Effects of Stress on Learning and Memory

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Abstract

Stress activates the hypothalamus-pituitary-adrenal axis, which causes the release of glucocorticoids, a class of adrenal steroid hormones. Stress also activates the sympathetic nervous system and thereby, the release of the transmitters adrenaline and noradrenaline. Stress has a memory-modulatory effect in humans as well as in animals.

In humans, the hippocampus, prefrontal cortex, and amygdala are rich in cortisol receptors. Acute and tolerable stress may increase memory performance, while excessive levels and chronic stress may have negative effects, thereby mimicking the pattern in animals. Stress in humans seems to have different effects on the various stages of memory (the memory process: encoding, consolidation, and retrieval) and can be enhanced by emotional arousal.

Animals learn to associate events in their environment. Studies of the effects of manipulation of corticosterone levels in animals have helped to disentangle the influences of stress on memory and learning, and indicated that low levels enhance spatial learning, whereas higher levels impair performance.

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EFFECTS OF STRESS ON LEARNING AND MEMORY IN HUMANS

Introduction

Etymologically, the term stress originates in the Latin word strictus, signifying something that narrows or a tightening. It has the meaning of a “force, pressure (or) strain” exerting psychological or physiological pressure upon the organism. In current scientific terminology, the word stressor is used to designate the stimuli that puts strain on the organism. Stressors may be either exteroceptive, that is represent external conditions that potentially evoke aversive reactions in the organism, such as extreme noise, timekeeping, or traumatic situations, or interoceptive, that is represent real or imaginary processes going on inside the body. A stressed state is experienced when...
the organism perceives that the demands of a situation exceed its resources to cope with it. Whether a situation is perceived as stressful or not depends on how the individual subjectively interprets the potentially stressful stimuli. To evaluate the situation and take a stand on the ability to cope with it, the individual mostly intuitively makes a cognitive appraisal. “A cognitive appraisal is an evaluation of the potential significance of a situation, along with one’s ability to control it.”

Psychologically, stress is associated with perceptions of “novelty”, “unpredictability”, “lack of control”, and “social-evaluative judgment”, as, for example, during public speeches, which are highly demanding situations. All these dimensions of perceived stress have been closely associated with activation of the hypothalamus-pituitary-adrenal (HPA) axis, further described below. If the situation is perceived as positive, the stimuli may be conceived as a challenge, stimulate efforts, and possibly ameliorate performance. On the contrary, if stimuli are deemed as negative, the situation is understood as potentially harmful, efforts will be disturbed or decrease and, as a consequence, performance may be lowered. The same pattern applies for fight-or-flight reactions, also named acute stress responses, which involve the sympathetic limb of the autonomous nervous system. Flight or flight is determined by central brain structures starting with the sensory cortex, thalamus, hypothalamus, amygdala, locus coerulceus and other brain stem nuclei, the limbic, and neocortex. The sympathetic-adrenal-medullary (SAM) and HPA systems are activated by higher brain centers in response to stress. To be properly interpreted, these types of reactions must be understood as the result of an instinctive experience of a situation as being harmful, but all the same positive, in the sense that the individual finds herself or himself being able to cope with it, either by a fight or a flight. A negative evaluation risks crippling the efforts. Neuroendocrinologically, the HPA and SAM are the main brain outflow systems that in response to stress act synergistically to release glucose from the liver, and in the case of SAM, increase cardiac output and shunt blood from skin and gut to skeletal muscle, all of which facilitates fight or flight. The glucocorticoids released by HPA action and the catecholamines released by the SAM do affect the brain, but the brain response to stress precedes the HPA and SAM responses. In addition, research has demonstrated that the immune and inflammatory defense systems are involved in the response to stress.

It is commonly recognized that stress may have both positive as well as detrimental effects on memory. It is also widely known that acute, as well as chronic stress, affect some aspects of memory, as demonstrated in psychologically traumatic events (e.g., being an eyewitness to an accident) or prolonged mental overload (e.g., time pressure and high task demands). In these situations, the recall is often inaccurate, particularly in details.

