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Review

Mechanisms of memory under stress

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SUMMARY

It is well established that stress has a major impact on memory, driven by the concerted action of various stress mediators on the brain. Recent years, however, have seen considerable advances in our understanding of the cellular, neural network, and cognitive mechanisms through which stress alters memory. These novel insights highlight the intricate interplay of multiple stress mediators, including—beyond corticosteroids, catecholamines, and peptides—for instance, endocannabinoids, which results in time-dependent shifts in large-scale neural networks. Such stress-induced network shifts enable highly specific memories of the stressful experience in the long run at the cost of transient impairments in mnemonic flexibility during and shortly after a stressful event. Based on these recent discoveries, we provide a new integrative framework that links the cellular, systems, and cognitive mechanisms underlying acute stress effects on memory processes and points to potential targets for treating aberrant memory in stress-related mental disorders.

INTRODUCTION

> Stressful events are arguably the most important ones to remember. An animal has to be able to tell immediately whether sounds, places, scents, and other animals are dangerous. An animal that has to mentally rehearse the sounds and smells of, say, a bushfire, is not likely to survive.—Bruce S. McEwen (2002, Page 108), 1938–2020

In medieval times, communities threw young children in the river when they wanted them to remember important events. They believed that throwing a child in the water after witnessing historic proceedings would leave a lifelong memory for the events in the child (McGaugh, 2003). Although this cruel tradition stopped—fortunately—centuries ago, modern research confirms that stressful or arousing experiences may indeed boost memory for surrounding events (McGaugh, 2015). Research over the past decades, however, painted a much more nuanced picture of how stressful events shape memory, showing that stress enhances some memory processes but impairs others, and that different stress response patterns associated, e.g., with different types of stressors, may affect what information is being encoded and how it is stored. Moreover, research in rodents and humans provided exciting insights into the brain mechanisms underlying the impact of stress on memory. In this review, we will discuss recent discoveries in the field that have transformed our thinking of how stress affects memory. From these findings, we will derive a new integrative framework of how acute exposure to a stressful event initiates—through the orchestrated action of multiple stress mediators and specific neural network shifts—recently uncovered changes in memory dynamics and flexibility.

Stress effects on memory are driven by the numerous neurotransmitters, hormones, and peptides that are released in response to stressful events and act directly, or indirectly via brainstem circuits, on medial-temporal and prefrontal areas crucial for memory (Joëls and Baram, 2009; Figure 1). Altogether, these stress mediators synergistically promote coping with an ongoing stressor by supporting an initial "fight-or-flight" response that allows the individual to respond appropriately to the situation at hand, followed by a later phase geared to rationalize and store the information linked to its context. Thus, stress-induced changes in memory processes are an integral part of the behavioral adaptation to stressors. These changes initially lead to prioritized attentional and appraisal processing of emotionally salient events, increase the reliance on well-established habits and routines, reduce distraction by stressor-irrelevant information, and—in the aftermath of stress—promote the storage of information most relevant of the stressful encounter to facilitate coping with similar future events (Diamond et al., 2007; Joëls et al., 2006; Vogel et al., 2016). While being generally highly adaptive, overly strong or aberrant stress effects on cognitive processing, particularly on memory formation, can become maladaptive and contribute to stress-related mental disorders such as posttraumatic stress disorder (PTSD) or anxiety disorders (de Quervain et al., 2017; Pitman et al., 2012).

These clinical implications of stress effects on memory may have contributed to the enormous amount of research in this area over the past decades, with different and sometimes paradoxical views (Figure 2). Research on the stress-memory link was stimulated half a century ago by the seminal discovery

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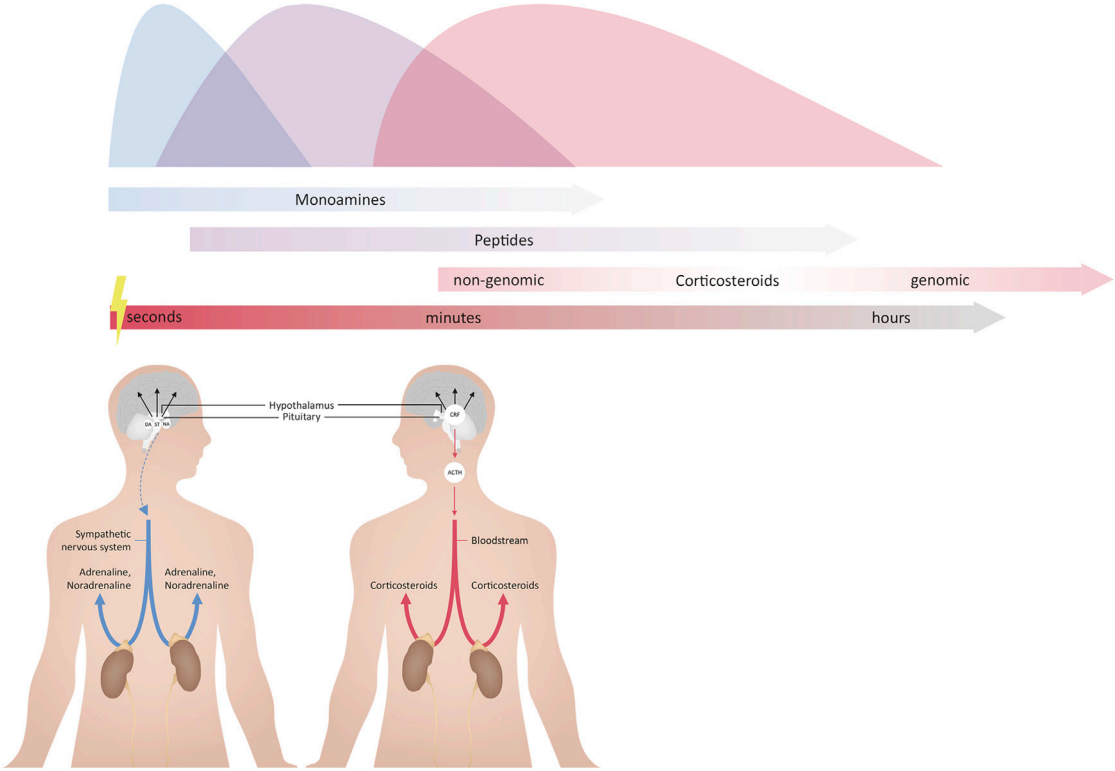


Figure 1. Multiple stress response systems

Within (milli)seconds after stressor onset, the release of monoamines, including dopamine (DA), noradrenaline (NA), and serotonin (ST), is increased in specific neuronal populations. Neurons in hypothalamic nuclei further rapidly activate the sympathetic nervous system, which triggers the release of adrenaline and NA from the adrenal medulla. In parallel, the hypothalamus stimulates the slower hypothalamus-pituitary-adrenal (HPA) axis, a hormonal cascade that includes the release of corticotropin-releasing factor (CRF), vasopressin and adrenocorticotropic hormone (ACTH) and leads within minutes to the secretion of corticosteroids (e.g., cortisol in humans, corticosterone in rodents) from the adrenal cortex. These multiple stress mediators are thus released in waves, reaching the brain at different time points (top). Each of the multiple stress mediators has its specific temporal profile of action on the brain (as indicated by the arrows). The temporal windows of action may overlap, thus enabling synergistic actions between stress mediators. For instance, while corticosteroids were traditionally thought to act via intracellular mineralocorticoid (MR) and glucocorticoid receptors (GRs) leading to slow, genomic actions, it is by now established that corticosteroids exert their actions also via near-membrane MR and GR, which enable rapid, non-genomic actions allowing interactions with the fast-acting noradrenergic system.

that corticosteroids can enter the brain and that their receptors (i.e., glucocorticoid receptors [GRs] and mineralocorticoid receptors [MRs]) are expressed at particularly high density in the hippocampus (McEwen et al., 1968; Reul and de Kloet, 1985), a key region for memory (Squire, 1992). Based on subsequent findings showing that stress or corticosteroids can block hippocampal synaptic plasticity (Diamond and Rose, 1994; Pavlides et al., 1995) and impair hippocampus-dependent spatial or declarative memory (Diamond and Rose, 1994; Lupien et al., 1997; Newcomer et al., 1994), the view at the end of the past century held by some was that corticosteroids disrupt memory (whereas catecholamines may enhance amygdala-dependent memory; McEwen and Sapolsky, 1995), although this was not unequivocal (Oitzl et al., 1997; Roozendaal and McGaugh, 1996).

