EXPLORING THE IMPACT OF ACUTE STRESS ON PREVIOUSLY ACQUIRED CONTEXTUAL FEAR MEMORY

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ABSTRACT

Exploring the Impact of Acute Stress on Previously Acquired Contextual Fear Memory

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Stress can significantly affect neurobiological processes crucial for learning and memory. While repeated stress enhances fear memory, it impairs memory retrieval. In most studies, however, stress exposure typically preceded fear and extinction learning. Thus, the impact of previously acquired memories formed before exposure to stress is not well understood. The goal of this thesis is to examine how acute stress impacts the ability to retrieve previously acquired fear memories. The results showed that stress impaired recall of recent fear memories, but stress seven days after conditioning did not affect memory retrieval. Analysis of c-Fos expression revealed increased neuronal activity in the medial prefrontal cortex (mPFC) of rats exposed to stress. Additionally, stress exposure decreased mRNA expression of Reelin, a glycoprotein in the mPFC. Notably, administering recombinant Reelin improved fear memory recall. These findings highlight potential pathways for research and interventions on stress-induced memory impairments.

Keywords: Stress, Learning and memory, Fear memory, Memory retrieval, Acute stress, c-Fos expression, Medial prefrontal cortex, mRNA expression, Reelin, Stress-induced memory impairments

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LIST OF ABBREVIATION

ACTH: Adrenocorticotropic Hormone

AMPA: α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid Receptor

BDNF: Brain-Derived Neurotrophic Factor

BLA: Basolateral Amygdala

CA1, CA2, CA3: Cornu Ammonis Subfields of the Hippocampus

CeA: Central Nucleus of the Amygdala

Cg1: Cingulate Area 1

CORT: Corticosterone

CREB: Cyclic-AMP Response Element-Binding Protein

CRH: Corticotropin-Releasing Hormone

ERK: Extracellular Signal-Regulated Kinase

GABA: Gamma-Aminobutyric Acid

GR: Glucocorticoid Receptor

GRs: Glucocorticoid Receptors

HPA: Hypothalamic-Pituitary-Adrenal Axis

IEGs: Immediate Early Genes

IL: Infralimbic Cortex

LTD: Long-Term Depression

LTP: Long-Term Potentiation

MAPK: Mitogen-Activated Protein Kinase

MeA: Medial Nucleus of the Amygdala

mPFC: Medial Prefrontal Cortex

MR: Mineralocorticoid Receptor

NMDA: N-Methyl-D-Aspartate Receptor

PFC: Prefrontal Cortex

PL: Prelimbic Cortex

PTSD: Post-Traumatic Stress Disorder

PVH: Paraventricular Hypothalamus

PVN: Paraventricular Nucleus

VGCC: Voltage-Gated Calcium Channels

CHAPTER 1

Introduction

1. Overview

Memory is a crucial cognitive ability that lies at the core of our experiences and contributes to shaping our identity (Christian et al., 2014; Heinz, 2017; Robertson, 2002). It acts as an internal representation of past events or experiences and enables us to navigate the present and anticipate the future (Robertson, 2002). Remembering autobiographical memories - memories that tell the stories about our own lives and experiences - plays a key role in anticipating the future (Nadel & Moscovitch 1997). These memories associated with significant or negative experiences, influence how we react to and anticipate similar situations in the future. More precisely, an individual's response or expectations in the same environment are frequently shaped by the context in which they experienced unfavourable events (James et al., 2023). As a result, it is not surprising that traumatic or unpleasant memories may be distinct from other types of memories because they can be formed relatively quickly and persist throughout an individual's lifetime (Fendt & Fanselow, 1999; Nadel & Moscovitch, 1997).

Stress is an inherent aspect of life. Stress biology and the stress system are highly conserved across species and enable organisms to respond to their environment and cope with current conditions (Del Giudice et al., 2018; Steckler et al., 2005). The stress system itself comprises a complex interplay of neuroendocrine, immune, and autonomic responses that operate to enhance survival (Del Giudice et al. 2018). Despite stress being a common experience in daily life, it can have significant effects on various aspects of cognitive and behavioural processes linked to learning and memory (Rosen et al., 2010).

Cognition is a broad concept that involves processes of receiving, recognizing, and interpreting perceived stimuli in the brain to produce a suitable response. These range from perception, and attention to various types of memory, language, and executive control processes (Sandi et al., 2005). The majority of studies examining the cognitive effects of stress have been quite comprehensive in covering the effects of stress on various aspects of memory function. Studies on the impacts of stress on memory have yielded mixed findings in relation to its influence on memory. A large body of work has shown that stress can impede our ability to recall information (Buss et al., 2004; de Quervain et al., 2000; Schwabe et al., 2012), despite sometimes stress can significantly enhance the retention of traumatic experiences (Cahill & McGaugh, 1998; McGaugh, 2004; Steidl et al., 2006). The contradictory findings on the impact of stress on memory lead to the question of when exactly stress impairs or enhances memory. The answer to this question depends on many factors including the timing of the stress exposure, and whether stress is experienced before learning, immediately after learning, or during post-learning stages (Joëls et al., 2011).

