Review

Biological Psychiatry

Memory Under Stress: From Adaptation to Disorder

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ABSTRACT

Stressful events are ubiquitous in everyday life. Exposure to these stressors initiates the temporally orchestrated release of a multitude of hormones, peptides, and neurotransmitters that target brain areas that have been critically implicated in learning and memory. This review summarizes recent insights on the profound impact of stress on 4 fundamental processes of memory: memory formation, memory contextualization, memory retrieval, and memory flexibility. Stress mediators instigate dynamic alterations in these processes, thereby facilitating efficient responding under stress and the creation of a decontextualized memory representation that can effectively aid coping with novel future threats. While they are generally adaptive, the same stress-related changes may contribute to the rigid behaviors, uncontrollable intrusions, and generalized fear responding seen in anxiety disorders and posttraumatic stress disorder. Drawing on recent discoveries in cognitive neuroscience and psychiatry, this review discusses how stress-induced alterations in memory processes can simultaneously foster adaptation to stressors and fuel psychopathology. The transition from adaptive to maladaptive changes in the impact of stress on memory hinges on the nuanced interplay of stressor characteristics and individual predispositions. Thus, taking individual differences in the cognitive response to stressors into account is essential for any successful treatment of stress-related mental disorders.

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Imagine being attacked by a stranger in a park. You can feel your heart beating and your breathing accelerating. These immediate bodily responses are driven by rapid actions of adrenaline and noradrenaline. In addition to these, numerous other hormones, peptides, and neurotransmitters are released during an acute stressor (1), including glucocorticoids that provide the body with energy in times of stress (2). Together, these stress mediators enable a fight-or-flight response and are thus essential for adapting to stressful events. Importantly, beyond their immediate bodily effects, these stress mediators may facilitate adaptation to stressful events in a less overt manner—by shaping cognition. The effects of stress on learning and memory processes are particularly prominent (3–5). By modulating these cognitive functions, stress mediators enhance the ability to cope with ongoing stressors, such as an attack in the park, while simultaneously preparing the organism for similar encounters in the future (6,7).

While generally highly adaptive, the effects of stress on memory, much like exaggerated bodily stress responses, can become maladaptive and contribute to the development of mental disorders. Stress is a well-established factor in various mental disorders, including posttraumatic stress disorder (PTSD) and anxiety disorders, in which maladaptive memory processes are prominent. Stress-induced alterations in memory processes are considered to be significant contributors to the onset and progression of these disorders (8,9). In particular, aberrant memory of the trauma is the hallmark feature of PTSD and has been linked to other diagnostic criteria such as avoidance and hyperarousal.

In this review, I discuss how stress-induced changes in memory facilitate adaptation to an ongoing stressor but can also fuel stress-related psychopathologies. In the first section, a concise summary of stress effects on memory is provided. The focus is particularly on memory processes that may play a crucial role in adapting to stressful events—and in maladaptive changes that contribute to psychopathology. The subsequent sections of this review explore how stress-induced alterations in memory can contribute to adaptation and, conversely, may be implicated in the development of mental disorders. The final section addresses factors that influence the transition from adaptive to maladaptive effects of stress on memory.

HOW STRESS SHAPES LEARNING AND MEMORY

The precise synchrony of increased noradrenergic activity and rapid, nongenomic glucocorticoid actions during an acute stressor triggers a shift from default mode and executive control networks, including the prefrontal cortex (PFC), to a salience network that encompasses the amygdala (10). The salience network prioritizes the processing of emotionally salient information, often at the expense of contextual details. Genomic glucocorticoid actions, which manifest hours after stressor onset, may subsequently reverse these effects and support the restoration of homeostasis (10) (Figure 1). Consequently, the impact of stress on memory is critically time