This idea of a global stress- or corticosteroid-induced memory deficit changed decisively when corticosteroid actions via the MR and GR as well as their interactions with the noradrenergic system were better understood, pointing to dose- and time-dependent effects of stress and stress hormones. In particular, it was shown that GRs and MRs have distinct functions in memory (Oitzl and de Kloet, 1992) and that corticosteroids exert dose-dependent effects on memory (Akirav et al., 2004; Sandi et al., 1997), partially due to the balance or imbalance of MR- and GR-mediated actions (de Kloet et al., 1999). The subsequent discovery that corticosteroids act not only via nuclear receptors mediating slow genomic actions but also via near-membrane receptors allowing non-genomic actions showed that corticosteroid effects can unfold much more rapidly than previously thought (Dallman, 2005; Di et al., 2003; Karst et al., 2005). This non-genomic mode of action enables corticosteroid interactions with the rapidly acting noradrenergic system, which represents a key mechanism through which stress enhances the consolidation (Cahill et al., 2003; Roozendaal et al., 2006), but impairs the retrieval of memory (Buchanan et al., 2006; de Quervain et al., 1998, 2000; Roozendaal et al., 2004). Together, these findings suggested that stress enhances memory for material encoded within the context and around the time of the stressor, when (non-genomic) corticosteroid, (nor)adrenergic and potentially neuropeptide activity are synchronized, but impairs memory for information that occurs out of context, when the activations of major stress response systems are desynchronized, i.e., do not overlap (Diamond et al., 2007; Joëls et al., 2006, 2011).

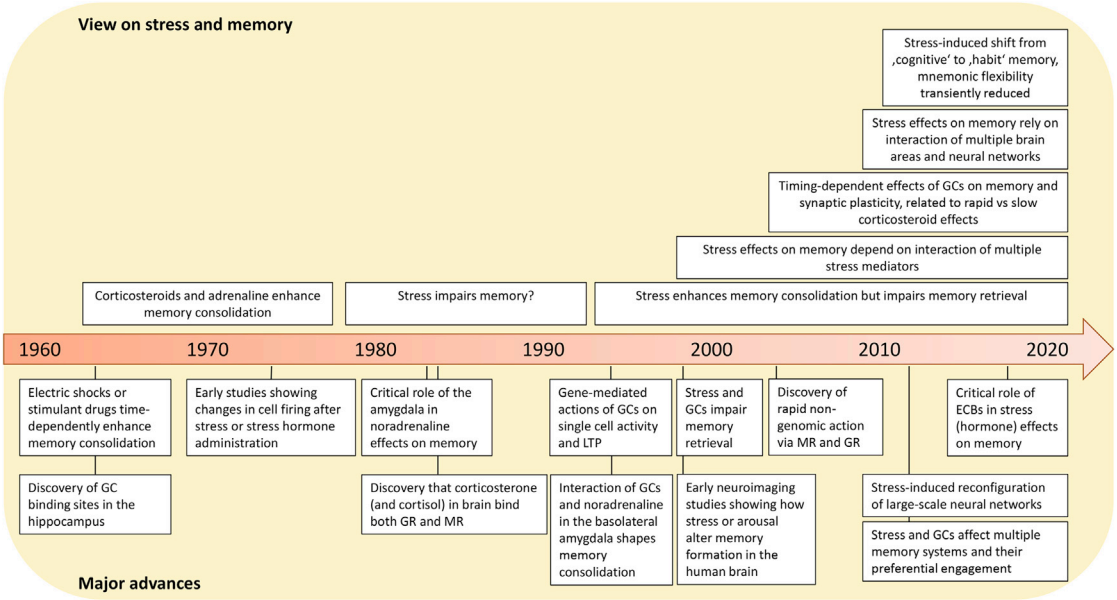


Figure 2. Historic progression of research on stress effects on memory
Overview of significant advances in our understanding of how stress and stress mediators affect memory and its neural underpinnings (bottom) and related changes in the predominant view of how stress shapes memory (top).
GC, glucocorticoids; LTP, long-term potentiation; GR, glucocorticoid receptor; MR, mineralocorticoid receptor; ECBs, endocannabinoids.

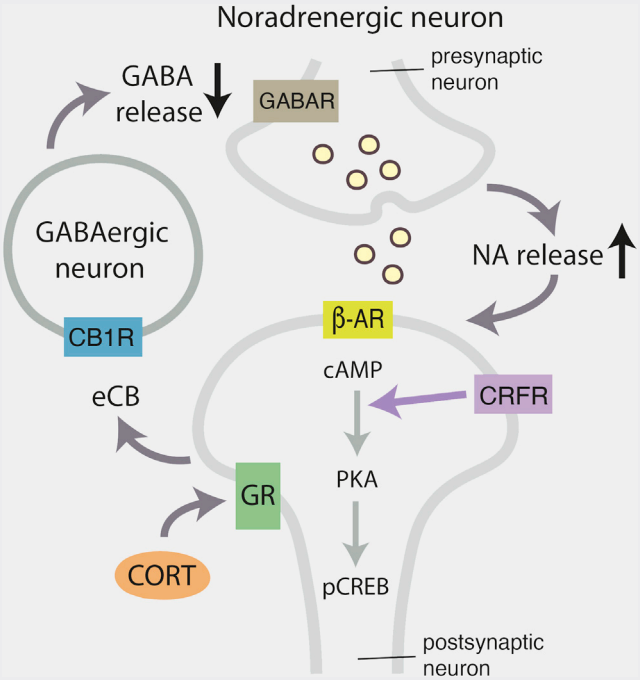
Building on these cornerstones, recent years have seen important advances that provide new insights into the mechanisms involved in stress effects on memory—especially in the human brain—and, at the same time, show that these effects are much richer and more complex than previously thought. For instance, it is becoming increasingly clear that the impact of stress on memory depends, as outlined below, critically on the history or state of the individual, e.g., a naive individual versus one that has recently experienced an acute stressor, and that this impact relies on large-scale network interactions rather than effects on isolated brain areas. Moreover, stress effects on memory may only be understood when taking the differential contributions of multiple anatomically and functionally distinct memory systems into account and that stress will influence memory over a wide range of time, from the initial memory encoding phase, through consolidation to storage, even months after the stressful event.

In this review, we will give an overview of the current state of thinking of how acute stress affects memory, with an emphasis on recent insights, at multiple levels of integration—from cells, through microcircuits and local systems, to whole-brain and cognitive consequences—in rodents and humans. These recent advances will then be integrated with previously established mechanisms to provide a new integrative framework that will link the cellular, neural network, and cognitive levels of the impact of stress on memory processes, from memory consolidation and retrieval to memory flexibility and dynamics. We primarily focus on the effects of acute stress on long-term memory processes. Effects of chronic stress on memory—same as other issues that we lack space to discuss in detail here, such as potential sex differences, stress-induced changes in working memory and executive functions, or in cognition across the lifespan—have been covered in excellent previous reviews (Andreano and Cahill, 2009; Arnsten, 2009; Conrad, 2010; Lupien et al., 2009; Shields et al., 2016).

CELLULAR MECHANISMS UNDERLYING THE IMPACT OF STRESS ON MEMORY

Understanding the mechanisms by which acute stress affects memory formation starts with the notion that a physiological stress response can be deconstructed into different waves of stress mediators, sequentially reaching and affecting brain cells (Figure 1). Stress mediators include catecholamines, such as adrenaline and noradrenaline (NA); neuropeptides, such as corticotropin-releasing factor (CRF); and corticosteroid hormones, primarily corticosterone in rodents and cortisol in humans (Joëls and Baram, 2009). Exactly which cells or brain regions are affected depends on (1) whether or not particular brain areas are reached by stress mediators, (2) the local expression of receptors, (3) the type and severity of the stressor, and (4) the nature of the learning task (Joëls et al., 2012). How neuronal activity is altered also depends on signaling pathways downstream of these receptors and the cellular context. Generally, catecholamines and neuropeptides act within minutes through membrane receptors while corticosteroids exert delayed effects, binding to intracellularly located receptors that serve as transcription factors, although more recently also rapid, non-genomic signaling was revealed. Altogether, stress mediators can change cell activity over a wide range of time, from minutes up to hours and days, partly explaining why even a brief stressor can change later phases of memory formation.

Box 1. Interaction of multiple stress mediators in shaping memory processes



Studies in rodents have provided a beautiful illustration how one can make the step from biochemical signaling at the level of cells and microcircuits to cognitive processing and behavioral output, serving as a bridge ultimately to human brain networks and cognitive processing. These *in vivo* studies allow investigation of multiple brain areas and levels of integration.

Animal studies have shown functional interactions between corticosterone and NA on memory. Corticosterone administration to rats after footshock delivery in an inhibitory avoidance task rapidly augments NA levels within the BLA (McReynolds et al., 2010). In contrast, attenuation of noradrenergic signaling with β-adrenoceptor antagonists infused into the BLA blocked the memory enhancement induced by a corticosteroid administered either systemically or directly into a variety of other brain regions such as the HP or PFC (Barsegyan et al., 2010; Quirarte et al., 1997; Roozendaal et al., 2002, 2006). CRF effects on memory are also dependent on interactions with both the noradrenergic and corticosteroid systems (Roozendaal et al., 2008). These interactions of corticosteroids and CRF with the noradrenergic system may provide a direct explanation for the finding that these stress mediators selectively enhance memory consolidation of emotionally arousing experiences (Buchanan and Lovallo, 2001; Cahill et al., 2003; Okuda et al., 2004; Roozendaal et al., 2006).