**KEY POINTS**

- Stress is associated with novelty, unpredictability, lack of control, and social-evaluative judgment (for review, see Ref. 1).
- Two brain regions important in regulating learning and memory are the hippocampus and amygdala, which contain receptors for stress hormones.
- Stress activates the hypothalamic-pituitary-adrenal axis (HPA axis) which causes a release of hormones called glucocorticoids: cortisol in humans, corticosterone in rodents and birds. This output of hormones is found to have memory-modulatory effects through its influence on the hippocampus and amygdala.
- Memory may be analyzed as a process, in encoding, consolidation and retrieval, and as systems, in episodic, semantic, working, procedural, and perceptual memory.
- Stress may be advantageous as well as detrimental for memory, and seems to have different effects on different processes and systems, depending on the stress load and the time when it occurs. Moderate levels of stress may enhance encoding and consolidation, but impair retrieval from long-term memory. High stress load usually has negative effects for memory.
- Stress has an impact on hippocampal function as it reduces levels of the neurotrophiin Brain-Derived Neurotrophic Factor (BDNF), suppresses neurogenesis in the dentate gyrus of the hippocampus, and impairs cognitive function.
- The amygdala exerts neuromodulatory influences in memory processing across diverse brain regions, including the hippocampus, entorhinal cortex, striatum, medial frontal cortex, and anterior cingulate cortex.

The Conceptual and Anatomical Basis in Humans of Learning and Memory

The contemporary conceptual frameworks of memory and learning emanate from experimental cognitive psychology and research in cognitive neuroscience. According to this model, human memory is not a unitary system, but composed of a series of interdependent systems characterized by different behavioral and brain features. The behavioral features of these systems vary in terms of time for registration of new information (fractions of a second to seconds and longer), type of information (sensory features vs. symbolic information),...
availability of consciousness (yes vs. no), activity at encoding (elaborating on target information or not), amount of information stored (limited or large), delay of retrieval (yes vs. no) and modes of retrieval (recognition vs. recall). The brain characteristics of these systems vary in terms of anatomical structures/networks involved. The processes, mapping, encoding, storage, and retrieval are related and undergo temporary physiological changes and long-term molecular structural changes.

It is commonly considered that there are two important aspects of memory: systems and processes, the latter sometimes also called stages. At least five systems are recognized: episodic, semantic, working, procedural, and perceptual. Three processes are recognized: encoding, consolidation, and retrieval. First stimuli are encoded into internal representations, which may be followed by consolidation of the memory trace and finally, there is the possibility to retrieve the information in memory. Below, the brain networks and mechanisms subserving the memory systems and processes are briefly presented. Recent research has shown that both processes and systems are affected by stress.

One major distinction of memory is that between declarative and nondeclarative memory. Declarative memory (also denoted as explicit) includes episodic (events related to time, location, and person), semantic memory (general facts), and short-term/working memory (limited information on-line). Nondeclarative memory (often denoted as implicit knowledge) includes procedural memory (motor and cognitive skills), perceptual representation memory (sensory features), conditioning, and habituation.

The episodic memory is primarily related to medial temporal lobe structures such as the hippocampus and adjacent regions, in which the stimuli are thought to be linked together as a memory trace. This trace may be consolidated as mediated by long-term potentiation (LTP), which refers to the reinforcement of synaptic connections in the nervous system during the memory process. The molecular changes that generate LTP are thought to play a key role in the encoding and consolidation of memories, but not in retrieval according to recent research. LTP helps understand how synaptic strength can be enhanced through repeated activation of signal transmission. The process of encoding and storage is influenced by conscious thought and effortful elaboration of the stimuli in focus. This conscious thinking is considered to be related primarily to dorsolateral prefrontal cortex of the brain. The medial temporal lobe and frontal areas are also involved in retrieval of the information.

The semantic memory system seems to rely on temporal lobe and/or other neocortical structures, but the extent to which semantic memory traces are dependent on hippocampal learning is still under consideration as exemplified by the complementary learning systems theory. There may be alternative ways of learning as suggested by individuals who have demonstrated semantic memory capacity, in the presence of hippocampal lesions. Studies are lacking regarding the effect of stress on this type of memory.