In the following sections of this Introduction, I will first discuss the biology of stress response, and how stress impacts the brain. Next, I will discuss the effect of acute stress on memory processes by describing what is known about the effect of stress on the acquisition or encoding of new information, the formation and consolidation of new information, and the subsequent recall of past learning or information. I will then discuss possible neurobiological mechanisms that may underlie the effect of stress on memory by focusing on the role of reelin, an extracellular glycoprotein important in synaptic plasticity but also known to be affected in several stress-related neuropsychiatric conditions, such as anxiety and depression. I will then conclude the Introduction with a discussion of the particular objectives and aims of my thesis research.

2. The Neurobiology of Stress

Stress can be seen as a state of “threatened homeostasis” that disrupts a biological system’s state of normal or optimal function. This disruption, in turn, evokes a complex series of physiological and behavioural responses intended to re-establish the return of this system to its original state (the “stress response”). The neurobiological and physiological response to stress is highly conserved across mammals and has been extensively studied (Arnsten et al., 2015; Atrooz et al., 2021; Dudai., 2004). The stress response is carried by multiple systems in the body but generally involves the activation of the sympathetic-adrenal-medullary system, which is important in maintaining alertness and mediating “fight-or-flight” reactions (Godoy et al., 2018). In addition, a slower response mediated primarily by neural mechanisms involves the hypothalamic-pituitary-adrenal (HPA) axis, which helps to maintain physiological homeostasis and adaptation to the environment (McEwen., 2017; McEwen et al., 2015; Sapolsky., 2015). In this section, I will briefly review the stress and stress system, as well as discuss the impact of stress exposure on the brain.

2.1. The Physiology of the Stress Response

Exposure to threats, either real or perceived, produces responses that are processed at various levels within the brain and body, with the HPA axis serving as the major entry point. The process begins with stressful stimuli stimulating paraventricular hypothalamic neurons, which in turn triggers the release of corticotrophin-releasing hormone (CRH) and arginine vasopressin into the hypophyseal portal circulation (Godoy et al., 2018; Pacák et al., 1993; Venihaki et al., 1997). Next, these neuropeptides stimulate the release of adrenocorticotrophic (ACTH) hormone from the anterior pituitary, leading to the rapid ("de novo") synthesis and release of glucocorticoids (or corticosteroids), including cortisol in humans and corticosterone in rodents (herein referred to as "CORT"), from the adrenal glands (Figueiredo et al., 2003). Once released into the systemic circulation, glucocorticoids play an important role in mobilizing energy substrates and other important cellular functions away from long-term metabolic processes towards those that promote survival and rapid adaptation to homeostatic challenges (Herman et al., 2012).

Levels of CORT and other glucocorticoids generally peak in blood within 5-30 minutes after exposure to a "stressor" (Lightman, 2008). The action of CORT is mediated through two intracellular steroid hormone receptors: the mineralocorticoid (MR or Type I) receptor and the glucocorticoid (GR or Type II) receptor (Herman et al., 2012). CORT induces rapid nuclear translocation of MR and GRs where they regulate gene transcription and subsequent protein synthesis events in the cell (Karst et al., 2005; Sapolsky., 2015). CORT shows higher affinity (approx 10-fold) and binding to MR than GR (Koning et al., 2019). It is the differential binding affinity of CORT to these receptors that has important functional implications for stress biology and the stress response. For example, MRs tend to be fully occupied when CORT concentration is low, while GRs are only activated when circulating levels of CORT are high, such as during waking and responses to stress. It is the activation of the lower affinity GR, which is thought to mediate the effects of glucocorticoids on energy mobilization inflammation and neural function (Koning et al., 2019).

Regulation and termination of the stress response is achieved through negative feedback action of CORT acting at GRs in both the paraventricular nucleus of the hypothalamus (PVH) and anterior pituitary, which inhibit the further release of CRH and ACTH (Godoy et al., 2018;

Spiga et al., 2017). This delectate negative feedback control mechanism is important for maintaining the secretion of ACTH and CORT within narrow levels and preventing excessive and/or long-lasting exposure to CORT which can have pathological effects (Godoy et al., 2018). In the brain, GRs are highly expressed in the hippocampus, amygdala, and PVH, while MRs are mainly expressed in limbic areas, with high expression levels within the hippocampus and moderate expression in the parts of the amygdala and medial prefrontal cortex (Godoy et al., 2018). As discussed below, the binding of CORT to corticosteroid receptors in these brain regions is important not only for the regulation of the HPA axis activity but also in mediating the effects of stress on both behaviour and cognitive functions.