Several experimental findings suggested that corticosteroid interactions with noradrenergic signaling might have an onset that is too fast to be mediated via transcriptional regulation in the nucleus and likely involve rapid, non-genomic interactions with the ECB system. Stressful training or a single injection of corticosterone rapidly elevates ECB levels in corticolimbic regions (Hill et al., 2010; Morena et al., 2014). Conversely, a CB1 receptor antagonist administered into the BLA blocked the enhancing effect of posttraining systemic corticosterone on memory consolidation (Campolongo et al., 2009). Further, a CB1 receptor antagonist infused into the BLA blocked the memory-enhancing effects induced by either a specific GR agonist or the membrane-impermeable ligand cort:BSA (Atsak et al., 2015), indicating that corticosteroid-ECB interactions on memory presumably involve the activation of a GR on or near the cell surface. Although the initial studies examining corticosteroid interactions with the ECB system on memory consolidation have focused on the BLA, subsequent studies have shown highly comparable interactions within the HP, PFC, and dorsal striatum (Morena et al., 2014; Siller-Pérez et al.,2019). Moreover, several studies have shown that corticosteroid effects on retrieval impairment also require an interaction with the ECB system (Atsak et al., 2012; Morena et al., 2015). Intriguingly, whereas corticosteroid-ECB interactions on memory consolidation appear to predominantly involve the ECB ligand anandamide (Morena et al., 2014), corticosteroid effects on memory retrieval have been shown to depend on 2-arachidonoylglycerol signaling (Morena et al., 2015).

Subsequent experiments indicated that such corticosteroid-induced recruitment of the ECB system is also critically involved in regulating the rapid effects of corticosteroids onto the noradrenergic system (Atsak et al., 2015). The ECB system might either

(Continued on next page)

Box 1. *Continued*

directly influence noradrenergic activity or, alternatively, alter noradrenergic function indirectly via a modulation of GABAergic or glutamatergic activity. Within the BLA, CB1 receptors are in particular abundantly expressed on GABAergic interneurons (Katona et al., 2001) and activation of CB1 receptors has consistently been shown to suppress the release of GABA (Ohno-Shosaku et al., 2001). Suppressing GABA activity is known to stimulate the release of NA (Hatfield et al., 1999). Together, these findings thus suggest that corticosterone might bind to a GR on the cell surface and rapidly induce the release of ECBs. The released ECBs then bind to CB1 receptors on GABAergic interneurons and inhibit the release of GABA that can then result in a change in excitation/inhibition balance and a disinhibition of noradrenergic transmission in BLA neurons (Di et al., 2016).

Although in principle many brain areas are reached by one or more stress mediators, most molecular, biochemical, and electrophysiological studies have been confined to a limited set of areas, i.e., subregions of the hippocampus and prefrontal cortex (PFC), the amygdalar nuclei and to a lesser extent the nucleus accumbens, ventral tegmental area, and hypothalamus (Bains et al., 2015; Joëls et al., 2012; Peng et al., 2021). This choice was guided by the behavioral or endocrine relevance of these areas and is clearly a limitation in our body of knowledge. Generally, NA increases excitatory transmission and synaptic plasticity through β-adrenoceptors, although a role of α-adrenoceptors is also indicated (Arnsten, 2009; Ferry et al., 1999). Similarly, CRF through CRF1 receptors mostly enhances limbic excitability and synaptic plasticity. For instance, acute stress and enhanced CRF levels in general cause rapid remodeling of CA1 hippocampal spines, promote glutamate release, and improve synaptic plasticity (Vandael et al., 2021). Conversely, CRF2 receptors are involved in the termination of the stress response (Henckens et al., 2016). Corticosteroids also yield a differentiated picture. In the mouse hippocampus (Karst et al., 2005), corticosterone quickly but reversibly increases glutamate release probability, through a non-genomic route involving the MR. This is paralleled by an MR-dependent increase in GluR2-AMPAR surface diffusion (Groc et al., 2008). In the basolateral amygdala (BLA) too, corticosterone quickly increases glutamate transmission through MR but here the effects are long-lasting (Karst et al., 2010). More recently, it has become evident that glutamate signaling of principal cells in the BLA is also boosted via rapid GR-dependent activation of endocannabinoids (ECBs)—upstream of noradrenergic signaling—which then retrogradely through inhibition of GABAergic cells causes local disinhibition (Campolongo et al., 2009; Di et al., 2016; see Box 1).

The rapid-onset corticosteroid effects are complemented by late, genomic actions via GRs, e.g., on glutamate signaling, causing increased glutamate responses in CA1 pyramidal neurons (Karst and Joëls, 2005) and layer V PFC cells (Yuen et al., 2009), while other forms of transmission are generally suppressed (Joëls et al., 2012). In hippocampal cells, GR activation also enhances synaptic dwell time of diffusing GluR2-AMPARs (Groc et al., 2008). Late effects, which take >1 h to develop, involve altered gene transcription, but to date, the signaling cascades—from receptor to effector molecule—remain elusive, despite many efforts to delineate these pathways, focusing e.g., on candidate molecules such as cAMP response element-binding protein (CREB; Buurstede et al., 2021) and tissue plasminogen activator (tPA; Bouarab et al., 2021), or investigating the entire genome (see Clayton et al., 2020). Thus, stress mediators have a quick and strong excitatory effect on particularly BLA neurons, while in hippocampal and particularly PFC principal cells the signal-to-noise activity is improved in a slow GR-dependent manner involving gene transcription (Joëls et al., 2018). The timeframe of these rapid and slow effects would allow modulation of memory encoding and consolidation, respectively, yet our knowledge is still limited with respect to the modulation of the neurocognitive processes subserved by the regions that have been in the spotlight so far, and at the cellular level these regions have been mostly examined in isolation.

Nearly all *in vitro* electrophysiological studies so far focused on glutamatergic transmission (mostly in principal neurons), which seems justified since GR knockout in glutamatergic neurons is important for, e.g., abolition of anxiogenic effects of stress, whereas GR knockout in GABAergic neurons proved to be ineffective (Hartmann et al., 2017). Yet, several recent studies underline that this may give an incomplete picture. For instance, after elevated platform stress GABAergic currents as well as the inhibition-to-excitation ratio were reduced in CA1 hippocampal neurons, which was related to impaired retrieval of spatial memory after acute stress (Shi et al., 2020). As mentioned, indirect corticosteroid effects on GABAergic interneurons in the BLA via retrogradely transported ECBs play a crucial role in the quick boost of local inhibitory transmission (Di et al., 2016; see Box 1). Recent evidence also supports a role of GR and ECBs in mitochondrial function that could relate to memory formation (Hebert-Chatelain et al., 2016) and anxiety (Filiou and Sandi, 2019). The relevance of GABAergic transmission and local circuitry for long-term emotional memory formation furthermore emerged from a recent study showing that *de novo* translation in somatostatin-expressing centrolateral amygdala interneurons is necessary for the consolidation of conditioned threat responses, which is distinct from the pathway involved in diminished responses to a safety cue, which depends on translation in another set of inhibitory neurons (Shrestha et al., 2020).

Not only principal neurons and interneurons are affected by stress mediators; it has become increasingly evident that (micro)glial cells might also be implicated in effects of acute stress on memory. For instance, mice with astrocyte-specific GR deletion showed impaired aversive memory expression (Tertil et al., 2018). This may involve altered glucose uptake in astrocytes by the glial isoform of serum/glucocorticoid regulated kinase 1 (Sgk1). Alternatively, this effect might be related to NMDA-dependent long-term potentiation (LTP) in hippocampal astrocytes during task acquisition (Adamsky et al., 2018). Thus, part of the memory-promoting effects of stress or corticosteroids could be

accomplished through astrocytes, as part of a tripartite synaptic complex (Popoli et al., 2011).

The approach to investigate one stress mediator or one area at a time has been helpful to generate a theoretical framework of how acute stress might alter local network function (Joëls et al., 2018). Nevertheless, it is a very reductionistic approach and does not do justice to (1) the complexity of the stress response and its multiple mediators, (2) the fact that stress effects depend on the history and state-dependent characteristics of the animal, including the state induced by the learning task, and (3) the notion that learning tasks involve integrated networks of brain areas that collectively lead to encoding and memory formation. An illustration of the first issue is the fact that waves of stress mediators overlap in time and space (Joëls and Baram, 2009), and one wave may affect the cellular response to the next ("metaplasticity"). This principle was illustrated for BLA neurons, where activation of β1-adrenoceptors suppressed the electrophysiological response to corticosterone administered 20 min later (Karst and Joëls, 2016). Consequently, low to moderate concentrations of β1-adrenoceptor agonists and corticosterone resulted in curtailed excitatory BLA responses, while high concentrations resulted in lengthy activation.

Metaplasticity also comes into play with repeated peaks of corticosterone, showing that cellular responses to corticosteroids may differ depending on whether they take place in a naive animal or one that has recently experienced an acute stressor; this emphasizes the relevance of the history and state-dependent characteristics of the animal. Thus, corticosteroid exposure of amygdalar cells in recently stressed mice "decreased" glutamatergic transmission via GR, as opposed to the MR-dependent increase in glutamatergic transmission seen in naive mice (Karst et al., 2010). A similar metaplastic switch, now for synaptic plasticity, was seen with respect to auditory fear conditioning in the lateral amygdala (Inoue et al., 2018). Also ultradian corticosterone pulses of variable amplitude, at different phases of the circadian rhythm (Lightman et al., 2020), can metaplastically change spontaneous BLA glutamate transmission, which could explain why tone-cue fear conditioning is most effective during the inactive phase of the day (den Boon et al., 2019).

