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NEUROBIOLOGY OF THE IMPACT OF AVERSIVE EXPERIENCES ON LEARNING: A SCOPING REVIEW

NEUROBIOLOGIA DO IMPACTO DAS EXPERIÊNCIAS AVERSIVAS NA APRENDIZAGEM: UMA REVISÃO DE ESCOPO

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ABSTRACT

INTRODUCTION: The memory processes sustain the activity of learning, which requires attention and directed focus. Classroom aversive experiences such as anxiety disorders, chronic stress and fear can modulate the learning processes. The mechanism consists in reorientation, mostly mediated by neurohumoral mechanisms, involving the hippocampus and the amygdala, impairing the acquisition of knowledge. **OBJECTIVE:** The aim of this study is to clarify the impact of aversive experiences on learning and identify the memory mechanisms involved from a neurobiological and educational perspective. **METHODOLOGY**: This study is a scoping review in which the online databases PubMed and LILACS were used to identify papers using an unified search strategy. 18 papers published between 2017 and 2022 composed the scoping review. **RESULTS**: The selected studies met the eligibility criteria of online availability, traumatic experiences and learning the association and correlation between frightening and stressful experiences with memory consolidation. As an acute consequence of stress, high amounts of norepinephrine and cortisol, a glucocorticoid, are released in the body. The interaction between these two agents, especially in the central nervous system, impairs working memory functioning and interrupts the attention functions of the prefrontal cortex, while directing attention only to threatening stimuli, making it hard to consolidate non-threatening information. Chronically, the adverse component is mostly mediated by cortisol, hindering learning through basically two mechanisms. One is by reducing hippocampal functioning and amygdala signaling, leading to long-term memory deficits and facilitating the persistence of fear memories. The other is through avoidance behavior, which works as a defense against unfavorable stimuli, leading the individual to create an obstacle to new learning. **CONCLUSION**: When in situations of stress, anxiety and fear, there are mechanisms in the hippocampus and amygdala mostly mediated by neurotransmitters and hormones that can impair memory consolidation and affect learning.

KEYWORDS: *Learning; Memory, Long-Term; Psychological Distress.*

RESUMO

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INTRODUÇÃO: Os processos de memória sustentam a atividade de aprendizagem, que requer atenção e foco direcionado. Experiências aversivas em sala de aula, como transtornos de ansiedade, estresse crônico e medo, podem modular os processos de aprendizagem. O mecanismo consiste em uma reorientação, mediada por mecanismos neuro-humorais, envolvendo o hipocampo e a amígdala, prejudicando a aquisição do conhecimento. **OBJETIVO:** O objetivo deste estudo é esclarecer o impacto das experiências aversivas na aprendizagem e identificar os mecanismos de memória envolvidos numa perspetiva neurobiológica e educacional. **METODOLOGIA:** Este estudo é uma revisão de escopo em que as bases de dados online PubMed e LILACS foram usadas para identificar artigos usando uma estratégia de busca unificada. 18 artigos publicados entre 2017 e 2022 compuseram a revisão de escopo. **RESULTADOS:** Os estudos selecionados atenderam aos critérios de elegibilidade de disponibilidade online, associação de experiências traumáticas e aprendizagem e correlação entre experiências assustadoras e estressantes com a consolidação da memória. Como consequência aguda do estresse, grandes quantidades de norepinefrina e cortisol, um glicocorticóide, são liberadas no organismo. A interação entre esses dois agentes, principalmente no sistema nervoso central, prejudica o funcionamento da memória de trabalho e interrompe as funções de atenção do córtex pré-frontal, direcionando a atenção apenas para estímulos ameaçadores, dificultando a consolidação de informações não ameaçadoras. Cronicamente, o componente adverso é mediado principalmente pelo cortisol, prejudicando o aprendizado basicamente através de dois mecanismos. Uma é prejudicando o funcionamento do hipocampo e a sinalização da amígdala, levando a déficits de memória de longo prazo e facilitando a persistência de memórias de medo. A outra é pelo comportamento de esquiva, que funciona como uma defesa contra estímulos desfavoráveis, levando o indivíduo a criar um obstáculo para novas aprendizagens. **CONCLUSÃO:** Quando em situações de estresse, ansiedade e medo, existem mecanismos no hipocampo e na amígdala mediados por neurotransmissores e hormônios que podem prejudicar a consolidação da memória e o aprendizado.