2.2. Stressor Types: Intensity, Timing and Duration of Stress

Stress can be categorized into acute and chronic types. Acute stress is defined as a recent, brief incidence of a single stressor, whereas chronic stress is defined as a persistent challenge that may or may not be a constant threat to an individual's life (Yaribeygi et al., 2017). The impact of stress is complex and can depend on many factors, including the type of stress, as well as the timing, duration and intensity of the stressor (Sandi & Pinelo-Nava, 2007; Yaribeygi et al., 2017). In addition to these distinctions, stress can also be classified into two physiological categories: psychological and physical stresses (Atrooz et al., 2021). Physical stress is characterized by physical pain in the body, including forced swimming tests and electric foot shocks (Atrooz et al., 2021). On the other hand, psychological stress may not cause physical pain, but it does lead to the expectation of bodily pain, discomfort, or anxiety (Bhatia et al., 2011). Examples of psychological stresses include maternal separation, loud sounds, elevated platform stress, immobilization, and predation (Atrooz et al., 2021).

Psychological stresses are experienced in an anticipatory state influenced by the reward system and mostly depend on limbic components (areas of the brain that control emotion, motivation, memory, and behavior regulation) (Godoy et al., 2018). The limbic circuits, along with the proencephalic nuclei, play a critical role in initiating and regulating the immediate stress response, while also helping in recovery from stress and adaptation to future stressors (Roozendaal et al., 2009). These circuits include the prefrontal cortex, amygdala, hippocampus, PVH, ventral tegmental area, and nucleus accumbens (Russo & Nestler, 2013).

In research, various models are employed to induce stress and elevate glucocorticoid hormone levels. This paper aims to center its attention on stress models within animal studies. Therefore, the subsequent paragraph will delve into an exploration of rodent stress models, particularly emphasizing the elevated platform model.

Animal models have played a significant role in advancing our understanding of stress physiology. Not only have they helped us uncover the pathophysiology of stress-related diseases, including anxiety disorders, depression, cognitive impairment, and post-traumatic stress disorder, but they have also allowed us to identify diverse stressor types. Studying the responses of animals to these different stressors can lead to the understanding of how the brain processes psychological and physical stimuli differently (Atrooz et al., 2021). Despite the differences in stressor types, the stress system is triggered in a coordinated method regardless of the stressor processing (Atrooz et al., 2021).

Several animal models have been used to investigate the influence of stress, one such model that has been demonstrated to be effective in increasing corticosterone levels is the elevated platform stress (herein referred to as “EPS”). An elevated platform model is a technique for creating acute stress in rats. The animal is momentarily placed on a small, raised platform

(Rocher et al., 2004). The platform is composed of two parts: the tower (10cm×10cm×100cm) and the platform itself. The rat will be placed in the center of the platform in an open area for a specific duration (Rocher et al., 2004). This paradigm has gained popularity in experimental investigations because of its ability to mimic acute stress situations (Kawakami & Koga, 2021). The EPS is a commonly used psychological stressor model to study the effects of acute stress in rodents (Kawakami & Koga, 2021). Studies have shown that when placed on the EPS, rodents exhibit stress-related behaviors such as freezing and anxiety-like behaviors (Kawakami & Koga, 2021). This model provides researchers with an effective tool to investigate the impact of acute stress on learning and memory processes (Kawakami & Koga, 2021). By using the EPS model, researchers can study the timing, duration, and intensity of stressors and their effects on memory and learning cognitive processes at the cellular and molecular levels.

2.3. Impact of Stress on Brain

Several forebrain structures, such as the hippocampus, amygdala, and medial prefrontal cortex, contribute to the regulation of the HPA axis and behavioural responses to stress. These brain regions serve as important anatomical substrates involved in learning, memory consolidation, executive control, and mediating emotional responses. Thus, changes in the function of these brain regions can serve as an important mechanism for mediating the effects of stress on various cognitive and behavioural functions.

2.3.1. Stress Effects: Paraventricular Hypothalamus

Before discussing the effect of stress on the forebrain, I will first review what is known about the initiation site of the HPA stress response: the PVH. The PVH is the primary regulator of the hypothalamic-pituitary-adrenal (HPA) axis, which controls how the body reacts to stress. The PVH is situated close to the third ventricle in the ventral diencephalon, and is engaged in a number of neurobiological functions, such as controlling complicated behaviors and unpleasant stress response (Jiang et al., 2022). Moreover, it regulates feeding, neuroendocrine, and autonomic control, and fever response which is necessary to maintain homeostasis (Herman et al., 2008; Jiang et al., 2022).