With respect to the third cause of complexity—the existence of interactive networks—it has become clear that many cells and brain regions will show changed activity after acute stress (Bonapersona et al., 2022), and it is the collective and integrated response in entire networks that determines the overall relevance for cognitive processing. *In vitro* experiments are ill-suited to study integrated effects of multiple brain areas at a time. To really appreciate the cellular effects accompanying acute stress and their relevance for memory formation, *in vivo* recordings are indispensable. Functional MRI in principle could provide a whole-brain overview of activity in rodents—thus bridging the methodology in animals and humans—yet this method is inherently stressful to rodents and therefore not suitable. Moreover, this approach does not provide information at the single-cell level. Simultaneous single-cell recordings across multiple areas will need to give an answer, and—though sparse—recent studies indeed give more insight. For instance, McCall et al. (2015) demonstrated that increased tonic activity of the locus coeruleus noradrenergic system, depending on CRF projections from the amygdala, is necessary and sufficient to induce anxiety-like behavior in an open field or elevated zero-maze; a potential cellular underpinning of the observation in humans that a salience processing network is involved in the initial stages of stressful learning (see below). Moreover, activation of a dense noradrenergic projection from the locus coeruleus to the dentate gyrus resulted in contextual generalization through β-adrenergic-mediated modulation of hilar interneurons (Seo et al., 2021). The importance of NA (as one of the stress mediators) for fear learning was also revealed using an activity-dependent tagging system (Leal Santos et al., 2021): the β-adrenoceptor antagonist propranolol, which blocks lower-affinity β-adrenoceptors that are occupied at higher tonic levels of NA observed directly after acute stress, acutely impaired fear memory traces and altered functional connectivity between the dorsal dentate gyrus, PFC, and BLA. These studies elegantly support the earlier *in vivo* observation that the BLA and dentate gyrus are important hubs in mediating interactive effects of NA and its interaction with corticosteroids on synaptic plasticity (Vouimba et al., 2007).

LARGE-SCALE NETWORK INTERACTIONS UNDERLYING THE IMPACT OF STRESS ON MEMORY

Extensive evidence indicates that the different stress mediators enhance memory by acting within many different brain regions. Notably, however, these brain regions are highly functionally interconnected (McGaugh, 2000; Roozendaal and McGaugh, 2011). For instance, previous rodent studies have implicated the BLA in orchestrating memory-enhancing effects of these stress mediators, not only by modulating neuroplasticity and memory processes elsewhere in the brain (Barsegyan et al., 2019; Bonapersona et al., 2022; Chen et al., 2018; Ikegaya et al., 1997; Lovitz and Thompson, 2015; McIntyre et al., 2005; Roozendaal and McGaugh, 2011), but also by enabling direct stress hormone effects in other brain regions, and thereby influencing functional interactions within larger brain networks (Barsegyan et al., 2019). Such observations of widespread network-level changes dovetail with observations from functional neuroimaging in humans, which indicate that memory formation is supported by activity across networks that span the entire brain (Ranganath and Ritchey, 2012). This neuroimaging work has revealed that certain network configurations are required to guide attention to salient stimuli and support mnemonic operations that form initial memory traces, while other network configurations critically support consolidation, transformation, and long-term storage of information. As we will describe below, stress-related neuromodulatory actions appear to play a critical role in guiding these network interactions and switches (Figure 3).

One large-scale network identified using human functional neuroimaging is the "salience" network (SN; Seeley et al., 2007). This network prominently includes the amygdala, but also encompasses dorsal anterior cingulate/dorsomedial PFC, anterior insula, temporoparietal junction, thalamus, striatum, and hypothalamus. It is thought to integrate neurocognitive systems required for an optimal response to homeostatic threats at all stages from optimizing sensory intake and initial appraisal to generating appropriate responses (Seeley, 2019),

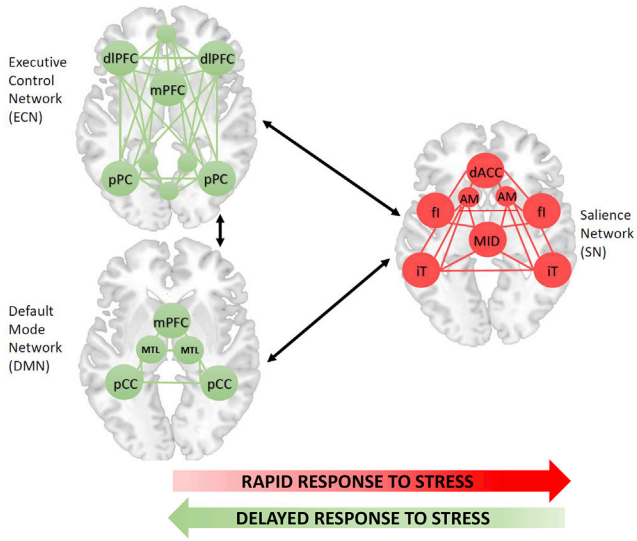


Figure 3. Stress-induced shift of large-scale neural networks
Acute stress leads to a rapid reconfiguration of large-scale neural networks, favoring the salience network over executive control and default-mode networks. The late phase of the stress response, however, may evoke a reversal of this network shift, now promoting the executive control and default-mode networks over the salience network.
dlPFC, dorsolateral prefrontal cortex; mPFC, medial prefrontal cortex; pPC, posterior parietal cortex; MTL, medial-temporal lobe; pCC, posterior cingulate cortex; dACC, dorsal anterior cingulate cortex; AM, amygdala; fI, frontal insula; MID, midbrain; iT, inferior temporal cortex.

including memory encoding (Hermans et al., 2014a). Indeed, human neuroimaging work has shown that activity of (key regions within) the SN is associated with subsequent memory retention specifically for emotionally arousing material (Hamann et al., 1999; Kim, 2011) and also predicts later involuntary intrusions (Visser et al., 2021). Thus, SN activation results in prioritized encoding of stress-relevant over peripheral information.

SN activation appears to be tightly coupled to noradrenergic signaling. In particular phasic activity of the locus coeruleus-noradrenaline (LC-NA) system, the main source of NA in the brain, is thought to engage SN regions to prompt task-set switches in response to salient stimuli (Corbetta et al., 2008). CRF is well known to interact with other stress mediators to regulate tonic and phasic activity of the LC and its communication with key regions of the SN such as the amygdala (Valentino and van Bockstaele, 2005). Further, as argued above, CRF projections from the amygdala can trigger a switch toward a tonic mode of LC-NA firing, which diminishes phasic firing to discrete stimuli, has an anxiogenic effect, and creates a hypervigilant and distractible attentional state (McCall et al., 2015). Functional neuroimaging work in humans has shown that functional connectivity within the SN is increased during exposure to highly negatively arousing cinematographic material (Hermans et al., 2011). Synchronization of activity within this network also fluctuated dynamically with levels of physiological arousal induced by these film clips (Young et al., 2017). Stress-induced SN connectivity furthermore diminished following administration of the β-adrenoceptor antagonist propranolol (Hermans et al., 2011). A stress-induced shift toward enhanced coupling between amygdala and striatal regions within the SN was furthermore shown to be reduced in carriers of a functional deletion variant of the gene encoding the α2b-adrenoceptor, resulting in increased NA signaling (Wirz et al., 2017b). Chemogenetic and optogenetic studies in rodents in recent years have borne out the causal link between LC-NA activation and anxiogenesis (Hirschberg et al., 2017), and increased connectivity within (a rodent homolog of) the SN (Zerbi et al., 2019). In addition to noradrenergic signaling, recent evidence indicates that in the immediate phase of the stress response, corticosteroid action via MR may have a synergistic effect with NA (Vogel et al., 2016; Wirz et al., 2017a). Together, these findings suggest that stress-induced tonically elevated levels of NA, potentially in synergy with rapid non-genomic corticosteroid effects via MR, switch the brain to a stimulus-unselective hypervigilant "encoding" or "memory formation" mode. These rapid effects congrue with the framework provided by the (earlier) cellular studies.