PALAVRAS-CHAVE: *Aprendizado; Memória de Longo Prazo; Angústia Psicológica.*

INTRODUCTION

Learning is a fundamental process in human life and development and it's involved in many aspects of life, being especially important in the academic environment[1]. The classroom is an environment in which learning can be both stimulated and repressed, acting as a significant modulator of this process. Some situations within the classroom environment such as the pressure for productivity and the sense of urgency can prejudice learning. This is because the enormous performance requirement, evaluation, deadlines and conflicting interactions with others can promote a continuous state of anxiety, stress and/or fear harmful to the learning stages[2].

Learning consists of a process of acquisition, conservation and evocation of knowledge, occurring from changes in the Central Nervous System when the individual is subjected either to stimuli or experiences that are transfused by brain changes[3]. Memory is essential for the process of learning and it sustains the ability to retain and recall information.

Learning and memory processes depend on the integrity of the hippocampus, striatum and prefrontal cortex[4]. Aversive memory is associated with an adverse stimulus, which is something that the brain recognizes as a threat, and, in order to lead to protective actions for survival, long-lasting and intense memories are consolidated[5]. This effect is believed to be the result of systems that act to modulate the process, especially glucocorticoid and noradrenergic, but also serotonergic[6,7].

Psychological distress associated with aversive experiences such as in anxiety disorders, chronic stress and fear involve the exacerbation of an aversive memory, which makes harmless stimuli look like a threat, leading to the body physiological response[8]. When it comes to learning something new, it is known that a safe and comfortable environment is required, since negative emotional states have a detrimental effect on memory[9].

In addition to this “acute” effect of emotions on learning, they play a crucial role in building future learning, because they work as architects of the mind[10]. The emotional factor provided by the aversive experience and acquired by mental abstraction generates brain stimuli that change the synaptic discharge pattern, causing a persistent modification in the brain circuit[2] and influencing learning.

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Even though memory consolidation and learning are largely studied topics, there are no satisfactory correlations between the direct situations of the classroom and the neuroscience behind events that induce fear, anxiety and stress responses. For this reason, a scoping review was performed following the research question “How does a frightening or traumatic experience interfere with the learning process and the consolidation of new memories?”. The aim of this paper is to clarify the impact of aversive experiences on learning and identify the memory mechanisms involved from a neurobiological and educational perspective at the undergraduate level, using experimental, theoretical and clinical data.

METHODOLOGY

This study is a scoping review in which the search strategy was created based on the following research question: “How does an aversive or traumatic experience interfere with the learning process and memory consolidation?”. The keywords were extracted and converted to Medical Subject Headings (MeSH) terms.

LILACS and PubMed were used to run in May 2024 the following search strategy: ("Fear" OR "Fears" OR “Medo” OR "Psychological Distress" OR "Emotional Distress" OR "Emotional Stress" OR “Angústia Psicológica” OR “Aflição Psicológica” OR “Angústia Emocional” OR “Esgotamento Emocional” OR “Estresse Emocional” OR “Estresse por Angústia” OR “Sofrimento Emocional” OR “Sofrimento Psicológico” OR "Psychological Trauma" OR “Trauma Psicológico”) AND ("Memory Consolidation" OR "Memory Consolidations" OR “Consolidação da Memória” OR "Knowledge Acquisition" OR “Aquisição de Conhecimento”).

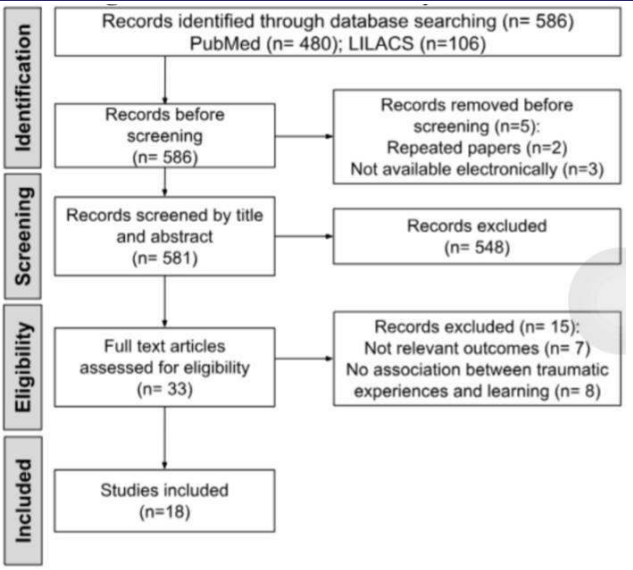
The final search results were exported into Mendeley References Manager and organized for posterior reading and analysis. The inclusion criteria were studies published in English, Spanish and Portuguese between 2017 and 2024, studies that correlate frightening and stressful experiences with the consolidation of memories and that address traumatic experiences and learning. The exclusion criteria were papers not available electronically and that do not associate traumatic experiences with learning were excluded.