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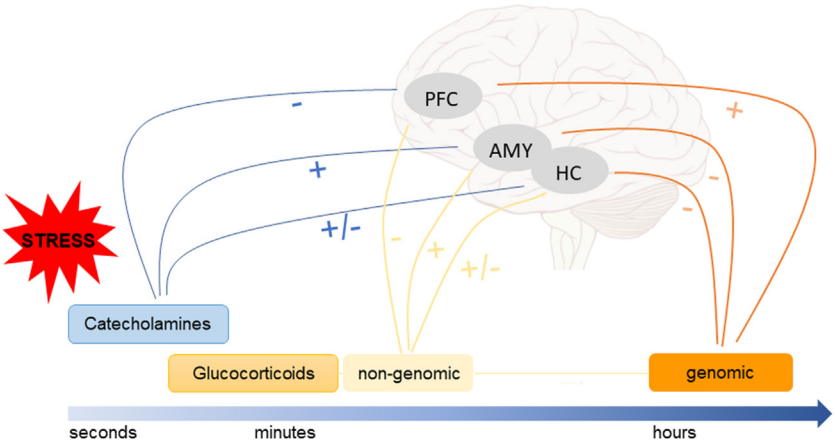

Figure 1. Effects of stress mediators on the functioning of brain structures critical for memory. Within (milli)seconds after stressor exposure, catecholamines are released from the adrenal medulla and specific nuclei in the brain. The catecholamine levels induced by intense stressors are thought to impair prefrontal cortex (PFC) functioning and enhance amygdala (AMY) functioning. For the hippocampus (HC), the effects are mixed. While some hippocampal functions (e.g., memory formation for the stressor) are enhanced, others are impaired (e.g., context processing or memory integration). Glucocorticoids are released from the adrenal cortex with a delay of several minutes. These glucocorticoids can exert rapid, nongenomic effects that are mediated via near-membrane receptors and slow, genomic effects via intracellular receptors. Rapid glucocorticoid effects appear to amplify catecholamine effects, especially if catecholamine and glucocorticoid actions are well synchronized in time and space. In contrast, slow, genomic glucocorticoids are assumed to exert opposite effects, leading to increased PFC functioning but reduced AMY and HC processing, presumably to normalize mnemonic functioning after a stressor (or shield the memory formation for the stressor from competing memory processes).

dependent, closely tied to the temporal profile of action of stress mediators (3,5,6), and contingent on the specific memory process. Here, the focus will be on the impact of acute stress on 4 key domains of memory: memory formation, contextualization, retrieval, and flexibility (for an overview of relevant studies, also see Table S1).

Enhanced Memory Formation

Stressful events, such as an attack by a stranger, are much better remembered than mundane events (11–13). This memory enhancement is due to enhanced encoding and attentional processes, which are driven by noradrenergic arousal-induced alertness and activation of the amygdala (14). Moreover, stress enhances memory consolidation (3,5,15). Specifically, noradrenergic arousal and glucocorticoids interact in the basolateral amygdala, which then modulates memory storage in other brain areas, such as the hippocampus (16,17). Consistent with this view, increased amygdala-hippocampal connectivity after an aversive event predicts subsequent memory of the event (18,19). Furthermore, recent research showed that the subsequent memory of a stressful event was linked to the representation of specific event features in the basolateral amygdala (20). Another key player in memory formation for stressful events is the locus coeruleus, the main source of noradrenaline in the brain. Locus coeruleus activity strengthens memory formation of prioritized information under arousal (21) and tracks the temporal organization of memories (22), the segmentation of which facilitates subsequent remembering (23). Interestingly, noradrenergic arousal may also alter the long-term dynamics of memory. More specifically, over time, memories can become independent from the hippocampus and more reliant on neocortical areas (24), and this change is accompanied by a time-dependent decrease in memory specificity (25). Postencoding noradrenergic arousal can reverse this process, rendering memories even more hippocampus dependent and specific over time (26,27). Importantly, while stress enhances memory formation, this memory enhancement is specific to events encoded around the time of the stressor. Sometime after the stressor, when noradrenergic arousal and glucocorticoids are desynchronized, stress impairs memory formation and hippocampal neuroplasticity (28–30).

Memory Decontextualization

Even though stressful events are often vividly remembered, this memory enhancement does not extend uniformly across all elements of a stressful episode. While memory for key features of a stressor is typically enhanced, memory for contextual details of a stressor can be impaired. For example, during an attack by a stranger, one may memorize specific features of the assailant, such as their voice, but not necessarily the details of the environment of the incident. Consequentially, models of memory formation under stress assume that arousal enhances item memory but impairs context memory (31,32). Consistent with this view, acute stress has been shown to facilitate cue-dependent fear learning at the expense of contextual fear learning (33,34). Moreover, while stress boosts the memory of the individual elements of an episode, it can hinder the memory of the links between these elements, which results in fragmented memories (35). The reduced contextual embedding of memories encoded under stress has been associated with nongenomic glucocorticoid actions (34,36). Rodent data revealed that these effects may be attributed to increased amygdala activity, promoting enhanced cue memory, and reduced hippocampal activity, leading to impaired memory contextualization (34). A key role of the hippocampus in glucocorticoid-induced memory decontextualization is supported by recent evidence linking this decontextualization to dentate gyrus granule cells (37). Importantly, while rapid glucocorticoid actions result in a decontextualization of events encoded under stress, delayed genomic glucocorticoid actions may reverse these effects (36,38).