Short-term/working memory refers to information that is attended to, and possibly responded to, in real time in the conscious individual. The memory is continuously updated across time and the amount of temporarily stored information is highly limited (a matter of seconds). Without efforts to keep the information in mind, items will be lost. Certain prefrontal brain regions in collaboration with the parietal regions seem to be responsible for the temporary storage and processing of memory. Procedural memory is primarily related to basal ganglia structures (striatum) in addition to prefrontal regions of the brain and the cerebellum (i.e., regions involved in motor performance). The acquisition of new skills (encoding) rely on the appropriate sequence of actions which involve repeated trials until the action has become satisfactory. Both acquisition and retrieval appear to operate in an unconscious manner. This feature stands in contrast to what is typical for declarative memory. So far, studies on human striatal-dependent learning and memory are sparse. However studies indicate that the hippocampal- and striatal-dependent learning and memory systems are integrated.

The perceptual memory system is another example of implicit memory and this system is primarily related to cortical regions in the brain subserving perceptual processes (i.e., primary projections areas in the brain). Conditioning may be viewed as learning a connection between, for example, threatening stimuli and the emotion of fear and behavioral reactions, which seem to involve parts of amygdala and other parts of the brain. This system may be seen as encoding and consolidation of recent experience and it is involved in many kinds of human psychopathology, for instance posttraumatic stress disorder (PTSD), anxiety disorder, and phobias.

Mechanisms Behind the Relationship Between Stress, Learning, and Memory

Most of the literature in the field concerns the effects of stress on memory, which from a definitional point of view is something different from learning. Memory is a question of remembering previous information, whereas learning has to do with the elaboration, generalization, and application of the acquired information to pertinent new situations. Thus, the following discussion will focus on the relationship between stress and memory.

During the last decade, knowledge about the mechanisms behind stress and memory has been considerably enhanced. The relationships between these parameters are complex, and depend on the influence of the
The hippocampus is a key structure for many memory systems. Together with other structures crucial for memory, (such as prefrontal cortex and amygdala), the hippocampus is known to be rich in receptors for glucocorticoids. The hippocampus also contains receptors for noradrenaline, a key stress hormone released by the sympathetic nervous system in the periphery and by the locus coeruleus and other brain stem nuclei. During stress, the levels of glucocorticoids, as well as noradrenaline, are increased. Together with the paraventricular nucleus, basolateral amygdala, and locus coeruleus, glucocorticoids and noradrenaline act synergistically to facilitate hippocampal receptivity for memory and learning modulation.

The hippocampus interacts with the amygdala, bilateral structures which are located in the anterior temporal lobe in close topographical relationship with the hippocampus. The amygdala plays an important role in memories linked to emotional arousal. It has foremost been associated with negative feelings, such as fear, and negative memories, but involvement in memories from positive emotional reinforcement is also evident.

Memory is most delicate and responsive to modulation immediately after encoding. During this phase it may be reinforced or weakened. Stress may be advantageous as well as detrimental for memory. Usually, amelioration of memory performance under acute stress follows the pattern of an inverted-U dose-response curve, so that the amount of stress corresponding to the memory performance at the top of the inverted U-shape may reflect the optimal stress level. Too low or too high levels of glucocorticoids may impair declarative memory. The phase under which memories are stabilized is the synaptic or cellular consolidation phase during which memories become more and more independent of hippocampus. During consolidation, the information will instead gradually be transformed to long lasting representations through the involvement of other brain structures committed to memory. With time, memory usually turns pale and loses its sharpness for contextual details. However, stress intensity during learning may modulate the quality of memories. Exposure to moderate stress during the encoding phase predicts a more detailed memory, rather than too high levels of stress which risk just shaping schematic or diaphanous representations. According to the Multiple Trace Transformation Model, memories are rich in contextual details during the hippocampus-dependent phase, but become less sharp when they enter the hippocampus-independent state. Thus, exposure to moderate stress directly after acquisition will prolong the hippocampus-dependent phase and with this, the acuity of mental representations.