Two different reviewers independently read and discussed all the same studies. The first triage step was reading the title and abstract. The next step was a full reading and, using the inclusion and exclusion criteria, the studies were selected. A third reviewer was consulted to solve the study selection and data extraction disagreements.

RESULTS

A total of 586 papers were found: 480 on PubMed and 106 on LILACS. 2 repeated papers and 3 not available for full reading were excluded. From the reading of the title and abstract, 33 papers were selected for full reading. Finally, 18 papers relevant to the research theme composed the scoping review. A flowchart was created to facilitate the visualization of the study selection process (Figure 01). Throughout the discussion, 25 references were included in addition to the aforementioned method, mostly obtained from the references of the selected articles.

FIGURE 1. Flowchart of study selection.



Prepared by the authors, 2024.

The selected studies were published between 2017 and 2022 and an increasing trend towards growing publications in this field is possible to be observed (2017–2018: n=5; 2019–2022: n=13). Among the studies, 2 papers were literature reviews, 14 were animal models randomized controlled trials and 2 were randomized controlled clinical trials.

The selected studies are summarized in the table below with information of the main author and year, purpose, methods and conclusions (Table 01).

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TABLE 1. Descriptive summary of studies included in the review. GC= glucocorticoid, CFC= contextual fear conditioning, NA= noradrenaline, BLA= basolateral amygdala, GR= glucocorticoid receptor, PTSD= post-traumatic stress disorders, PFC= prefrontal cortex.

Author/Year	Purpose	Methods	Conclusions
BRUECKNER, A. H., 2019.	To examine whether extinction can be enhanced by administering cortisol after extinction training.	50 participants were exposed to a CFC paradigm with neutral faces as conditioned stimuli and traumatic film clips as unconditioned stimuli. They received either cortisol or placebo immediately after extinction.	Cortisol influences fear extinction by promoting the consolidation of extinction learning. Inhibition on aversive memory is an inhibitory potentiator of the association between conditioning and non-conditioning stimuli, decreasing threat expectation and attenuating fear-induced responses.
DE MEDEIROS, G. F., 2019.	To investigate the role of corticosteroid-binding globulin (CBG) in contextual and recognition long-term memory according to stress intensity.	Adult male mice totally deficient in CBG were used to examine their performance in contextual and auditory fear conditioning, both at short (1h) and long-term (24h).	GCs are important in the memory process in their free form and associated with CBG. This protein is important to the consolidation of long-term memories involving hippocampal activity, such as CFC and recognition memories. The amount of free GCs must be ideal to increase learning performance, because when it is too high, it impairs this process.
DOS SANTOS CORRÊA, M., 2021.	To investigate whether post-training corticosterone (CORT-HBC) injections, given after different training intensities affects contextual fear memory specificity at several time points.	Male Wistar rats were trained on the CFC task using two footshock intensities and immediately after the training session were administered CORT-HBC systemically. Animals were classified as generalizers or discriminators based on freezing time.	GCs initially have a discriminative modulatory effect on aversive memory. NA acts synergistically with the GC to consolidate features of an aversive event. NA and GC injection in a mild intensity CFC enhances memory specificity, while NA and GC in a moderate CFC induces fear generalization.
DREXLER, S. M., 2017.	To establish the modulating role of GCs on memory reconsolidation.	Literature review of pharmacological studies.	GCs, released in stressful events, enhance the consolidation of emotional memories, while impair memory retrieval. Chronic stress, differently from acute stress, is likely to impair memory functioning by GC receptors in the hippocampus and amygdala.
ESPEJO, P. J., 2021.	To evaluate whether stress could affect the expression of Lys-48 polyubiquitinated proteins within the BLA, important to memory destabilization.	Male Wistar rats were subjected to stress or handling sessions and were fear conditioned one day later, in which they received foot-shocks. One day after, animals were re-exposed to the training context without receiving shocks and sacrificed for BLA dissection.	Memory recall induces an increase in the expression of polyubiquitinated proteins in fear memory, since memory destabilization depends on protein degradation. Increased stress before aversive memory recall affects memory trace encoding, offering greater resistance to the destabilization process and thus affecting later reconsolidation.
GILMAN, T. L., 2018.	To evaluate how activating BLA Thy1-expressing neurons using DREADDs (designer receptors exclusively activated by designer drugs) affected the consolidation, expression, reconsolidation, and extinction of contextual fear.	A cre-dependent virus that codes for the activational Gs-coupled DREADD rM3D specifically into the BLA was infused in Thy1-Cre mice To selectively activate Thy1-expressing neurons within the BLA. An inhibitory avoidance paradigm was employed and the influence of activating BLA Thy1 neurons at fear processing was examined.	The activation of Thy1-expressing neurons in the BLA plays a critical role in the attenuation of aversive memory consolidation and reconsolidation processes. In addition, they promote the improvement of extinction learning. These actions, together, imply the suppression of fear. An inability to inhibit fear responses can lead to PTSD disorders and anxiety-related disorders.
HAGSÄTER, S. M., 2021.	To assess the impact of serotonin depletion on acquisition, consolidation, and expression of conditioned fear.	Male Sprague–Dawley rats were exposed to foot shocks as unconditioned stimulus and assessed freezing behavior when re-subjected to context. Serotonin depletion was induced by administration of a serotonin synthesis inhibitor.	Higher extracellular levels of serotonin have a greater tendency to promote the fear conditioning process by affecting the acquisition and expression of an aversive memory.