Impaired Memory Retrieval

Stress can impair memory retrieval (13,39). Similar to the stress-induced enhancement of memory consolidation, this

retrieval impairment after stress requires concurrent noradrenergic and glucocorticoid activity in the basolateral amygdala, which then modulates retrieval processes in areas such as the hippocampus (40,41). In the hippocampus, the stress-induced retrieval deficit has been linked to reduced long-term depression (42). Recent neuroimaging findings revealed that stress impaired the capacity of the hippocampus to reinstate memory representations in neocortical representation sites (43). Moreover, acute stress may alter memory retrieval by shifting recall from hippocampal to dorsal striatal control (44). Interestingly, initial evidence suggests that stress not only impairs recall performance but also affects the capacity to voluntarily control (i.e., suppress or activate) the retrieval of specific information, linked to disruptive effects of glucocorticoids on the crosstalk between the PFC and hippocampus (45).

Reduced Memory Flexibility

Stress induces a shift from flexible cognitive memory systems, such as the hippocampus or PFC, to more rigid habitual memory systems, such as the dorsal striatum. This shift from cognitive to habit memory has been demonstrated across various memory domains (33,46–51). An increased reliance on single cues under stress at the expense of relational processing is common to these domains. For example, the stress experienced during an attack by a stranger may result in strong memory of individual elements of the incident (e.g., sounds or odors) but impaired memory of how the adverse event unfolded. The stress-induced bias toward habit memory is mediated by glucocorticoids acting rapidly via mineralocorticoid receptors (7,52,53), presumably in interaction with noradrenaline (49,54,55), and orchestrated by the amygdala (49,53,54). Closely tied to the prevalence of habit memory, stress disrupts memory flexibility. This diminished mnemonic flexibility under stress is evident in more rigid navigational behavior (56), a reduced ability to integrate information from separate episodes (57,58), or an impaired capacity to incorporate new information into existing knowledge structures (59).

THE BRIGHT SIDE OF IT: HOW STRESS RESPONSE SYSTEMS TUNE MEMORY TOWARD ADAPTATION

The various effects of stress on memory exhibit remarkable consistency across species (3,60). Their preservation throughout evolution suggests that these stress effects serve an adaptive purpose by aiding in coping with ongoing stressors or similar future events.

Enhanced Memory Formation

Enhanced memory for key features of stressful events is, at least partially, attributable to the arousal-driven recruitment of the salience network (10) and subsequent heightened attention to these stimuli (61). Thus, memory enhancement for stressful events can be considered a byproduct of the increased attentional processing of the most salient stimuli in a stressful situation. Increased processing of these stimuli, such as the assailant during an attack, is essential for survival during threatening encounters. Memory itself supports adaptive behavior by allowing past experiences to guide future actions (62). Specifically, the enhanced memory for stressful events, which is driven by the interaction of catecholamines and glucocorticoids, serves the purpose of preparing for similar stressors in the future. Notably, the fact that there is no global memory enhancement for a stressor and that memory can even be severely impaired for stressor-irrelevant material encoded under stress (63) suggests a pruning of the memory of a stressor (i.e., reducing the memory strength for stressor-irrelevant information), which may facilitate efficient preparation for similar future events.

Memory Decontextualization

This pruning of memory formation under stress can also contribute to reduced memory for contextual details of a stressful event. The resulting decontextualized memories may be essential to transfer these memories to situations that have never been encountered before (64). To achieve this transfer, abstract conceptual knowledge that goes beyond the specific experience and allows multidimensional similarity judgments is important (65). Decontextualized memories reduce complexity because they enable individuals to focus only on the features that are most relevant during a threatening encounter (66). Similarity judgments based on decontextualized memories further promote generalization to novel stimuli and hence the mobilization of defensive behaviors to potentially threatening events without the need for direct aversive experiences with these events, thereby reducing potential harm to the organism (64).