The hypothalamic paraventricular nucleus (PVN), which contains three functionally separate neuronal populations that modulate various stress effectors, is responsible for a major part of stress reactions: (1) magnocellular neurons that secrete neurohypophysial peptides; (2) hypophysiotropic neurons that directly control the activity of the HPA axis; and (3) neurons that regulate autonomic functions and project to the brainstem and spinal cord (Herman et al., 2016). Peptidergic neuroendocrine neurons found in the PVN medial parvocellular division plays a crucial role in regulating the HPA axis (Herman et al., 2008) by release CRH, and production of ACTH. Within hypophysiotropic neurons, chronic stress leads to increased expression of secreted products, reduced expression of glucocorticoid receptor and GABA receptor subunits and enhanced glutamate receptor expression (Herman et al., 2008). Moreover, chronic stress causes morphological plasticity in these neurons, sustained activation leads to alterations in GABAergic and glutamatergic innervation as well as changes in cell size (Herman et al., 2008).

The PVN is also one of the primary sites where glucocorticoid negative feedback regulates the HPA axis (Herman et al., 2016). GRs, which are mostly active when glucocorticoid levels are raised, such as during stress responses, are principally responsible for mediating this negative feedback. The GR is co-localized with CRH and is highly expressed in the medial parvocellular PVN, placing it in an ideal location to regulate the output of the neurons that trigger the HPA axis (Herman et al., 2016). This GR-mediated negative feedback within the PVN, often referred to as "fast feedback," is most likely non-genomic glucocorticoid signaling occurring at or near the cell membrane (Herman et al., 2016). Because genomic mechanisms would not act quickly enough to halt HPA axis activation, the rapid inhibition of CRH neurons through this non-genomic pathway is crucial for limiting the duration of glucocorticoid production following acute stress (Herman et al., 2016).

In addition to inducing the hormone response to stress, the PVH has a major impact on stress-related behaviors. It receives and integrates information from the prefrontal cortex, hippocampus, and amygdala, three brain regions essential for processing and interpreting stress-associated stimuli (Ulrich-Lai & Herman, 2009). Through this integration, the PVH can regulate behavioral responses to stress, such as fear, anger, and anxiety (Herman & Tasker, 2016). Chronic stress, however, often leads to dysregulation of PVH function, which can trigger maladaptive stress reactions and contribute to the development of stress-related disorders, including anxiety and depression (McEwen, 2007). This dysfunction highlights the PVH's critical role in maintaining the balance between adaptive and maladaptive stress responses.

2.3.2. Stress Effects: Prefrontal Cortex

The prefrontal cortex plays an important role in decision-making, emotion regulation, and cognitive functions. Furthermore, the prefrontal cortex has a critical role in regulating the encoding of threat-related behaviors, and the emotion of fear, as well as in threat inhibition, extinction and avoidance (Alexandra et al., 2022). Anatomically, the prefrontal cortex can be divided into the medial and lateral regions. The medial region can be further subdivided into the infralimbic (IL), prelimbic (PrL), and cingulate area 1 (Cg1) in rodents (Arnsten et al., 2015), is involved in fear learning and stress response in various ways. The PFC plays a significant role in the early generation of fear memories and in controlling the expression of fear depending on previously learnt information (Kesner and Churchwell., 2011).

Accumulating evidence has also found that the medial prefrontal (mPFC) is important in regulating HPA responses to stress. For example, medial prefrontal cortical neurons show robust c-Fos induction (a marker of neuronal activation) following exposure to acute and chronic stressors (Arnsten, 2009; Arnsten et al., 2015). Furthermore, bilateral lesions of the anterior cingulate or the prelimbic cortex have been found to increase ACTH and CORT responses after exposure to stress (Diorio et al., 1993; Figueiredo et al., 2003). This implies that the mPFC may exert modulatory effects on the HPA axis and corticosteroid responses. Indeed, anatomical tracing studies have revealed topographically unique projections of the mPFC to specific parts of the HPA axis circuit (Huang et al., 2013; Sullivan & Gratton, 1999; Riaz et al., 2019). For instance, infralimbic neurons project extensively to the amygdala, bed nucleus stria terminalis, and the nucleus tractus solitary, which may lead to indirect activation and modulation of PVH neurons and HPA axis responses (McEwen et al., 2015). In contrast, prelimbic and anterior cingulate neurons show modest projections to parts of the ventrolateral preoptic area, dorsomedial and peri-periventricular regions, and tend to be involved in suppressing HPA axis responses (McEwen et al., 2015).

The mPFC also shows a high level of GR expression, making it a key site in the brain for providing negative feedback regulation of CORT on stress-induced HPA axis activity (Figueiredo et al., 2003). For example, infusion of CORT into the medial prefrontal cortex blocks ACTH and CORT secretion to acute (20 min) restraint stress but does not appear to block HPA axis responses to acute ether stress, suggesting that the medial prefrontal control of HPA activity may depend on the type of stressor (Figueiredo et al., 2003).