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ITO, W., 2019.	To investigate whether the silent synapses generated by observational fear (OF) participate in the OF-enhanced inhibitory avoidance learning.	The OF procedure was performed in a fear conditioning chamber. Footshocks were delivered to the mouse. The observer mouse was returned to the home cage and housed alone. After that, animals were trained for inhibitory avoidance.	In humans, observing others in fear or pain is a form of psychosocial stress that can lead to PTSD. The OF-generated silent synapses likely enable plasticity that may enhance the consolidation of inhibitory avoidance memories by facilitation of amygdala responses.
MERINO, J.J., 2020.	To ascertain whether beta chemokines could play a role in fear memory consolidation and evaluate whether chronic stress restraint could regulate levels of these beta chemokines in CFC trained rats.	Chemokines levels were measured in the hippocampus and PFC of chronically stressed rats, 24h after CFC post-training, and compared with undisturbed CFC trained rats.	Hippocampal and PFC chemokines levels did not differ between rats subjected to chronic stress restraint and unstressed animals. However, when rats were re-exposed to the context without electrical footshocks, the proinflammatory cytokine IL-6 levels were higher in the hippocampus of chronically stressed rats, contributing to aversive conditioned behavior.
NITTA, Y., 2020.	To examine whether avoidance behavior during postretrieval extinction training prevents the modification of fear memory.	There were 25 participants and two different aversive sounds were used: an unconditioned stimuli (US) to avoid (AUS) and a US not to avoid (CUS). On day 1, participants listened to AUS and CUS. On day 2, one AUS and one CUS were presented at the retrieval phase. On day 3, the participants underwent reextinction training to test spontaneous recovery of the fear response.	Avoidance behavior occurs in various forms of strategy to reduce discomfort experiences, including safety-seeking and suppression behavior. Under the post-recovery extinction training condition with behavioral avoidance, the fear response is not reduced as much as under the non-avoidance condition. Avoidance behavior prevents a person from obtaining new safe information during post-retrieval extinction training, resulting in fear memory persistence.
PARK. H. A., 2022.	To describe how neural circuits are involved in fear memory and discuss therapeutic interventions for PTSD and anxiety-related disorders.	Narrative literature review using keywords fear memory, neural circuits, proneurogenic efficacy, therapeutic intervention, in vivo, and clinical study at PubMed and Google.	Fear learning and memory consolidation depends on hippocampal long-term potentiation. Upregulated responsivity of the amygdala and anterior cingulate cortex, such as in PTSD and anxiety-related disorders, reduces hippocampal and medial PFC function.
PEDRAZA, L. K, 2017.	To understand the influence of sequential learning in CFC with different training intensities in the time-course of hippocampal dependency and contextual specificity.	Male adult Wistar rats were used for CFC. Rats received shocks in context A and 48h later were put in context B and also received shocks. Then rats were put in context C with no shocks.	Sequential learning with high-intensity shocks during CFC induced generalization of context A and maintained specificity of context B. Subsequent experiences reorganize brain structures involved in retrieval, making it possible for two aversive experiences with the same emotional intensity be consolidated at different rates and be structurally independent for retrieval.
PONCE-LIN A, R., 2020.	To investigate if an aversive learning task would induce GR phosphorylation in the dorsal (DH) and the ventral (VH) hippocampus.	Rats were trained in CFC using different foot-shock intensities. After training, animals were sacrificed and had their corticosterone levels quantified. Brains were collected to evaluate the immunoreactivity to GR in phosphorylation sites in DH and VH.	GC activity in the hippocampus is dependent on the intensity of the learning experience and one of the mechanisms by which GCs modulate fear memory consolidation is through GR phosphorylation in DH and VH. High levels of stress lead to increased GR phosphorylation and fear memory generalization.
SCHMIDT, S.D., 2017.	To investigate, in the CA1 region of the dorsal hippocampus, whether serotonergic receptors are involved in the consolidation and reconsolidation of CFC memory.	Male Wistar rats received after the CFC training or reactivation session infusions of agonists or antagonists of the 5-HT5A, 5-HT6 and 5-HT7 serotonin receptors in CA1 of the dorsal hippocampus. After 24h, animals were subjected to a 3-min retention test, with no shocks.	5-HT5A are important for aversive memory reconsolidation and 5HT-6 participate in the consolidation and reconsolidation processes of CFC memory. 5-HT7 receptors participate in consolidation and reconsolidation in an opposite way to the others, since their antagonists do not prevent these processes from happening, but facilitate them to occur.