### Vulnerability of Human Memory

The current concept of human memory posits that the order of development during ontogenesis is reversed when the brain is exposed to various adverse influences such as aging, somatic (e.g., metabolic syndrome) and psychiatric (e.g., depression) disease, toxins, inflammatory agents, and stress (e.g., acute stress, PTSD). The implication of this hypothesis is that more sophisticated memory systems, such as declarative memory, are hit more severely and earlier than other memory systems, when an individual is exposed to chronic stress and the brain is affected. In line with this hypothesis, the majority of studies on stress and memory have dealt with episodic memory and few studies have investigated the effect of stress on the perceptual memory and conditioning. However, there are some recent studies on procedural memory.

### Encoding, Consolidation, and Retrieval in Stressful, and Emotionally Loaded Situations

The research about the effects of stress on memory is dominated by two types of experiments, one that studies the effects of cortisol, and another that focuses on the consequences for memory of the interaction between glucocorticoids and adrenergic activation, mostly under the influence of acute stress. Chronic stress is foremost associated with a PTSD.

Acute stress affects memory formation in another way than chronic stress. Most indications are that the effects of acute stress are stage-dependent (acquisition, consolidation, and retrieval). Each part of the memory complex seems to have its specific neurobiological profile, meaning that stress, brought about by the release of cortisol or cortisone, may have different effects on the various phases of the memory process, and consequently, with these phases, interconnected memory systems. Chronic
Stress may have more widespread implications for cognition, by causing a cumulative and enduring overload of hippocampus, with implications for its functioning and morphology. When the stress is chronic, the effects for encoding and retrieval are reported to be negative.\textsuperscript{20-23}

During the memory process, there appears to be some kind of reallocation of energy resources: Stress-induced cortisol secretion may ameliorate encoding, but hinder memory recall from long-term memory. An explanation for this is that cortisol, in order to make the brain ready for the encoding of new material, impedes the brain from the recall of old material.\textsuperscript{24,25} This raises the intriguing question whether it is possible to utilize several memory systems at the same time, or if the brain must focus on one memory stage/system at the time. Cortisol has also been reported to enhance memory consolidation.\textsuperscript{12,26}

One hook in cortisol studies is that it may be difficult to isolate the consequences of cortisol for distinct phases/systems since cortisol is not stabilized until 90 min after inducement.\textsuperscript{14}

High levels of stress may lower hippocampus-dependent memory performance, whereas emotionally arousing tasks may increase the remembrance for positively or negatively emotionally salient stimuli. Findings indicate that bilateral amygdala activation during memory acquisition is connected with an amelioration of episodic recognition memory for emotionally arousing visual stimuli, agreeable, as well as disagreeable, as compared to neutral material. According to the memory modulation hypothesis, memories of aversive episodes are better remembered because of the interaction between noradrenaline and cortisol in the basolateral nucleus of the amygdala during memory acquisition. Emotional arousal during encoding has also been found to reflect a reinforcement of the interconnection from the hippocampus to the amygdala, which supports the memory-modulation hypothesis emanating from animal studies, that amygdala controls the mediation of information in the hippocampus.\textsuperscript{13,27} An efficient encoding is an absolute prerequisite for remembrance whatsoever, and a deficient encoding will prevent the transfer of the information to the short-term memory and other memory systems in the memory sequence.

Since different types of stress—with or without emotional arousal—are reported in the literature, the results are not always comparable, although it seems as if the results merge in a stage dependency for stress on memory, with or without emotional load.

**Summary**

Memory is created during a process of encoding, consolidation, and retrieval of information, and is stored in explicit or implicit memory systems. Stress influences memory through the activation of the HPA axis, which release cortisol. The effects of this hormone seem to be stage- (encoding, consolidation, and retrieval) and system-dependent, and it has been found that acute and tolerable stress may enhance encoding and consolidation, but impair retrieval from long-term memory. One mechanism behind this irregularity is that while cortisol operates in preparation for the encoding, it shuts down the recall. Emotionally arousing memories under stress are more readily remembered than neutral, through the interaction between noradrenaline and cortisol in the basolateral nucleus of the amygdala during memory acquisition. Chronic stress may impair memory as well as cognition.