Impaired Memory Retrieval

The retrieval impairment often observed under stress may reduce distraction by facilitating focused attention on the ongoing stressor. While reduced retrieval performance shortly after stressor exposure is commonly interpreted as a specific retrieval impairment, it could also result from competition between retrieval processes and memory formation processes for the stressful event, with the latter being given priority (67). This raises an intriguing question: Why should stressful events be preferentially stored in memory if they cannot be readily accessed during future stressors? One argument posits that strong memories aid survival by enabling the prevention of stressor exposure while in a state of safety (64); therefore, their value may not necessarily depend on their immediate accessibility under stress. Alternatively, the accessibility of information under stress may hinge on the relevance of the information to the stressor. For example, recalling your last birthday while under attack in a park would be distracting, but remembering the pepper spray in your handbag would be highly beneficial. There is initial evidence that stress-induced arousal enhances the retrieval of stressor-related information (68), consistent with previous reports of the facilitating effects of noradrenaline on memory retrieval (69). However, these beneficial effects on memory retrieval were reversed when stress-induced glucocorticoids rose to peak levels (68), thus corroborating the impairing effects of glucocorticoids on retrieval (39). Consequently, the stress-induced retrieval impairment appears to be specific to stressor-unrelated material that could distract from the ongoing stressor, and it is most pronounced when the organism stores the stressful event in memory for future use.

Reduced Memory Flexibility

When under stress, individuals operate on autopilot, relying on well-established habits and routines (70). These habits, initially formed due to their association with desirable outcomes, carry the highest probability of yielding beneficial outcomes and facilitating efficient responding. The engagement of habits under stress serves to conserve cognitive resources for coping with the stressor. Moreover, habits primarily involve striatal areas (71), which play a lesser role in memory formation for stressors (3,16), thereby minimizing the competition between behavioral responding and memory storage. The adaptive significance of habitual responding under stress has been exemplified in studies that have shown that the shift toward striatal habit memory rescued performance under stress (52,53).

THE DARK SIDE OF IT: HOW STRESS-INDUCED CHANGES IN MEMORY MAY CONTRIBUTE TO PSYCHOPATHOLOGY

While specific alterations in memory under stress may facilitate coping with stressful events, these same changes can become maladaptive and features of stress-related psychopathologies.

Enhanced Memory Formation

Overly strong memory of highly stressful events is the hallmark feature of PTSD (72). Beyond PTSD, enhanced memory for arousing events is also prominent in mood and anxiety disorders (73,74). The painful strength of emotional memory in these disorders may be driven by aberrances of the well-known mechanisms that underlie memory formation under stress. Specifically, accumulating evidence suggests an involvement of the salience network, which prioritizes the encoding of emotionally salient information, in these disorders (75,76). The findings of a recent longitudinal study that demonstrated that stress-induced changes in the coupling of the salience network predicted the development of PTSD after trauma exposure are particularly intriguing (77). Similarly, salience network activity can predict subsequent depressive symptoms (78). Apart from changes in the recruitment of the salience network, it has been proposed that aberrant emotional memory enhancement in these stress-related disorders may be linked to an overconsolidation of memory for emotional (traumatic) events, which is driven by the excessive release of stress mediators and amygdala hyperactivity (9). Interestingly, while excessive catecholamine levels have been linked to trauma memory, PTSD is not characterized by increased glucocorticoid concentrations (79). Instead, blunted glucocorticoid levels appear to be associated with PTSD risk, and it has been suggested that glucocorticoid administration after trauma reduces the risk of PTSD (80,81) [but see (82)]. It is tempting to speculate that this seemingly paradoxical pattern points to a role of delayed genomic glucocorticoid actions that serve to rationalize or contextualize stressful events (36,38).