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SIDDIQUI, S. A., 2019.	To understand region-specific changes within the amygdala and PFC regarding the roles of histones deacetylases (HDAC) in the consolidation and extinction of fear memories.	Male Sprague–Dawley rats were trained on the CFC task using noxious mild shock. Freezing was used as a measure of the conditioning. Changes in specific areas of the amygdala and PFC were analyzed.	The consolidation of fear and extinction memories have been shown to be epigenetically regulated through histone acetylation and deacetylation. In amygdala and PFC, following fear and extinction learning, HDAC1 promoted extinction and conditioning through neuronal activation, HDAC2 promoted conditioning and extinction through neuronal suppression.
VALIATI, F. E., 2017.	To investigate the effects of a histone deacetylase (HDAC) inhibitor infused into the BLA at several time points after training, or immediately after retrieval, on the consolidation and extinction of inhibitory avoidance (IA) memory in rats.	Rats received a bilateral infusion of a HDAC inhibitor into the BLA at different times after IA training to examine the memory consolidation. After this, memory extinction was tested.	HDAC proteins are involved in epigenetic processes that influence long-term aversive memory and HDAC inhibitors are pharmacological agents that modulate these mechanisms. Higher histone acetylation in the BLA increased consolidation and reconsolidation of inhibitory avoidance after memory consolidation and impaired the extinction learning.
WIKTOROWSKA, L., 2021.	To evaluate the role of astrocytic GRs in the central nucleus of the amygdala (CeA) in various aspects of the stress response.	Aldh1l1-Cre transgenic mice had their astrocytic GR in the CeA disrupted by a lentiviral vector. In the CFC training animals received shocks and had three memory retrieval tests. Animals were suspended by the tail to assess stress.	Knockdown of the astrocytic GR in the CeA diminishes conditioned fear expression and anxiety. This consequence is probably the result of an impaired consolidation of aversive memory, indicating that astrocytic GR may contribute to the formation of trauma-related memories and anxiety.
YU, J., 2021.	To examine whether exposing mice to a neutral context similar to a conditioned context induces fear generalization immediately after CFC.	C57BL/6 mice were put in context A in which they received shocks. After that, the animals were put in context B, a similar place to context A, and context C, a completely different environment. Fear in these mice is defined as the freezing time.	After 6 hours, mice showed fear generalization to context B but not to context C. It shows that exposure to a similar neutral context after CFC can induce fear generalization to that context immediately after memory consolidation.

Source: Prepared by the authors, 2024.

DISCUSSION

The processes of learning, and memory can be subdivided into encoding, consolidation, retrieval, and reconsolidation[11]. It is important to highlight that the activity of glucocorticoids (GCs) is susceptible to modulation by neurotransmitter's involved in stressful situations, such as serotonin, and noradrenaline[6,7]. During a stressful event, GCs are released into the bloodstream, and being fat-soluble, easily cross the blood-brain barrier[12]. GCs modulate learning by promoting a memory consolidation state through binding to glucocorticoid receptors (GR)[13].

When a situation becomes a trauma, multiple memory traces interact with each other, and with the different brain structures, which reinforces that intense emotional memories are stored in a way that makes them stronger, and long lasting[14]. Therefore, understanding the neurobiology involved in these circumstances, both acutely, and chronically, contributes to understanding how those different processes reverberate in daily academic contexts.