**EFFECTS OF STRESS ON LEARNING AND MEMORY IN ANIMALS**

**Introduction**

Animals learn about the relationship or association between two events. In classical conditioning the animal learn to associate a stimulus such as a tone (conditioned stimulus) with food (unconditioned stimulus). In operant or instrumental conditioning, the animal learns to associate a response. For instance, pressing a lever (instrumental response) is associated with food reward (reinforcement). It has been suggested by some researchers\textsuperscript{28} that associative learning mechanisms have been shaped by evolution to enable animals to detect and store information about real causal relationships in their environment.

**Stress Hormones and Learning**

The impact of stress hormones in modulating associative learning and cognitive function in animals has been a subject of continued investigations. The studies that have documented the relationship of levels of stress hormones with cognitive function, such as attention, perception, and memory have been done predominantly in rodents where investigators have examined the influence of stress hormones on acquisition, consolidation and retrieval of information. Glucocorticoids are the stress hormones secreted by the adrenal glands in animals. In primates and dogs, the naturally occurring glucocorticoid is cortisol, whereas in rodents and birds, it is corticosterone.

In response to emotional arousal, the stress hormones adrenaline and corticosterone are secreted in the adrenal glands with the concomitant release of several neurotransmitters and neuropeptides in the brain. Fluctuations in cortisol levels can be said to reflect emotional states related to stress. In experimental animals, changes in hormonal levels can be achieved by pharmacological means or environmental manipulations and their effects assessed. Several studies show that stress and
Glucocorticoids influence cognitive function. The administration of low levels of corticosterone improves performance in learning tasks in animals. However, whereas short-term exposure to low levels of corticosterone can enhance cognitive function, it is known that short-term exposure to higher levels, as well as long-term effects of high levels of corticosterone (e.g., through sustained exposure to restraint stress), has deleterious effects on learning, memory, and cognitive function.

The effects of corticosterone on cognitive function are mediated through binding of the stress hormones to specific receptors in the brain. These receptors, known as glucocorticoid receptors (GRs), have been found to be abundant in the hippocampus, a brain region that is critically involved in modulating learning and memory. Another region in the brain that participates in cognitive function is the amygdala, which also has moderate amounts of receptors for corticosterone. The actions of corticosterone in the hippocampus and amygdala can be induced by the administration of selective drugs that interact with the GRs. Drugs include those that enhance the effects of corticosterone (glucocorticoid agonists) or those that block or attenuate the effect of corticosterone (glucocorticoid antagonists). These drugs have provided powerful tools in dissecting the role of stress hormones in the hippocampus and the amygdala in modulating cognitive function in rodents. Pharmacological or environmental manipulation of the GRs influences cognitive function in rats. For example, administration of the GR antagonist RU38486 impairs fear memory reconsolidation in rats; and neonatal stimulation (handling) of rat pups causes increased density of GRs in the hippocampus during aging and enhances spatial learning.

**Hippocampus and Learning in Animals**

Glucocorticoids exert numerous effects on the central nervous system that regulate the stress response, mood, learning and memory, and various neuroendocrine functions. The actions of corticosterone in the brain are mediated via two receptor systems: the mineralocorticoid receptor (MR) and the GR, both of which are highly localized in the hippocampus. The hippocampus is characterized by, among other things, the presence of GR and MR receptors, neurotrophins such as Brain-Derived Neurotrophic Factor (BDNF), and neurogenesis in the dentate gyrus region, all of which have been found to be affected by stress. For example, exposure to stress reduces levels of BDNF in the hippocampus (e.g., Ref. 32) and suppresses neurogenesis in the dentate gyrus. Corticosterone effects on GRs and MRs, hippocampal BDNF and neurogenesis have an impact on learning, including LTP, which is thought to be or mimic the neurophysiological process associated with learning and memory. Thus, exposure to stress has been shown to impair LTP in the CA1 region of the hippocampus.