Memory Decontextualization

While memory of the traumatic event is typically extremely vivid in PTSD, memory of the context of this event is often weak (83). This decontextualization is both a predictor of PTSD (84) and a factor that aggravates the disorder (85). Moreover, it has been suggested that decontextualized memory contributes to the debilitating nature of trauma memory; when disconnected from its spatiotemporal context, the traumatic memory can be reactivated by any trauma-related cue, even in contexts that are clearly distinct from the trauma's context, which leads to the uncontrollable intrusions characteristic for PTSD (83). Beyond PTSD, decontextualized memories of threatening events can contribute to generalized fear responding in anxiety disorders, resulting in exaggerated fear or avoidance behavior even in response to nonthreatening stimuli in safe contexts (86,87). For example, after an attack by an assailant wearing a red cap, exposure to a reddish hat may result in strong fear responses, even in safe environments, such as a clothing store. This overgeneralization of fear memories has been linked to stress and glucocorticoids that affect hippocampal representations of fear (37,88,89) and to dysfunctional input of the hippocampus to the amygdala (90,91).

Impaired Memory Retrieval

While overgeneralized fear responding may result from reduced integration of contextual details into the memory trace, it could also result from stress interfering with the ability to recall specific context information (92,93), thereby hindering the distinction between threatening and safe environments. Furthermore, stress-induced retrieval deficits may compromise the retrieval of information about effective coping strategies or past experiences of successfully managing stressful events (e.g., repelling an assailant), thus limiting the individual's ability to effectively deal with challenging situations. Similarly, stress has been shown to reduce individuals' ability to actively control memory retrieval processes (45), and a breakdown of this PFC-dependent retrieval control capacity has been linked to PTSD (94,95).

Reduced Memory Flexibility

An overreliance on habit memory while under stress may contribute to the disintegrated, fragmented memory of PTSD (83,96). Such memories are difficult to integrate into autobiographical memory, which is typical under the control of hippocampal cognitive memory (97). Furthermore, the predominance of habit memory under extreme stress has been associated with excessive stimulus-response learning mechanisms, laying the basis for the strong emotional response to single trauma-related cues commonly observed in PTSD. Beyond PTSD, aberrant habitual stimulus-response memory is also prominent in anxiety disorders, obsessive-compulsive disorder, and addiction (98–100). Habit memory is characterized by automatic, routinized behaviors (101). In the context of stress-related disorders, such inflexible habits may hinder adaptive coping, preventing individuals from effectively adjusting their responses to changing circumstances. Furthermore, stress may drive individuals to adopt habits that provide a temporary escape from distress but are ultimately harmful (102).

ON THE TRANSITION FROM ADAPTATION TO DISORDER

How can the generally adaptive mnemonic responses to stress become maladaptive? The answer to this fundamental