While unselective encoding of as much information as possible during a stressful experience may be adaptive, it would run into capacity limits, interference, and poor signal-to-noise ratio when prolonged for too long. A critical question is therefore how the brain balances the need of retaining all potentially relevant information with the need to avoid excessive storage of irrelevant material. The solution appears to lie in a comprehensive reconfiguration of large-scale network activity that initiates robustly and immediately after external demands (e.g., due to a stressor) subside. This switch to an "offline" mode, away from externally and toward internally directed cognition, involves robust and consistent activation within (ventro)medial PFC, inferior parietal, posterior cingulate, and retrosplenial regions, which are together referred to as the default-mode network (DMN) (Raichle, 2013). Notably, the DMN also exhibits strong intrinsic functional connectivity with the medial-temporal lobe (MTL), including both hippocampus and amygdala (Buckner et al., 2008). Although its precise function remains debated, there is growing consensus regarding a role for the DMN in mnemonically related operations such as prospection or, more broadly, "offline" associative processing (Bar, 2021). These notions concur with findings in both rodents and humans of persistent experience-specific activity patterns following learning in hippocampal-cortical circuits (Ji and Wilson, 2007; Tambini and Davachi, 2019), including medial PFC (Takehara-Nishiuchi and McNaughton, 2008; Van Kesteren et al., 2010). DMN activation is therefore thought to support integration of novel information into existing associative "schemas" and thereby facilitate early stages of the gradual shift toward cortico-cortical dependency of memory that is referred to as systems consolidation (Gilboa and Moscovitch, 2021).

Similar to the switch to an "encoding" or "memory formation" mode, the early stage of systems consolidation appears to be tightly controlled by stress-related activation of the LC-NA system and its effect on amygdala-centered networks, likely in synergy with corticosteroid actions. Notably, such effects occur during time windows in which arousal-related noradrenergic activity remains tonically elevated following stressors. In line with electrophysiological studies in rodents (Pape and Paré, 2010; Paré, 2003; Popa et al., 2010; Seidenbecher et al., 2003), human

neuroimaging work has shown that specific patterns of activation within the amygdala persist during "offline" periods shortly following learning (Hermans et al., 2017). Furthermore, phenomena of sequential reactivation ("awake replay") of hippocampal neurons are potentiated following salient learning experiences such as novel or rewarding events (Singer and Frank, 2009), but also fear learning (Wu et al., 2017).

Phenomena of preferential re-instatement of learning-related activation patterns is not limited to single regions. For instance, increased synchronized theta-band oscillations were observed between lateral amygdala and CA1 hippocampal region after fear learning (Seidenbecher et al., 2003), and coupling between lateral amygdala and CA1 increased following immobilization stress (Ghosh et al., 2013). In humans, functional connectivity between amygdala and hippocampus measured using BOLD-fMRI was increased following fear learning, and this increase was associated with stronger fear memories (Hermans et al., 2017). Task-independent intrinsic functional connectivity between amygdala and hippocampus, measured at baseline, was furthermore predictive of later stress effects on declarative memory (de Voogd et al., 2016), and categorical fear learning was shown to result in preferential reinstatement of neocortical representations of fear-associated semantic categories (de Voogd, 2016). It has been proposed that the amygdala "gates" hippocampal-neocortical communication by controlling the entorhinal-perirhinal pathway (Bauer et al., 2007), suggesting that the amygdala and specifically stress-related noradrenergic activation plays a critical role in permitting selective reactivations of memory representations and hippocampal-neocortical crosstalk.

These noradrenergic effects may be complemented by functionally synergistic corticosteroid actions. For instance, corticosteroids have been shown to gradually shift dominance of functional connectivity of the amygdala away from the SN and toward regions involved in the DMN (Henckens et al., 2012), which may prevent an overactivity that could be damaging if not controlled for. Corticosteroids are further critically implicated in the upregulation of another large-scale network, the executive control network (ECN), in the late phase of the stress response, i.e., >1 h after stress onset. This network, which supports higher-order cognitive functions such as working memory, involves more dorsal prefrontal areas (dorsolateral PFC [dlPFC], precentral/superior frontal sulci, and dorsomedial PFC) as well as posterior parietal areas (Hermans et al., 2014a; Vincent et al., 2008). In line with rodent work showing that acute stress induces after >1 h a long-lasting GR-dependent potentiation of excitatory neurotransmission in PFC (Yuen et al., 2009), human research has shown that administration of hydrocortisone exerts delayed positive effects on PFC function (Henckens et al., 2011). This time delay of several hours is consistent with the temporal window of potential genomic effects of corticosteroids. These examples of a gradual "counterregulation" by corticosteroids in DMN and ECN in the aftermath of a stressful event represents a clear example of the complementary effects of quick noradrenergic versus delayed corticosteroid activity (Hermans et al., 2014a). It further suggests an active role for slow effects of corticosteroids in promoting consolidation and integration of information encoded during the acute phase of the stress response to promote behavioral adaptation.

DYNAMIC CHANGES OF MEMORY UNDER STRESS

For long, stress research focused almost exclusively on stress-induced changes in hippocampal spatial or declarative memory formation or retrieval, and it was assumed that non-hippocampal memory would not be influenced by stress (Lupien et al., 1997; Newcomer et al., 1994). This assumption, however, has been challenged by findings showing that stress and stress hormones can affect memories that are independent of the hippocampus such as dorsal-striatum-based stimulus-response memories. Systemic stress hormone administration or corticosteroid injection directly into the dorsal striatum affects these non-hippocampal memories in a similar manner as hippocampal memory, again enhancing the consolidation and impairing the retrieval of these memories (Guenzel et al., 2013; Medina et al., 2007).

Even more importantly, research over the past decade demonstrated that stress does not only result in quantitative changes in the performance of a single hippocampal or non-hippocampal memory system but also in the balance between anatomically and functionally distinct memory systems (Packard and Goodman, 2012; Vogel et al., 2016). Often, multiple memory systems are active at the same time that differ in the information processed and may support different behavioral responses (McDonald and White, 1993). Although highly relevant in stressful situations, the differential contributions of these different memory systems could hardly be separated in tasks that were commonly used in previous research on stress and memory. This changed only when more complex learning tasks were employed. Closely related to the stress-induced reconfiguration of large-scale neural networks described above, accumulating evidence now suggests that stress determines which of these multiple memory systems governs behavior. More specifically, it has been demonstrated across tasks and species that stress or corticosteroid administration before learning induces a rapid shift from reflective "cognitive" memory systems, such as the hippocampus or PFC, to more reflexive "habit" systems, such as the amygdala or dorsolateral striatum (Kim et al., 2001; Schwabe et al., 2007; Siller-Pérez et al., 2017; Simon-Kutscher et al., 2019; Vogel et al., 2017; Wirz et al., 2018).

Converging lines of evidence from pharmacological and behavioral genetics studies suggest that this initial shift toward "habit" memory under stress is operated by non-genomic corticosteroid action via the MR (Schwabe et al., 2010, 2013; Wirz et al., 2017a), presumably in close interaction with noradrenergic activity (Packard and Goodman, 2012; Wirz et al., 2017b), while the consequent consolidation of striatal memory depends on the GR (Siller-Pérez et al., 2017). Notably, this shift from "cognitive" toward "habit" memory is not only observed during initial memory formation but also at retrieval (Elliott and Packard, 2008; Zerbes et al., 2020; Zerbes and Schwabe, 2021). Thus, if multiple "cognitive" and more "habitual" memory traces exist in parallel, acute stress leads to the predominance of habitual memory retrieval, allowing well-established routines to guide behavior under stress. We assume that the stress-induced bias from "cognitive" to "habit" memory is a direct consequence of the neural network shift toward the SN, which includes, among other regions, the amygdala and dorsal striatum.

Building directly on the stress-induced shift toward "habit" memory, recent research asked whether stress may impact—beyond the known effects on consolidation and retrieval—the flexibility of memory. A key feature of adaptive memory is its capacity to flexibly guide future retrieval and hence behavior (Shohamy and Adcock, 2010). Recent findings suggest that stress hampers this mnemonic flexibility. For instance, stressed participants who were trained in a virtual navigation task showed an increased reliance on familiar paths and reduced traversal of shortcuts when these became available. Neuroimaging data revealed that this deficit in flexible retrieval enabling efficient navigation was linked to reduced neural replay of memory for future locations and reduced activity relevant for mental simulation during probe trials (Brown et al., 2020). These findings dovetail with recent evidence suggesting that stress may interfere with the capacity to flexibly and intentionally control memory retrieval processes (Quaedflieg et al., 2020). Likewise, stress shortly before initial learning or pharmacological elevations of noradrenergic activity have been shown to impair participants' ability to generalize across past experiences when required to flexibly transfer memories to novel situations (Dandolo and Schwabe, 2016; Kluen et al., 2017a). This stress-related impairment in memory flexibility appears to extend to the ability to link existing memories with new information. Specifically, stress, NA, or corticosteroids (administered shortly before training) impaired the efficient use of existing knowledge to support new learning of related material (Kluen et al., 2017b; Vogel et al., 2018) as well as the flexible updating of established memories in light of new information (Nitschke et al., 2019; Raio et al., 2017). These impairments in mnemonic flexibility regarding incorporation of new information may be closely linked to the reduced recruitment of the DMN and ECN under stress, presumably driven by NA and rapid, non-genomic corticosteroid action via the MR. Initial evidence suggests that these impairments in mnemonic flexibility may be primarily owing to impaired flexibility of memory retrieval (Quaedflieg et al., 2020; Vogel et al., 2018; Zerbes et al., 2020). However, this conclusion might be premature because participants were exposed to stress shortly before training in many studies which complicates a distinction between effects on initial acquisition and subsequent retrieval processes. Furthermore, probes of memory flexibility typically involve the processing of new information against the background of prior knowledge, i.e., a close interplay between acquisition and retrieval processes.