1. Amygdala

The presence of GR in the amygdala is crucial to the formation of emotional memories, enhancing this process, and making it resistant to extinction[15]. While acute stress may have various effects on memory, chronic stress is related to impaired memory consolidation, and retrieval[16]. In Post-Traumatic Stress Disorder (PTSD), and anxiety-related disorders, the over-responsivity of the amygdala can lead to reduced hippocampal, and medial prefrontal cortex function, impairing memory processes, such as consolidation, and causing an uncontrolled fear response[17].

An important output station on many amygdala circuits, the amygdala central nucleus, had its GR functioning disrupted in mice in a controlled randomized trial[18]. The influence of GCs in the amygdala became even clearer when this study showed that these mice had reduced fear expression, indicating that

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the consolidation of aversive memory is a glucocorticoid-dependent process.

In a study in which the aim was to evaluate the effect of stress on the expression of Lys-48 polyubiquitinated proteins, located in the basolateral amygdala (BLA) important to memory recall, increased stress caused a greater resistance to these proteins's action[19]. Thus, stress is a barrier to memory recall, and later reconsolidation — creating an environment in which not only the process of remembering is impaired but also the modification of memories such as in PTSD.

Epigenetic factors like behavior and lifestyle can modulate the function of the amygdala through histone acetylation, and deacetylation using histone deacetylases (HDAC) proteins[20]. Higher acetylation in the BLA impaired extinction learning of inhibitory avoidance, and enhanced its consolidation, while the predominant deacetylation in the amygdala and prefrontal cortex appears to promote conditioning and extinction, whether by activating or suppressing specific neuronal subregions[20,21]. These findings suggest that situations of fear, anxiety, and stress, when chronified in anxiety syndromes or PTSD, can epigenetically set a state of avoidance behavior, and create a barrier to new consolidation of safe information, resulting in fear memory permanence[22].

There are, in BLA, neurons that express the protein coding gene Thy-1, important to the suppression of fear with actions of attenuation of aversive memory consolidation, and reconsolidation[23]. The maintenance of this capacity of inhibiting fear is necessary to avoid the development of PTSD, and anxiety-related disorders, regarding that when this ability is compromised, there is a stimulus of avoidance of the experience considered unpleasant.

Another mechanism of amygdala fear modeling is the synapses generated by the observational fear — that is, the feeling of observing others in a distressful situation of fear or pain — that facilitate amygdala pathways by enabling plasticity, and leading to improvement of the circuits of avoidance behavior, suggesting that not only personal experiences can modulate amygdala responses[24].

2. Hippocampus

A large amount of GR is distributed in the hippocampus, which can be divided into dorsal, and ventral, and each of these regions can be functionally subdivided into three layers CA1, CA2, CA3, and the dentate gyrus (DG). This makes the hippocampus highly sensitive to stressors, and trauma[17]. Ponce-Lina et al. (2020) reaffirms in their study that GR acts as a transcription factor that becomes phosphorylated after hormone binding, modulating hippocampus' activity. Two well-known phosphorylation sites are serine 232 (pSer232), and serine 246 (pSer246).

About 20 minutes after a stressful event, there is a peak in the concentration of free cortisol in the dorsal hippocampus. In this region, specifically in CA1, there is potentiated action of pSer246, generating a decrease in gene expression, and promoting connection with other brain areas related to cognitive processes, and memory processing, such as the anterior cingulate gyrus[25].

In the ventral hippocampus, the cortisol peak occurs later, around 90 minutes later. When the activation of the CA3 layer is significant, there is an increase in the activity of pSer232, which induces the gene expression necessary for the establishment of long-term memory, and its recovery[25].

For fear conditioning to occur, layers CA1, CA3, and DG are essential. The hippocampal trisynaptic circuit begins with the transmission of signals from the entorhinal cortex to the DG via the perforating pathway. Mossy fibers from DG project to pyramidal cells in CA3, which transmit collateral signals to neurons in CA1. This signal returns to the entorhinal cortex, completing the cycle of memory storage, and consolidation[17].

GCs are responsible for protein kinase, and cyclic adenosine monophosphate activity increasing in the medial prefrontal cortex, BLA, and hippocampus[26]. It leading to increased emotional memory consolidation, and impaired working memory functioning[27]. The interaction between BLA, and hippocampus is also seen in the effect of acute, and chronic stress, since the acute effect seems to have a positive influence on cognitive processes, and learning, while the chronic effect involves the impairment of synaptic plasticity, and learning performance[9].