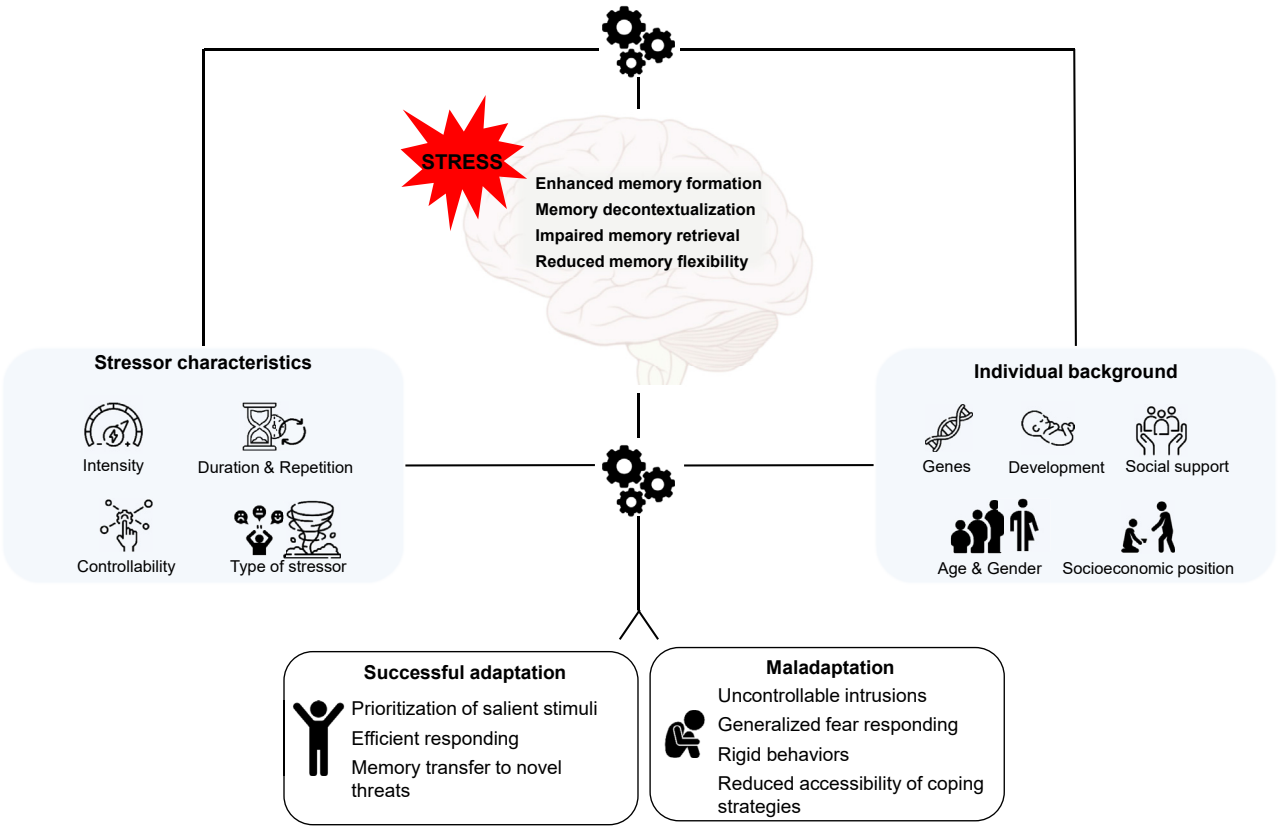

Figure 2. Model of (mal)adaptive changes in memory under stress. Exposure to a stressor results in enhanced memory formation for central features of the stressor, memory decontextualization, impaired memory retrieval, and diminished memory flexibility. These stress-induced changes in memory can aid adaptation to ongoing and future stressors but can also fuel psychopathology. The background of the individual and stressor characteristics (and their interaction) have a major impact on the stress response and its adaptive or maladaptive influence on memory. (Icons designed by Freepik, Leremy, Design Circle, and Parcival 1997 from flaticon.com.)

question in the field of stress and memory likely involves characteristics of the stressor and the background of the individual, as well as the interaction between the two (Figure 2), which is reflected for example in stressor appraisal or coping style, which are known to modulate memory (103,104). Taking these factors into account is essential for effective intervention strategies and personalized psychiatry approaches [for more extensive discussion of some of these factors, see (105–109)].

Stressor Characteristics

Intensity. The impact of stress on memory is intricately linked to the (subjective) intensity of the stressor (11), and instances of PTSD-like memory aberrations are more prevalent following exposure to extreme stressors (34). Notably, the intensity-dependent impact of stress on memory is mirrored in the dose-dependent effects of major stress mediators, with higher dosages yielding more pronounced changes in memory (17,110,111).

Duration and Accumulation. It has been documented that repeated and chronic stress yield notable memory dysfunctions, including excessively strong cue-related fear memories and impairment in spatial memory (105,112,113). Observed memory impairments following chronic stress are attributed to a dysregulation of major stress response systems and concomitant alterations in crucial brain regions such as the amygdala, PFC, and hippocampus (112,114,115).

Type of Stressor. Physiological stress responses are critically dependent on the type of stressor (116,117). Initial evidence suggests that stressor type may also modulate stress effects on memory, with psychosocial stressors leading to more pronounced memory alterations than mere physical stressors (13). Moreover, traumas that involve negative social interactions are more likely to result in later PTSD than, for example, natural disasters (118).

Controllability and Predictability. Compared with controllable stress, uncontrollable stress exerts particularly detrimental effects on memory and neuroplasticity (119,120). Recent findings have also shown that the subjective perception of uncontrollability, rather than the objective (un)controllability of adverse events, plays a pivotal role in driving the adverse impact of stress on memory processes (121). In close association with stressor uncontrollability, the unpredictability of stressors appears to be a key factor that influences both

physiological stress responses and subsequent effects on memory (122,123).