Another line of recent research asked how stress hormones affect the long-term fate of memories. During systems consolidation, initially hippocampus-dependent memories are thought to become increasingly reliant on neocortical areas (Squire and Alvarez, 1995). This time-dependent reorganization is assumed to be accompanied by a transformation from a detailed, episodic memory trace to a more gist-like memory representation (Dandolo and Schwabe, 2018; Moscovitch and Gilboa, 2021). Although this transformation may be generally adaptive to build up abstract semantic knowledge structures, maintaining specific and vivid memories over time may be particularly relevant for emotionally arousing or stressful events (Bahtiyar et al., 2020). A recent study in rats tested whether NA administration into the BLA shortly after training on an inhibitory avoidance discrimination task affects the specificity of memory tested 28 days later (Atucha et al., 2017). Results indicated that, compared with saline-treated rats that showed the expected transformation to gist-like memory, memory remained detailed and specific at the 28-day retention test in NA-treated rats. Strikingly, this maintenance of memory specificity after NA treatment was not only associated with a maintenance of hippocampal dependency over time but even with increased hippocampal dependency, accompanied by changed patterns of DNA methylation and mRNA expression of memory-related genes in the hippocampus and neocortex after 28 days, suggesting that NA may not only slow down but even reverse systems consolidation. This pattern of results was replicated in a very recent neuroimaging study in humans (Krenz et al., 2021). Here, increased noradrenergic activity shortly after encoding of pictures reduced the time-dependent decline in memory at a 28-day delayed test (relative to a 1-day delayed test) compared with placebo. In line with the rodent data, fMRI findings showed that the noradrenergic stimulation led even to a time-dependent increase in hippocampal activity and episodic reinstatement during retention testing, accompanied by a time-dependent decrease in neocortical activity.

While these findings point to a critical impact of NA on the dynamics of memory formation and retrieval over time, another question relates to the potential role of corticosteroids in the long-lived changes in memory quality. Interestingly, there is initial evidence to suggest that NA and corticosteroids might play complementary, or even opposite, roles in the dynamics of memory, underlining the idea that different stress mediators may have distinct roles in memory formation (see above): whereas post-encoding noradrenergic stimulation enhanced both memory strength and memory accuracy in the long run, most likely by increasing long-term hippocampal involvement in memory, corticosterone led to strong but more generalized memories, presumably by enhancing neocortical storage (Roozendaal and Mirone, 2020). The finding that NA reinforces episodic-like accuracy is consistent with other findings indicating that posttraining NA administration into the BLA enhances the accuracy of the association of an object with its specific training context in an object-in-context recognition task (Barsegyan et al., 2014) and maintains long-term accuracy of the shock-context association on the inhibitory avoidance discrimination task (Atucha et al., 2017). The finding that corticosterone induces a generalized strengthening of memory is in agreement with previous evidence indicating that posttraining corticosterone administration also induced a generalization of fear memory and increased the freezing response to an innocuous auditory stimulus (Kaouane et al., 2012). Moreover, Dos Santos Corrêa et al. (2019) recently showed that a higher shock intensity during contextual fear conditioning was associated with an enhanced freezing response to a novel context, and that this generalization effect positively correlated with corticosterone levels during the post-learning consolidation period.

In sum, research over the past two decades showed that acute stress does not result in a global memory impairment—a view held by some decades ago—but rather that stress impairs some memory processes while enhancing others, critically dependent on the exact timing of learning and retention testing relative to the temporal profile of action of major stress mediators

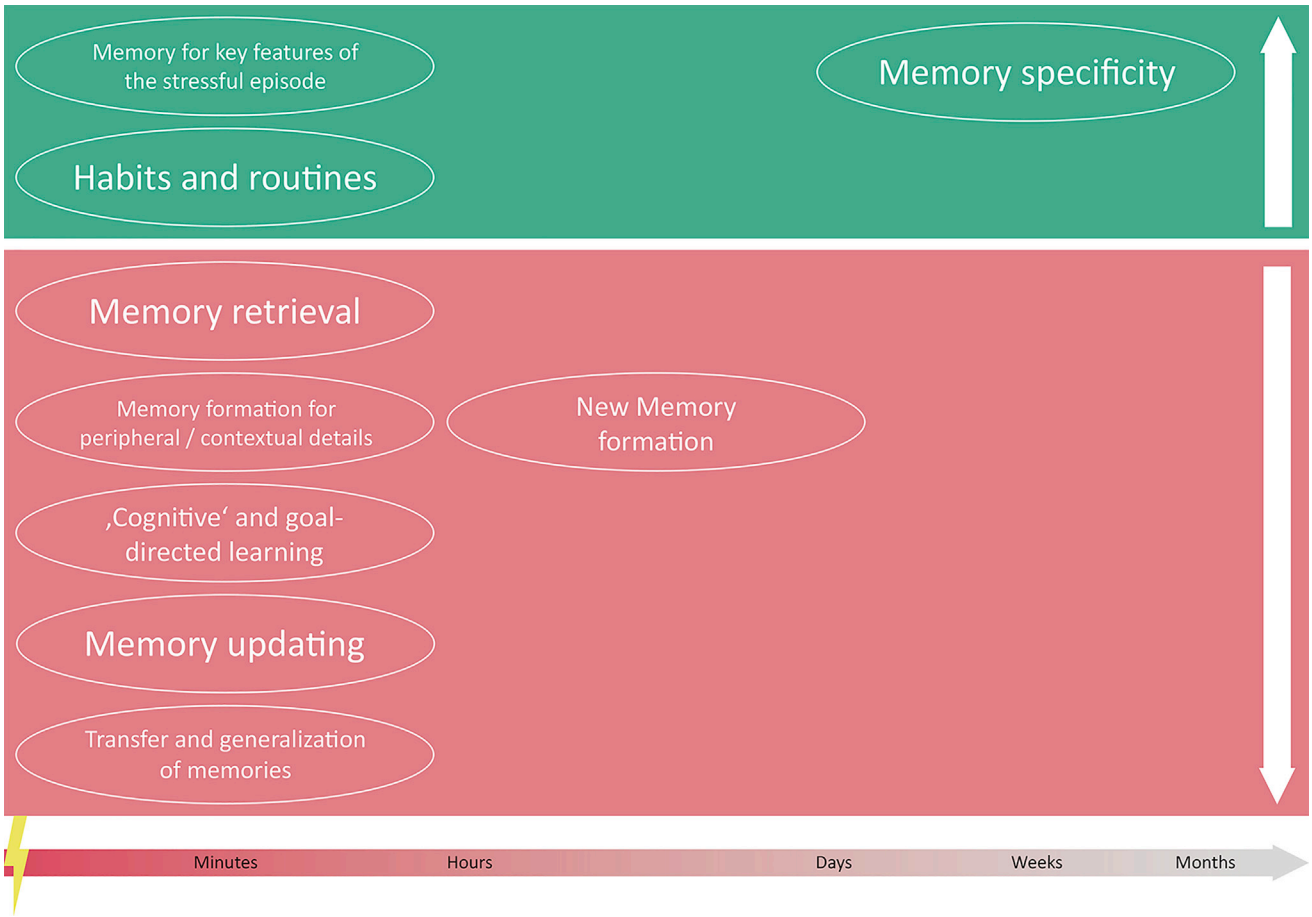


Figure 4. Memory changes under stress

Acute stress induces time-dependent changes in memory, enhancing some processes (green) while impairing others (red). These time-dependent changes in memory are thought to be directly linked to the temporal profiles of action of major stress mediators (see Figure 1). Memory for key features of the stressful event itself is typically enhanced. Further, stress may facilitate habitual forms of learning and memory. At the same time, stress can impair the formation and retrieval of stressor-unrelated information as well as memory flexibility, as reflected in reduced goal-directed learning, impaired memory updating and hampered transfer of memories to new situations. Both, the enhancing and impairing effects of stress are driven by rapidly acting catecholamines and corticosteroids, presumably in interaction with other mediators such as the endocannabinoid system (but also peptides and other monoamines). Delayed, genomic corticosteroid actions, however, may increase the threshold for encoding new information. This transient impairment in new memory formation might shield the consolidation of the stressful event from interference and thus contribute to the recently shown long-term specificity of memories for arousing events.

and the experimental paradigm (Figure 4). Beyond the consolidation and retrieval of hippocampal memory, stress has been shown to modulate non-hippocampal forms of memory as well as the balancing of multiple, functionally distinct memory systems. Most recent research further revealed that stress mediators may impair the flexible use and modification of memories but enhance the long-term specificity of memory (unless the situation is extremely stressful; Dos Santos Corrêa et al., 2019), with different stress hormones playing different roles in the latter. We assume that these various effects of stress on memory processes represent different shades of a common mechanism characterized by the time-dependent interplay of multiple stress mediators and associated shifts in neural network balance. The exact nature of the stress-induced changes in memory may further depend on the specific hormones that are released, influenced in part by the specific learning task but also individual characteristics.

