impaired learning significantly [21]. Moreover, stressed mice that switched to S-R learning in a dual-solution task performed comparable to non-stressed controls, whereas mice that kept using a spatial strategy after stress were severely impaired in their learning performance, both compared to controls and stressed S-R learners [21]. In the same vein, hippocampal activity during classification

learning correlated negatively with learning after stress in humans [42]. These findings suggest that the attempt to engage impaired 'cognitive' systems after stress disrupts performance, while the shift to 'habit' systems rescues performance after stress.

This unimpaired performance, however, may come at the cost of reduced behavioral flexibility. Habit learning is rather rigid and bound to certain contexts or stimuli [47,48]. It may therefore hamper transfer to novel situations and adaptation to changing environments. In vulnerable phenotypes, the stress-induced shift from 'cognitive' to 'habit' memory systems may even contribute to the pathogenesis of disorders such as depression, post-traumatic stress disorder (PTSD), or addiction. For many of these disorders, stress is a major risk factor [49,50]. Moreover, many of these disorders are characterized by reduced cognitive flexibility, rigidity, or dysfunctional behavioral routines and rituals [51–54]. PTSD patients, for instance, have considerable difficulties to integrate their traumatic experiences into their (declarative) autobiographical memory and suffer from intrusions that are often triggered by single trauma-related cues [55–57], pointing to a preponderance of a 'habit' memory system. A predominant 'habit' system may also be present in drug addiction which has been conceptualized as the endpoint of a number of transitions from initially voluntary, goal-directed to habitual and ultimately involuntary, compulsive drug taking [58,59]. In this context, it has been argued that the stress-induced shift from 'cognitive' to 'habit' memory may be an important risk factor for the development of psychopathology [60,61]. Thus, the modulatory effect of stress on the engagement of 'cognitive' and 'habit' memory systems appears to be another example of a generally adaptive response to stress that may, under certain conditions, contribute to maladaptive thinking and behavior [2].

Concluding remarks

Stress effects on memory have been the topic of intensive research for decades. Whereas earlier studies focused mainly on quantitative changes within a single (mostly hippocampal) memory system as a result of stress, recent evidence demonstrates that stress may also alter the engagement of multiple memory systems [62]. In particular, it has been shown that stress favors dorsal/dorsolateral striatal 'habit' over hippocampal or prefrontal cortical 'cognitive' memory systems. This shift may be related to the recently reported effects of stress on exploration vs exploitation, with (moderate) stress leading to more exploitation and less exploration behavior [26,41]. Most recently, several pharmacological and fMRI studies in humans have begun to examine the neuroendocrine mechanisms underlying the modulatory effects of stress on 'cognitive' and 'habit' memory. Exactly how stress induces the shift towards 'habit' memory, however, remains largely elusive. Moreover, it is still unclear how stress effects on multiple memory systems are modulated by other motivational or dispositional influences; such complex interactions may be elegantly addressed by computational modeling [26]. Future research on these topics will not only provide novel insights into the impact of stress on learning and memory but may eventually contribute to a better understanding of

psychiatric disorders that are characterized by dysfunctional stress systems and aberrant memory processes.

Acknowledgments

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