There is one more modulating component of hippocampal activity: cortisol-binding globulin (CBG). Through experiments conducted by De Medeiros et al. (2019), mice with total depletion of this protein (Cbg KO) showed lower long-term hippocampal responses compared to normal mice. That is, in the short term, hippocampal activity is dependent on the processes triggered by free circulating GCs, but in the long term, the influence of CBG proved to be essential for the consolidation of contextual fear conditioning, and recognition memories.

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Another finding that suggests that the hippocampus is particularly vulnerable to stress is that the insulin receptors located in the hippocampus have their functioning, and signaling impaired while in a state of chronic stress[29]. The action of insulin on the hippocampus is to promote neuronal development, and learning, while its absence leading to long-term memory deficits, and increased anxiety-like disorders[30].

Hypothalamic-pituitary-adrenal axis dysfunction with high GCs levels associated with inflammation, and oxidative stress, can lead to reduced neurogenesis in DG, and neuronal atrophy[31]. There is, in PTSD, and chronic stress, an accentuated volume reduction in CA3, and DG mostly mediated by the neurotoxic effects of prolonged high levels of GCs in the hippocampus[32]. These findings accentuate the unsuitable functioning of memory processes in high stress conditions such as anxiety, and chronic stress.

In a recent study, it was found that chronically stressed rats presented high levels of the proinflammatory interleukin-6, probably contributing to the establishment of the aversive conditioned behavior in face of a generalized fear[33].

This mechanism of fear generalization, which is the activation of a fear response to a different stimulus than the original situation that originated the aversive memory, can occur immediately after fear consolidation[34]. It indicates that in a short period of time, an aversive experience can generate an avoidance behavior which, in the academic context, means avoiding a specific subject based on how unpleasant the last experience was.

3. Neurotransmitter's

3.1. Serotonin

In controlled experiments, different serotonin receptors present in the hippocampus, specifically in the CA1 layer of the dorsal hippocampus, participate in the consolidation of contextual fear memory. The results showed that serotoninergic 5-HT6 receptor antagonists impair CFC in the determined hippocampal region. On the other hand, 5-HT7 receptor antagonists facilitate consolidation, while 5-HT7 receptor agonists had no significant effect on freezing time (fear response) during the retention test[7].

According to a specific study, rats with an inhibition of the tryptophan converting enzyme to serotonin had reduced freezing time when exposed to the conditioning stimulus[35]. That is, even though different serotonergic receptors act in different ways, the final role of serotonin is to facilitate the fear conditioning process, and future responses related to the conditioning factor. However, its absence does not directly compromise the fear memory.

While the correct functioning of serotonergic neurotransmission is necessary for consolidation, and expression of fear, low levels of serotonin may have a role in anxiety genesis, mediating memory forgetting, and compromising learning[36].

3.2. Noradrenaline

The level of arousal during the acquisition of aversive memory modulates the role played by GCs[6]. Studies indicate that more arousing experiences result in greater noradrenergic activity[37].

Experiments with light intensity CFCs leading to a consolidation process in which the GCs sustain a memory specificity. On the other hand, experiments with higher intensity CFCs give rise to a consolidation in which the GCs facilitate the generalization of fear[6].

More stressful events increase the amount of noradrenaline, which acts synergistically with GCs in the amygdala, recruiting areas of the brain associated with more rigid learning, such as the striatum, and parahippocampal cortex. This contributes to the focus, during acquisition, being more precise on central features of the aversive event, and less on contextual details, favoring time-dependent generalization of fear, and faster reactions to threatening stimuli[11].

The overactivation of the autonomic nervous system is seen in PTSD patients that have this over releasing of noradrenaline in face of a situation that is remotely similar to the one related to the trauma, making those effects of noradrenaline in important memory brain structures even more pronounced[38].

4. Effects of Aversive Experiences on Learning

After understanding the amygdala, hippocampus, and different neurotransmitter's actions and influence on aversive memories, it's necessary to elucidate how exactly these processes impact learning activities in an academic context. To illustrate how aversive experiences can influence the moment of learning, take, for example, the moment of exposition in a classroom, in which the students must pay attention, and be involved enough in the subject to understand the teacher's explanation.