TOWARD AN INTEGRATIVE FRAMEWORK OF MEMORY UNDER STRESS

The recent progress in our understanding of the stress-memory link at the cellular, neural network, and cognitive levels that we have discussed in the preceding sections allows us to propose an integrative framework of how stress shapes memory. This framework assumes that specific, time-dependent neural network shifts during and after stressful events represent an interface linking the orchestrated activity of multiple stress mediators at the molecular and cellular level within areas, with distinct—but presumably interdependent—stress effects on the flexibility and long-term dynamics of memories at the cognitive level (Figure 5). Closely related to these time-dependent effects of stressors are potentially distinct roles of catecholamines and corticosteroids both in the shift between (areas belonging to) neural networks (Hermans et al., 2011; Van

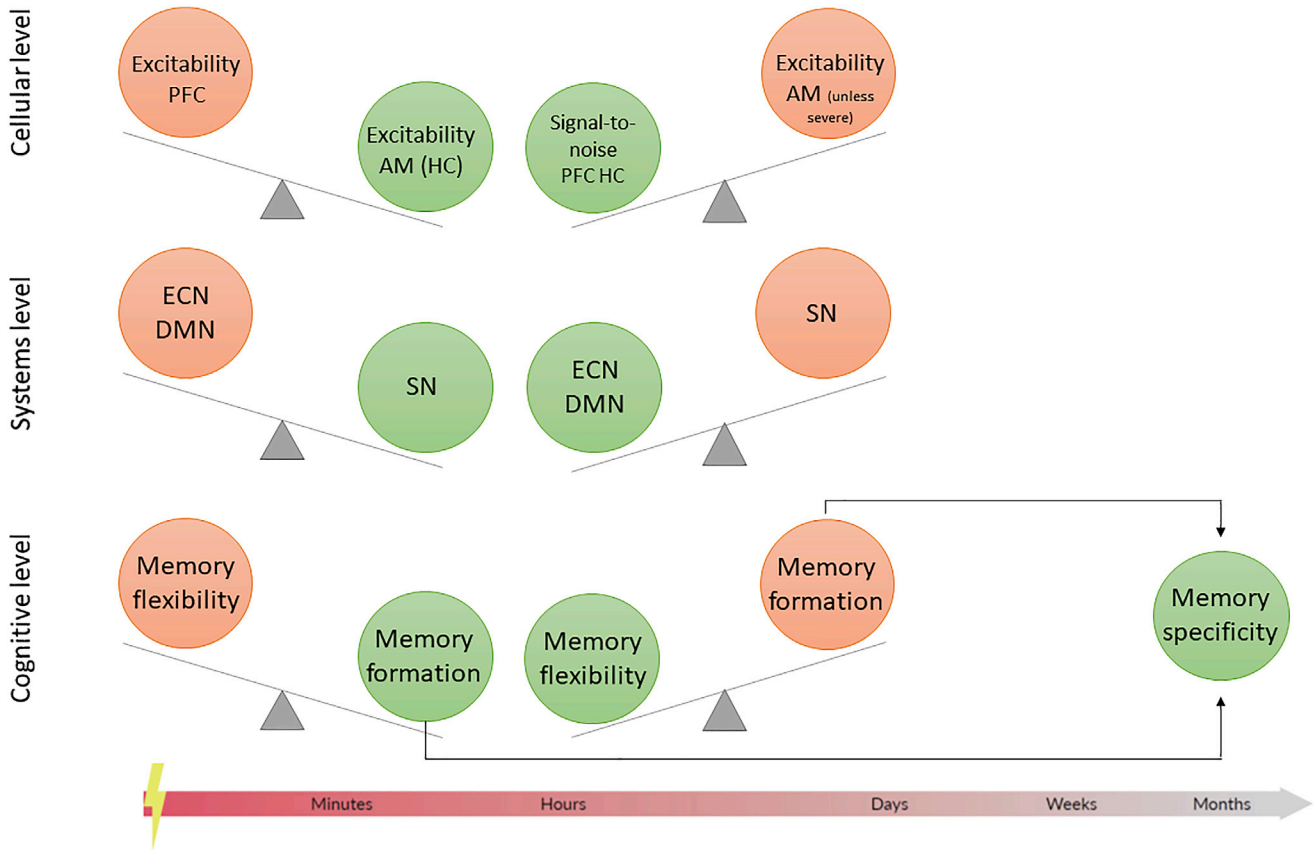


Figure 5. Integrative framework of how acute stress alters memory processes

Top: at the cellular level, rapid, non-genomic actions via MR in hippocampus (HC) and amygdala (AM) cells promote, directly or indirectly (e.g., through disinhibition), excitatory transmission. This is subsequently complemented by delayed, gene-mediated, and GR-dependent changes in cellular function that increase signal-to-noise ratio in higher brain areas, such as hippocampus and prefrontal cortex (PFC).

Middle: these time-dependent cellular changes, linked to the specific temporal profiles of action of major stress mediators (see Figure 1), trigger time-dependent reconfigurations of large-scale networks. During and shortly after a stressful event, when catecholaminergic and rapid corticosteroid actions prevail, there is a shift toward a salience network (SN), at the expense of the executive control network (ECN) and default-mode network (DMN). At later stages, when catecholamine effects have vanished and slow, genomic corticosteroid actions have developed, the network reconfiguration reverses.

Bottom: these network shifts translate directly into time-dependent changes in memory processes. The predominance of the salience network aids memory formation for the stressful event, at the expense of the flexibility of memory and other processes, such as working memory or memory retrieval. The delayed shift toward the ECN and DMN, transiently reduces memory formation but enhances mnemonic flexibility which might help to rationalize the stressful encounter. Both the initial enhancement of memory formation and the delayed impairment of memory formation for new information, which may shield the memory formation for the stressor itself, are assumed to contribute to the long-term specificity of memories for stressful or arousing events.

Stegeren et al., 2010) and in memory processes (Roozendaal and Mirone, 2020).

During a stressful event, the rapid release of catecholamines from brainstem nuclei is thought to have a circuit-breaking function (Corbetta et al., 2008). It induces an increase in neural excitability of regions constituting the SN, which sets the stage for a network reconfiguration (Sara and Bouret, 2012). Key to this neural reconfiguration under stress is the amygdala, which integrates the action of multiple stress mediators. Within the amygdala, non-genomic corticosteroid actions via near-membrane receptors amplify NA effects on neuronal activity (Karst and Joëls, 2016; McGaugh, 2015; Roozendaal et al., 2004, 2006). In addition, corticosteroids trigger the release of ECBs, which then bind to CB1 receptors on GABAergic interneurons to inhibit GABA release (Di et al., 2016). This, in turn, may disinhibit the release of NA from presynaptic sites and hence further increases neuronal activity in the amygdala (Atsak et al., 2015; Campolongo et al., 2009). It is well established that the amygdala can modulate memory processes in other brain areas such as the hippocampus or dorsal striatum (McGaugh, 2015). Beyond these modulatory influences on single brain areas, the amygdala has been shown to be critically implicated in orchestrating the shift from "cognitive" to "habit" memory systems under stress (Kim et al., 2001; Schwabe et al., 2013; Vogel et al., 2017), presumably governed by non-genomic corticosteroid actions via the MR and closely related to the large-scale neural network reconfiguration directly after stress from the ECN and DMN to the SN, specialized in processing emotionally arousing events (Hermans et al., 2011, 2014b). These small- and large-scale neural network changes, mainly driven by the rapid effects of multiple stress mediators on both excitatory and inhibitory neurons, form the basis

for the manifold changes in mnemonic processes that are observed during and shortly after stress. Specifically, the amygdala-induced modulation of hippocampal activity and plasticity—presumably paralleled by facilitating effects of rapid corticosteroid actions directly in the hippocampus (Wiegert et al., 2006)—results in the enhancement of memory formation for the stressful event itself (Kalbe et al., 2020; Sandi et al., 1997; Vogel and Schwabe, 2016). Notably, this memory enhancement is only observed for information directly relevant to the ongoing stressor, whereas the encoding of information that is present during the stressful episode but not directly relevant to stressor is even reduced (Kalbe et al., 2020; Schwabe and Wolf, 2010). The boost in memory formation for the stressful event itself may be driven by the shift toward the SN, which involves also sensory representation areas, known to interact with the hippocampus in forming long-lasting memories of stressful events (de Voogd, 2016). The large-scale shift toward the SN further promotes the predominance of habits and routines that are frequently observed under stress and rely on striatal areas belonging to the SN (Vogel et al., 2016; Wirz et al., 2018).