The mPFC, PL and IL cortices also regulate context-dependent behaviour (Riaz et al., 2019). The PL is associated with the expression and consolidation of fear memories. It also helps to preserve the retrieval of fear memories and maintain the expression of conditioned fear by promoting the amygdala's activity during fear conditioning (Riaz et al., 2019). On the other hand, by suppressing the amygdala's activity, the IL promotes the suppression of conditioned fear responses and plays a key role in the extinction of fear memories (Cardoso et al., 2023). The Cg1 is associated with the attention and cognitive control processes essential for fear learning by integrating sensory and emotional information and regulating reactions to fear stimuli. This, in turn, aids in the acquisition and expression of fear memories (Huang et al., 2013). The amygdala and Cg1 both have Fos-like immunoreactivity associated with fear conditioning, while Cg2, the piriform cortex (Pir), and the entorhinal cortex (Ect) are among the other regions involved in the extinction of fear (Huang et al., 2013).

Prolonged exposure to stress can alter gene expression in the PFC, affecting its role in fear and stress responses (Arnsten et al., 2015). To sustain adaptive behaviour in response to environmental stressors, the balance between the PL and IL in stimulating or inhibiting fear and stress reactions is essential. Disruption of this equilibrium, such as from ongoing stress, can lead to disruptive stress responses and contribute to the development of stress-related conditions like depression and anxiety (Godoy et al., 2018; McEwen, 2007). These diverse and occasionally complex functions of the IL, PL, and Cg1 in fear learning and stress response underscore the importance of these PFC subdivisions in coordinating behavioural responses to stress and fear.

2.3.3. Stress Effects: Hippocampus

The hippocampus is an important part that responds to both psychological and physical stimuli (Godoy et al., 2018). The development of permanent declarative (or explicit) memory in humans and spatial (or contextual) memory in rodents depends on the hippocampus, a structure in the medial temporal lobe (Godoy et al., 2018). The hippocampus is divided into subfields, which include the dentate gyrus, Cornu Ammonis 1 (CA1), CA2, CA3, and the subiculum (McEwen et al., 2015). The dentate gyrus, as the primary input region, takes information from the entorhinal cortex and transfers it to CA3, which then relays it to the subiculum and CA1 in the hippocampal circuit before projecting it back to the entorhinal cortex and other brain areas (McEwen et al., 2015).

The hippocampus is also a crucial area of the brain that plays a critical role in memory and the control of stress hormones (Kim & Diamond, 2002). Because it has one of the largest densities of CORT receptors, it is also a target of stress hormones. The hippocampus is known to play a role in the neuroendocrine termination of the stress response by inhibiting the HPA axis through glucocorticoid-mediated negative feedback (Kim & Diamond, 2002). The hippocampus is rich in both type I MRs and type II GRs (Starkman et al., 1992). Among these, the lower-affinity GRs are primarily associated with the adverse effects of stress on the hippocampus. Under stress, GRs become heavily occupied by corticosteroids, a process linked to elevated cortisol levels, which in turn can lead to memory loss and intensely negative emotions (Labar & Cabeza, 2006; McEwen et al., 2015).

The hippocampus plays a crucial role in the HPA axis stress response (Herman et al. 2012) via PVH. GRs and MRs mediate this control, in reaction to stress, the adrenal glands release glucocorticoids, which bind to hippocampus receptors. When GRs are activated, particularly in the hippocampus, the PVH gets inhibitory signals and downregulates the HPA axis (Godoy et al., 2018). This feedback system decreases the release of CRH, which subsequently lowers cortisol synthesis (Herman et al., 2012). After a stress reaction, this mechanism helps restore homeostasis (Starkman et al., 1992). However, prolonged HPA stimulation can lead to glucocorticoid dysregulation.

Stress significantly affects the hippocampus, altering both its structure and function due to the high density of glucocorticoid receptors. Acute exposure stress, for instance, to elevated platform stress can disrupt the transmission of signals within the hippocampus (Fan et al., 2019). Elevated platform stress reduces the efficiency of GABAergic feedforward and feedback activity in the CA1 area, potentially leading to long-term depression at synapses. This diminished inhibitory activity can compromise hippocampal function, which may result in memory problems (Fan et al., 2019). In addition, stress from being on elevated platform stress for half an hour made the long-term potentiation at synapses from the hippocampus to the prefrontal cortex weaker in rats (Rocher., 2004). This is similar to dysfunction that happens in people who are depressed, showing how acute stress negatively affects the brain's ability to change and adapt in key areas that deal with memory and cognition (Rocher., 2004).

Chronic stress, in contrast, results in more pronounced changes. Daily restraint stress or three weeks of corticosteroid injections that elevate glucocorticoid levels can induce dendritic atrophy, especially in the apical dendrites of the CA3 region (McEwen, 2000). This decreases dendritic branching and synaptic connections (McEwen, 2000). This shrinking impairs the hippocampus's ability to receive and store information, exacerbating memory and spatial orientation issues. Chronic stress also inhibits neurogenesis in the dentate gyrus and CA1 (Sousa et al., 2000), exacerbating cognitive decline and making people more vulnerable to mood disorders such as depression (McEwen, 2000). Stress-induced dendritic atrophy has been demonstrated to be mitigated by medications that decrease excitatory amino acid neurotransmission, lower serotonin levels, or enhance GABAergic levels (Kim & Diamond, 2002), suggesting potential avenues for mitigating stress-related hippocampal damage.