Individual Characteristics

Gender and Age. The prevalence of stress-related mental disorders is significantly higher in women than in men (124), which may be due to gender-related inequalities, a heightened exposure of women to domestic violence, or the potential influence of sex hormones (124–126). Arousal mechanisms and the neurocircuitry underlying emotional memory also exhibit gender differences (126), which may have implications for gender-specific influences of stress on learning and memory (93,113). In addition to gender, age has emerged as a potential risk factor for the detrimental effects of stress on memory. The brain is particularly susceptible to the impact of stressors during critical developmental periods, such as adolescence and old age, which coincide with the onset of psychopathologies (105). Importantly, interactions between gender and age may further modulate these effects. For example, women display heightened sensitivity to stress and its impact on cognition during periods of hormonal change, such as puberty or menopause (127).

Genetic Background. Physiological stress responses and stress effects on memory are at least partially genetically determined. For example, genetic variants that code receptors for glucocorticoids or noradrenaline have been shown to modulate memory formation for arousing events or stress-induced bias toward habit memory (49,128–130). Moreover, these variants have been linked to PTSD risk in trauma survivors (130). Intriguingly, recent findings indicate that a gene related to the glucocorticoid receptor is also associated with the success of PTSD therapy (131).

Early-Life Experiences. Early-life stress has a profound impact on brain development and emotional memory processes later in life. For example, stress levels shortly after birth, or even prenatally, have been linked to altered fear learning, reduced memory flexibility, and decreased hippocampal neuroplasticity during adulthood (132–135). At the same time, early-life stress has been linked to psychopathology in adulthood, including anxiety disorders and PTSD (136,137).

Brain Structure. Both genetic background and early-life experiences have a significant impact on brain maturation and structure. In the context of stress-related mental disorders, there has been particular focus on the hippocampus, which is not only a key structure for memory but also a main target of stress mediators and is critically involved in the regulation of stress response systems (1). Longitudinal studies and studies of monozygotic twins suggest that smaller hippocampi, commonly observed in PTSD (138), constitute a risk factor for rather than a mere consequence of PTSD (139,140).

Socioeconomic Position. Accumulating evidence has demonstrated an important link between cognitive functions and stress responses and individuals' socioeconomic position. For example, lower parental education has been associated with lower hippocampal volume in children, which was mediated by hair cortisol as a proxy for chronic stress levels (141). Furthermore, blunted cortisol reactivity, another indicator of chronic stress, was linked to poorer memory performance (142) and increased amygdala reactivity to emotional stimuli in children from low-income families (143). These socioeconomic position-related changes in stress and cognition may contribute to the higher prevalence of stress-related mental disorders in individuals with a low socioeconomic position (144).

Social Support. Social support, or its absence, plays a crucial role in individuals' resilience to adverse events; whereas social support can buffer stress responses (145), social isolation acts as a constant stressor (112). Recent research revealed that the presence of a friend after a traumatic film can mitigate aberrant memory formation, as evidenced by a reduction in intrusive memories (146). Similarly, receiving social support in the aftermath of a trauma has been associated with a decreased risk of developing stress-related mental disorders (118).

CONCLUSIONS

Stress can influence memory in various ways, including enhancing memory formation for central features of the stressor while reducing memory for its context, impairing memory retrieval, and diminishing memory flexibility. These changes facilitate efficient responses to the stressor and create a robust memory representation that can be effectively generalized to novel threats. However, when stressors are extreme or frequently repeated, without a sense of control, they may lead to maladaptive memory changes, particularly in individuals with genetic or developmental vulnerabilities and insufficient social support.

Research on the impact of stress on memory holds promise for the development of new approaches to treating or preventing stress-related psychopathologies. Pharmacological interventions that target glucocorticoid or noradrenaline signaling pathways have been explored to modify dysfunctional memory processes (8). More recently, new approaches have been suggested based on insights into the neural and cognitive mechanisms that underlie stress effects on memory. For example, mice were re-exposed once to the trauma context, which promoted a recontextualization of memory so as to attenuate PTSD-like memory (147). These findings may be translated into virtual or in sensu recontextualization approaches in patients with PTSD. In humans, anodal stimulation of the PFC has been shown to prevent stress-induced memory deficits (148). Furthermore, the predictability of significant events has been manipulated to counteract the overly strong memory formation for stressful events (149) and to make therapeutic interventions more effective (150). The efficacy of these pharmacological and behavioral strategies may depend on the nature of the stressor and the individual's background. Understanding the mechanisms involved in the interindividual variability in stress effects on memory is essential for developing personalized strategies to address the maladaptive alterations that occur along with the generally adaptive changes in learning and memory under stress.

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