This bias toward the SN, however, may come at the cost of the ECN and DMN, including medial and lateral PFC. These prefrontal areas are crucial for flexible, goal-directed behavior (Balleine and O'Doherty, 2010). Moreover, memory retrieval processes, the transfer and generalization of memories, memory updating as well as learning against the background of existing knowledge, all of these processes are heavily dependent on the PFC and its crosstalk with MTL areas (Preston and Eichenbaum, 2013; Shin et al., 2019). Thus, both the impairment of memory retrieval and the reduced mnemonic flexibility under stress may be due to the large-scale neural reconfiguration at the expense of the ECN and DMN. At the same time, the downregulation of prefrontal and parietal storage sites may lay the ground for an altered systems consolidation process. Combined with specific synaptic changes within the hippocampus after increased noradrenergic stimulation, altered communication between the hippocampus and neocortical storage sites is thought to contribute to the subsequent increase in long-term specificity of and increased hippocampal involvement in remote memories (Atucha et al., 2017; Krenz et al., 2021). Thus, we assume that the transiently impaired flexibility of memory and its long-term specificity reflect two sides of the same coin, both being due the downregulation of the ECN and DMN during and shortly after a stressful experience. These network changes, in turn, are thought to be driven by rapid catecholamine and non-genomic corticosteroid actions.

Once the stressful event is over, catecholamine effects vanish rapidly and genomic corticosteroid actions develop within 1–2 h after stressor onset (Joëls and Baram, 2009). These delayed stress effects are assumed to reduce hippocampal and amygdalar neuroplasticity related to the encoding of new information (Diamond et al., 2007; Joëls et al., 2006), shifting the organism to a "memory storage mode" (Roozendaal, 2002; Schwabe et al., 2012) that further protects the consolidation of the stressful event from interference and allows the synaptic reorganization required for the long-term specificity of memory. Moreover, the large-scale network reconfiguration is assumed to be reversed in the late phase of the stress response, now favoring the DMN and ECN over the SN (Hermans et al., 2014b). Indeed, PFC functions appear to be enhanced when genomic corticosteroid actions are active (Henckens et al., 2011; Yuen et al., 2009), whereas emotional reactivity closely related to the SN is reduced (Putman et al., 2007). This delayed network reversal may thus not only help the organism to restore homeostasis but also to rationalize, contextualize, and store the stressful experience into long-term memory.

Importantly, the accumulating evidence suggesting that different stress mediators, in particular catecholamines and corticosteroids, may play distinct roles in neural network changes and long-term memory specificity (Hermans et al., 2014b; Roozendaal and Mirone, 2020; Van Stegeren et al., 2010) indicates that the specific effects of a stressful experience on memory depend on the specific endocrine stress response pattern, which may differ across individuals and types of stressors.

CLINICAL IMPLICATIONS

Given that several mental disorders are characterized by altered stress response patterns and that stress-induced changes in memory are thought to be a driving force in stress-related mental disorders, research on the impact of stress on memory comes with the hope that it will promote our understanding of these disorders and might ultimately lead to novel treatment approaches. Indeed, several interventions that build directly on basic research on the stress-memory link have been suggested. For instance, pharmacological treatments targeting corticosteroid or NA signaling were used to either facilitate the consolidation of therapeutic interventions or interfere with the retrieval of dysfunctional memories in phobia or PTSD (for a review see de Quervain et al., 2017), and more lately in addiction (Soravia et al., 2021). Beyond pharmacological treatments, cognitive interventions were recently introduced that aim at either contextualizing or intentionally controlling overly strong memories for highly stressful, traumatic events (Abed et al., 2020; Mary et al., 2020).

The recently discovered changes in memory under stress that we have discussed here may enhance our understanding of mental disorders such as PTSD. For instance, the long-term specificity of memory due to increased noradrenergic activity shortly after encoding (Atucha et al., 2017; Krenz et al., 2021) may contribute to the vividness and longevity of trauma memory. Furthermore, the transient decrease in memory flexibility may result in rather rigid memories (Wirz et al., 2018) that lack contextual details (Simon-Kutscher et al., 2019; van Ast et al., 2013). Such rigid memories could explain the overly strong emotional responding to single trauma-related cues (e.g., odors and tones) in PTSD patients and may complicate therapeutic interventions. There is further recent evidence that directly links an impairment of the flexible control of memory retrieval, as observed under acute stress (Quaedflieg et al., 2020), to PTSD symptoms (Catarino et al., 2015; Mary et al., 2020).

Beyond the enhanced understanding of the potential mechanisms contributing to stress-related mental disorders, several specific routes for intervention can be directly derived from the mechanistic framework that we propose here. First, in light of

the recently identified role of ECBs in stress effects on memory, potential pharmacological interventions targeting both corticosteroid and ECB signaling might be particularly promising (Neumeister et al., 2013), presumably in combination with exposure therapy. Second, as we have argued above, large-scale neural network changes may be the driving force in stress-induced changes in memory, and hence, we assume that stress-related mental disorders originate from changes at the network level. Indeed, there is accumulating evidence suggesting such network changes in disorders such as PTSD (Fonzo et al., 2021), which might derive from a disbalance in stress response patterns. Here, recent evidence is of interest showing that transcranial magnetic stimulation (TMS) over defined cortical sites can be used to modify entire networks of interconnected brain areas (Philip et al., 2018). Given the assumed importance of the quick shift from the ECN and DMN to the SN early on in stress-induced changes of memory, (repeated) TMS over cortical nodes of the ECN or DMN may be employed to prevent a prolonged or dysfunctional network reconfiguration under stress. Moreover, deficits in memory retrieval or flexibility under stress might be attenuated by rebalancing cortical excitation and inhibition, recently shown to be altered under acute stress (Han et al., 2020), via transcranial direct current stimulation over cortical sites of the ECN or DMN (Barron et al., 2016; Koolschijn et al., 2019). Finally, the identified mechanisms could help to identify relevant (epi)genetic (Vukojevic et al., 2020) or neural (van Leeuwen et al., 2019) risk markers, e.g., related to ECB signaling, expression of stress hormone receptors or large-scale network balance, for individuals who are particularly vulnerable to maladaptive stress effects on memory. The individual vulnerability to stress-related disorders may be linked to different stages of memory (formation versus retrieval) and to specific phases of the stress response (rapid versus delayed). Balancing the different stress response phases to avoid either overshooting or failing memory formation for the stressful event appears to be crucial to prevent aberrant stress effects on memory and ultimately protect mental health.

CONCLUSIONS AND FUTURE DIRECTIONS

We have provided an inevitably selective review of recent advances in our understanding of the mechanisms through which stressful events shape memory. Recent evidence indicates an interaction between multiple stress mediators, in which each of these mediators appears to play a distinctive role, with complementary or sometimes even opposite effects of major stress mediators, such as NA and corticosteroids, depending on the time after stress and the receptors involved. It is further becoming increasingly clear that stress effects on memory cannot be understood at the level of isolated cells or even brain areas, such as the hippocampus or the amygdala, despite the fact that these have been useful for a guiding theoretical framework, but that these effects rely on complete microcircuits and shifts in large-scale neural networks. These network shifts translate into behavioral and cognitive changes that are much more complex and longer-lasting than previously thought. Based on these advances, we propose an integrative framework that links the orchestrated action of multiple stress mediators at the cellular level with time-dependent large-scale network shifts at the systems level and specific changes at the cognitive level, which restrict the possibilities to flexibly update and readjust memories but may pave the way for long-lasting enhancements of memory specificity.

The progress in research on stress and memory that we have seen over the past decades was at least partly linked to emerging technical advances. For instance, optogenetics or genetic modifications in rodents are now providing tools to target the mechanisms underlying stress-induced changes in memory with unprecedented precision. In humans, the investigation of large-scale neural networks became only possible with the advent of whole-brain fMRI. However, research on stress and memory has recently only begun to leverage the potential associated with multivariate analyses of neuroimaging data, machine learning, or cognitive modeling to elucidate the neural and cognitive mechanisms involved in memory under stress (Gagnon et al., 2019; Lenow et al., 2017; Meier et al., 2021). These and the technical or methodological advances to come may allow us tackling the fundamental questions related to the stress-memory link that remained unanswered so far.

One key question for future research is how the different stress response waves, such as rapid, non-genomic, and slow genomic corticosteroid actions, relate to one another, not only at the cellular level but also at the integrated network level; how the waves interact and which prevails if they overlap. Closely related, it is not well understood exactly how the interaction of multiple stress mediators results in a temporally dynamic reconfiguration of large-scale networks. How can ECBs regulate stress-induced network shifts? Further, if the amygdala, as proposed here, plays a critical role in this configuration, how does this process work? And how can the amygdala operate the switch between networks depending on the prevailing stress response mode? In general, while many studies focused on the effects of stress around encoding or retrieval on subsequent memory, less is known about the delayed effects of stress on memory formation or retrieval and its neural basis, in particular in humans (but see Henckens et al., 2010, 2011). Moreover, although recent findings show that stress hormones can bidirectionally modulate systems consolidation processes and influence memory specificity weeks to months later (Atucha et al., 2017; Krenz et al., 2021; Roozendaal and Mirone, 2020), which cellular and network mechanisms enable such long-lasting effects remains completely unknown. Finally, a major challenge for future research relates to how existing ideas about the role of stress and memory in the development of mental disorders now based largely on findings in healthy humans can be put to test in specific patient populations and be ultimately translated into (personalized) interventions for disorders characterized by maladaptive changes in memory under stress.

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AUTHOR CONTRIBUTIONS

All authors contributed to the conceptualization, writing, and editing of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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