2.3.4. Stress Effects: Amygdala

The amygdala, a crucial region involved in emotional processing, is composed of 13 distinct subnuclei, with the most clearly defined being the basolateral nucleus (BLA), the middle nucleus (MeA), and the central nucleus (CeA) (LeDoux, 2007). The amygdala plays a key role in processing physiological and behavioural responses to stress, detection and interpretation of potential dangers in the environment and is characterized by high resting tonic inhibition mediated by gamma-aminobutyric acid (GABA). The inhibition is attributed to the activation of glucocorticoid receptors rather than MR (Zhang et al., 2018). Among them, the BLA is most activated by stressors and plays a significant role in processing psychological stress (Janak & Tye, 2015).

Under long-term stress conditions, persistent HPA axis hyperactivation and resulting high circulating glucocorticoid levels can impair the amygdala's structure and function through receptor activation (Gray & Bingaman, 1996). Conversely, the neurons in CeA of the amygdala via its direct projection to the PVN of the hypothalamus or via indirect GABAergic projections to the bed nucleus of the stria terminalis, contribute to a further activation of HPA axis and release of CORT into the systemic circulation (Davis & Shi, 1999). Furthermore, the MeA of the amygdala also induces disinhibition of the PVN via GABAergic projection neurons (Jankord & Herman, 2008). However, basal HPA activity and the HPA axis responses to social interactions remain unaffected when the BLA is damaged, indicating that the connection between the BLA and HPA axis is relatively weak (Jankord & Herman, 2008). Unlike the hippocampus and medial prefrontal cortex, amygdaloid neurons stimulate glucocorticoid synthesis and the release of CORT into the systemic circulation, with the medial and central nuclei playing a critical role in regulating the HPA axis response to stress (Roozendaal et al., 2009).

Amygdaloid neurons have been shown to alter the stress response and glucocorticoid secretion. In addition, BLA neurons exhibit sustained increases in spontaneous impulse rates during emotional arousal, aiding in the emotional memories consolidation (Pelletier et al., 2005). The BLA-PFC pathway is especially important for memory consolidation and stress response (Burgos-Robles et al., 2017; Felix-Ortiz et al., 2016; Laviolett & Grace, 2006). There are significant monosynaptic glutamatergic connections using the neurotransmitter glutamate between BLA and PFC (Dilgen et al., 2013; McGarry &Carter, 2016), which are important for emotional memories, anxiety-like behavior, and fear-related reactions. The effects of prolonged stress exposure reduce glutamatergic projections to BLA interneurons, leading to BLA hyperexcitability and stress-related behavioral disorders (Wei et al., 2017). Chronic stressors and excessive corticosterone levels have been demonstrated to upregulate corticotropin-releasing factor (CRF) expression in the amygdala, resulting in increased anxiety-like behaviour (Shekhar et al., 2005; Callahan et al., 2013). The administration of a selective CRF1 receptor antagonist has been found to prevent these anxiety-like behaviours generated by elevated corticosterone, indicating the amygdala's function in HPA axis regulation. (Myers et al. 2005).

Pharmacological interventions added insight into the amygdala's role in stress regulation. For example, administering a 5HT2 receptor antagonist into the amygdala has been shown to suppress the ACTH response to photic stress, implying that serotonin may affect HPA axis activity via upstream stress effectors in the amygdala (Feldman, 1998). Furthermore, lesion studies have shown that selective damage to the CeA reduces ACTH and corticosterone release in response to various stress paradigms, such as immobilization stress, photic/olfactory stimuli, and fear conditioning (Beaulieu et al., 1986; Feldman et al., 1994; Van de Kar et al., 1991).

The MeA also plays an important role in HPA axis integration, while selective stimulation has been found to increase corticosterone release and possibly improve adrenal sensitivity to ACTH in rats (Dunn & Whitener, 1986; Saito et al., 2009). On the other hand, the basolateral amygdala (BLA) has gained a lot of attention for its role in stress regulation. This region is particularly responsive to anticipatory stressors such as restraint, swim test, and footshock, but responds significantly less to cytokine stimulation, potentially due to complex interactions between stimulation parameters (Cullinan et al., 1995; Herman et al., 2003).