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When something that is out of the person's control leading to distress, either causing anxiety symptoms or causing stress, considerable high amounts of noradrenaline, and cortisol, a GC, is released in the body. In stress' chronification the predominant actor is the hormone cortisol. When these neurotransmitter's, and hormones interact with the body in general, and specially the nervous system, they induce a state of diminished attention by impairing working memory functioning, and disrupting prefrontal cortex attention functions in general, while directing attention to threatening stimuli only[39,40,41]. This diminished level of attention can be a damaging memory effect that occurs in the moment of learning — which has attention as a crucial component.

Stressful situations direct attention and focus to emotional components of the stressor of the current event, acting as a distractor during encoding[42]. It leading to impaired memory formation, which points out to the damaging effects of learning under conditions of stress.

Beyond the effects of aversive experiences in the moment of learning, there are consequences for future learning, especially when it comes to fear, stress, and anxiety related emotions. It is known that emotionally arousing experiences are strongly remembered mainly because of GCs, and noradrenaline interactions with the brain memory structures[11]. In the classroom, these experiences can be represented by a frightful look of a teacher, by the voice tone used or by an inadequate treatment, which, in a stressful condition, can lead to the genesis of anxiety-like disorders or PTSD.

The mechanisms behind how these disorders affect learning are through avoidance behavior, and impaired memory consolidation. Avoidance behavior serves as a defense mechanism against aversive stimuli that remotely recall the event that triggered the trauma, allowing the individual to sidestep the situation, potentially eliciting a fight-or-flight response due to the visceral desire to escape what is perceived as an imminent threat[43]. In an academic learning context, the main effect of this behavior is to get away from the subject or theme, creating a barrier to new learning.

In addition to the avoidance behavior, it is known that chronic stress, even when isolated from other disorders, can impact on learning by impairing hippocampus functioning, and amygdala signaling, leading to long-term memory deficits, and facilitation of fear memories persistence[17,44]. This scenario causes not only learning difficulties by affecting memory consolidation, but also creates an extra layer of resistance to escaping traumas.

This study had some limitations that should be highlighted. Most of the experimental studies included in this review are based on animal models (n=14, 77%), that is, many assumptions were established by inference, and the relevance of fear conditioning in rats to human stress still remains a matter of speculation. Two studies were based on clinical trials, however, it is known that individual differences, including past learning experience, cognitive characteristics, and gender, affect the acquisition of fear conditioning, factors not considered in both studies.

By including several modulators of the learning process amid a stressful environment, each one of them has its own limitations, highlighted by their authors, showing that future studies are necessary to conclude specific questions disseminated in literature.

No study has correlated the specific modulator and the aversive experience with its direct impact on future learning, especially concerning academia, and further investigations are needed to shed light on the exact role of stress in this condition.

CONCLUSION

Learning, as an intrinsic activity of humanity, depends on multiple processes to occur and like any other body function, is modulated by the environment. This study provides evidence that whether in the moment of learning or the future learning of something new, when in situations of stress, anxiety and fear, there are mechanisms in the hippocampus and amygdala mostly mediated by neurotransmitter's and hormones, especially glucocorticoids, that can impair memory consolidation processes.

Stressful events are present in multiple situations in the educational environment, mainly aimed at academics, who present enormous pressure for performance, which must support and meet the expectations imposed by the infinity of exams, assessments, tasks, and deadlines. Thereby, the importance of understanding the impact of these processes on learning is given by the possibility of reversing the "negative atmosphere", adopting healthy classroom practices, such as stimulating dialogue and friendship, in addition to creating a safe and secure environment that goes against the homeostatic imbalance mechanisms mentioned in this paper. This would help to promote an optimized education, which is

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extremely important for the individual, as it lays the necessary foundations for later success in the profession.

A question that remains pending is about the real impact of aversive experiences on academic development when it comes to learning, in a qualitative perspective, indicating the need for more investigations in this area. Despite the significant advances that the field has made, several unknowns still need to be clarified, especially concerning the inter-individual divergences of the effects of stress on memory, because with this knowledge, it is possible to establish personalized, and targeted approaches to the prevention of distressing environments.

Furthermore, more research is needed to define the effect of stress on memories over time, as it is still not exactly clear when the intensifying and detrimental effects of stress on memory formation arise and how long they last. Also, currently, most studies have not explicitly distinguished the effects of stress on different types of memory, making future studies that evaluate possible divergences between them essential, which could provide important information on how stress and fear impact on learning and memory. Answering these questions can help in the management of specific learning configurations of the individual and enhance this process, mitigating cognitive deficiencies that negative emotions can generate.

CONFLICTS OF INTERESTS

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