Considerable evidence shows that the hippocampus mediates spatial learning in rodents. Spatial learning in rodents can be examined by the use of a water maze known as the Morris maze. The procedure involves placing an experimental animal in a large pool of water of about 1.5 m in diameter. The animal has to use spatial cues in the experimental room to locate an invisible escape platform that is hidden 2 cm below the surface of the opaque water. After a few days of testing, the animals learn to locate the platform within seconds. It has been demonstrated that rats perform poorly in this test if hippocampal function is impaired. Thus, aged rats with pathological changes in the hippocampus show impaired spatial learning in the water maze compared to aged rats that do not show pathological hippocampal changes. Aged rats that have been exposed to repeated restrained stress have a reduction of GRs in the hippocampus. This results in, among other things, an impaired spatial learning ability. In contrast, animals that have higher levels of GRs in the hippocampus show an increased ability for spatial learning. Administration of a GR antagonist in the brain appears to impair information processing during spatial learning.

To sum up, spatial memory in animals is dependent on hippocampal function. Through their action in the hippocampus, stress hormones facilitate spatial information processing so that low levels of corticosterone improve learning, whereas higher levels impair performance.

**Amygdala and Learning in Animals**

The amygdala is a region of the brain that plays a crucial role in acquisition and expression of fear responses. Binding of GRs in the basolateral nucleus is known to affect memory storage. It was found that administration of glucocorticoid agonist in this area immediately after training enhanced retention of a passive avoidance response. Many studies have examined the effects glucocorticoids on the acquisition of new information. In a test of memory retrieval of long-term spatial learning, it was found that stress caused impaired performance, and this impairment could be related to circulating levels of corticosterone. These findings point to a critical involvement of the amygdala in regulating stress hormone effects on learning and memory.

The amygdala is thought to influence memory storage processes in other brain regions, such as the hippocampus and cortex. Accumulating evidence from the studies by McGaugh and Roozenendaal has established the amygdala to be critically involved in mediating stress-related modulation of hippocampal function. These investigators have provided evidence for the crucial
involvement of amygdala—via its interaction with other brain regions—in regulating stress hormone effects on such memory processing phenomena as memory retrieval, memory extinction, and working memory. An interaction of stress hormones and amygdala nuclei appears to be important in modulating memory consolidation for emotional events. Roozendaal and McGaugh have presented convincing evidence that activation of noradrenaline in the amygdala is crucial in enhancing memory consolidation. Emotional arousal experience induces release of noradrenaline into the basolateral amygdala. And this noradrenergic activity in the amygdala exerts neuromodulatory influences in the hippocampus on memory consolidation.

For example, pharmacological blockade of noradrenaline receptors in the amygdala can impair LTP (the neurophysiological substrate of memory) in the dentate gyrus of the hippocampus.

What has now emerged from intensive research is that the amygdala exerts neuromodulatory influences in memory processing across diverse brain regions, including the hippocampus, entorhinal cortex, striatum, medial frontal cortex, and anterior cingulate cortex. To conclude, the amygdala is a region of the brain known to be importantly involved in emotions. Stress hormones can affect the memory storage of emotional events by their action on the amygdala, which can interact with other brain regions to promote memory processes.

Summary

Two brain regions important in regulating learning and memory are the hippocampus and amygdala, which contain receptors for stress hormones. The effects of stress hormones on learning are mediated by these receptors in the hippocampus and amygdala. However, research in rodents points to the involvement of other brain regions in stress-related learning. Emotional arousal activates the amygdala which exerts neuromodulatory influences on memory processing across diverse brain regions, including the hippocampus, entorhinal cortex, striatum, and medial frontal cortex.

Glossary

Amygdala A group of nuclei involved in the medial anterior part of the temporal lobe concerned with fear and the regulation of emotion and certain types of learning.

Corticosterone A steroid hormone in many species, including rodents, produced by the adrenal cortex and involved in response to stress and immune reaction.

Cortisol A steroid hormone in humans produced by the adrenal cortex, involved in response to stress and that has direct influence on the nervous system.

Emotion Mental state of arousal.

Hippocampus A region of the cerebral cortex in the basal medial part of the temporal lobe thought to be important for learning and memory.

Learning A relatively permanent change in cognition as a consequence of the acquisition of new information and experience, directly influencing behavior.

Memory Encoding of information, storage, and recall.

Stress hormones Hormones of the adrenal glands that serve to maintain bodily homeostasis in response to challenging external and emotional environment. These hormones are the glucocorticoids and adrenaline.

Stressor Stimulus that puts an extra demand on the organism.

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