The amygdala also regulates fear responses. Specifically, CeA controls many aspects of the fear response, including regulation of cortisol release by the paraventricular nucleus of the hypothalamus, elevation of the startle response by the midbrain, and regulation of the autonomic nervous system by the lateral hypothalamus (Zhang et al., 2018). Brain imaging studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have found that fear stimuli, such as fearful faces, fearful-inducing images, and fear-conditioned stimuli, activate the amygdala (Ressler, 2010; Phan et al., 2002). In addition to imaging studies, patients who have undergone temporal lobectomy and consequent loss of the amygdala have demonstrated impaired fear-conditioned startle sensation (Funayama et al., 2001).

3. Effect of Stress on Learning and Memory

Stress is well known for its effects on neurocognitive processes, with ample data suggesting that it can alter functions such as attention, memory, learning and decision-making. Despite this broad understanding, the particular processes by which stress influences learning and memory remain unclear. Specifically, it is unclear which components of these cognitive processes are most susceptible to the impacts of stress. (Sandi & Pinelo-Nava, 2007)

3.1.1. Neural mechanisms underlying learning and memory

Memory can be broken down into a process that includes three main stages encoding, consolidation, and retrieval. Acquiring and processing information and then translating it into a form the brain can store is known as encoding (Liu et al., 2021). Consolidation is the process of stabilizing and integrating memory into long-term storage making it resistant to interference and deterioration (Goedert & Willingham, 2002). Memory consolidation can be influenced by different factors, including sleep and stress (Sridhar et al., 2023). Finally, retrieval is the process of accessing, selecting, and reactivating or reconstructing stored memory to access previously encoded information (Sridhar et al., 2023). Retrieving memories requires activating relevant neural networks while reconstructing encoded information. This process can be influenced by contextual or retrieval cues and familiarity with the content (Sridhar et al., 2023).

Georg Müller and Alfons Pilzecker originally put out the hypothesis of memory consolidation in 1900. According to Müller and Pilzecker (1900), it entails the stabilization of recently learned knowledge into durable, long-term memory (Genzel & Wixted, 2017). Memory is formed through the formation of memory traces, which are labile and vulnerable to damage or loss (Kandel et al., 2014). However, over time, a cascade of cellular and molecular events occurs within neurons and at synapses, stabilizing connections and forming memory traces that are difficult to disrupt (Kandel et al., 2014; Schafe et al., 2000). This process is called cellular consolidation and can take up to 100 hours to complete (Kandel et al., 2014). This process occurs in two stages, an initial protein synthesis-independent stage, followed by a protein synthesis-dependent stage (Kandel et al., 2014).

The protein synthesis-dependent stage activates in response to memory-evoking stimuli, calcium ions enter neurons via NMDA (N-methyl-D-aspartate) receptors and L-type voltage-gated calcium channels (VGCC). This activates protein kinases leading to the phosphorylation of mitogen-activated protein kinase (MAPK) and cyclic-AMP response element-binding (CREB), promoting the transcription of immediate early genes (IEGs) (Bailey & Kandel, 1993; Nimchinsky et al., 2002). The subsequent changes in neuronal structure, such as increased dendritic spine density, improve communication between neurons, a process known as synaptic plasticity (Majewska et al., 2000). The ultimate goal of consolidation is to convert transient changes in the synapse into long-term structural changes, which enable memories to be retained for an extended period of time (Kandel et al., 2014).

Synaptic plasticity is a fundamental concept in neurobiology that plays a pivotal role in the mechanisms underlying memory formation and recall. It refers to the brain's remarkable ability to modify the strength and efficiency of connections, or synapses, between neurons in response to experiences and learning (Majewska et al., 2000). These modifications include changes in synaptic structure, neurotransmitter release, and receptor sensitivity. Synaptic plasticity is a dynamic process with two primary forms: long-term potentiation (LTP), which strengthens synaptic connections, and long-term depression (LTD), which weakens them (Kandel et al., 2014).

In the 1970s, Donald Hebb developed the concept of long-term potentiation (LTP) in the hippocampus (Squire et al., 2009). These key results prompted a major and ongoing effort to describe a synaptic phenomenon that is now widely accepted to be a biological correlate of memory formation (Squire et al., 2009). Long-term potentiation refers to the persistent strengthening of synapses, leading to a long-lasting increase in synaptic transmission within a neural network (Baudry, 2001).

Hebbian plasticity refers to the processes that are known to play a role in the establishment and maintenance of synaptic plasticity, specifically associative plasticity. Early research found that the characteristics of LTP reflect the Hebbian learning rules (Baltaci et al., 2018). This process is considered to be essential to associative learning (Martin et al., 2000; Tsien, 2000; Bliss & Collingridge, 1993). According to Hebbian plasticity rules when pre- and postsynaptic cells are activated concurrently, associative links are created between them (Blair et al., 2001; Bauer et al., 2002). This results in long-term alterations in the synaptic effectiveness of the two neurons. Calcium influx into postsynaptic neurons via excitatory amino acid receptors, especially NMDA receptors and VGCC, is commonly acknowledged to be the event that starts Hebbian plasticity (Blair et al., 2001; Bauer et al., 2002).

Similar to memory consolidation, memory retrieval is also a complex process that requires reactivating neural patterns generated during encoding, which allows the brain to recall specific memories (Sridhar et al., 2023). Contextual or retrieval cues can influence this process, and their presence frequently also determines the success of memory retrieval (Sridhar et al., 2023). Retrieving the past memories, centred mostly on the hippocampus, prefrontal cortex, and amygdala. The hippocampus is important for consolidating and retrieving episodic memories, which are distinctive from previous events (Wagner, 2007). During retrieval, the hippocampus reactivates the neuronal patterns associated with the memory's original encoding, allowing for the retrieval of context details (Cabeza & Nyberg, 2000; Wagner, 2007). The prefrontal cortex organizes and coordinates the recall process, which includes memory reconstruction and contextual aspects (Gershberg, 1995; Li et al., 2022). The connection of these regions, mediated by neuronal networks and synaptic plasticity mechanisms such as LTP, enables precise retrieval of earlier memories. The amygdala also participates by adding emotional components of memory, particularly in the context of fear (Li et al., 2022). It influences the strength and stability of fear memories by interacting with the hippocampus and prefrontal cortex. The amygdala's involvement is especially critical in the retrieval of fear memories because it helps prompt an appropriate emotional reaction when the event is retrieved and plays crucial role in processing fear memory (Wagner, 2007).

Fear memories are important for survival. These memories elicit appropriate context-specific responses that is crucial for survival, enabling animals to anticipate danger from seemingly neutral contexts (Fanselow, 2018; Alexandra Kredlow et al., 2022). The neurobiology of contextual fear memory retrieval involves complex neural circuitry that allows for the retrieval of fear responses associated with specific environmental contexts (Maren et al., 2013). This process is coordinated by the hippocampus, PFC, and amygdala. The amygdala plays a crucial role in the formation and expression of fear memories (Zhang et al., 2021). Excessive fear learning can lead to changes in the composition of glutamate receptors within the amygdala, contributing to the development of maladaptive memories (Wang et al., 2009; Conoscenti et al., 2022). Additionally, other regions such as the retro splenial, infralimbic, prelimbic, and cingulate cortices, as well as the reuniens and paraventricular nuclei of the thalamus, are also involved in the regulation of fear memory (Alexandra Kredlow et al., 2022; Haubrich & Nader, 2023).

The hippocampal-PFC circuit is important role as hippocampus encodes and sends contextual information to the PFC, which subsequently governs how fear is expressed based on that context. This regulation enables for adaptive reactions to environmental changes, allowing fear to be expressed or suppressed according on the context. In addition, the Hippocampal-Amygdala Circuit is responsible for integrating emotional reactions with cues (Kim & Cho, 2020). The hippocampus is important in retrieving fear memories because it sends contextual representations to the amygdala, which combines these signals with unpleasant stimuli to construct and retrieve fear memories. This hippocampal-amygdala controls fear responses' intensity and relevance, ensuring that fear is directed appropriately toward circumstances that indicate danger (Apps & Strata, 2015) and the activation of specific hippocampal neurons, in the ventral CA1 region, conveys this contextual information to the amygdala, resulting in conditioned fear responses (Kim & Cho, 2017).

Memory engram cells in the hippocampus and amygdala - neuronal ensembles responsible for encoding and storing memories - are critical in the encoding and retrieval of fear memories (Guskjolen & Cembrowski, 2023). These engram neurons, when reactivated during learning, can facilitate memory retrieval, in line with the encoding specificity principle, which suggests that restoring the brain state present during memory encoding is essential for effective retrieval. Additionally, memory retrieval intermittently increases engram excitability, enhancing memory performance, particularly in tasks that require contextual discrimination (Guskjolen & Cembrowski, 2023).

Despite these insights, the exact mechanisms by which these engram cells interact and how the synaptic strength between them is modified to encode contextual fear memory and the processes underlying fear memory retrieval remains unclear.

3.2. Impact of acute stress on learning and memory

Stress has memory-modulating properties in both humans and animals. The human hippocampus, prefrontal cortex, and amygdala are crucial brain regions for memory and are notably rich in cortisol receptors. The presence of these receptors highlights how stress interacts with critical brain systems, causing complicated and diverse impacts on learning and memory. These effects differ depending on various parameters, including the type and level of stress (acute, chronic, mild, moderate, or severe), the timing of stress within the memory process (encoding, consolidation, and retrieval), and the nature of the learning stimuli (neutral or emotionally stimulating). While stress may enhance memory formation, especially when it is intense and emotionally charged, it can sometimes have detrimental effects.

3.2.1 Effect of acute stress on learning

The effects of acute stress on learning and memory have been extensively studied, with both human and animal models indicating that stress may enhance learning processes. For example, a 20-minute session of elevated platform stress improved learning and memory performance by activating stress hormones (Yuen et al., 2009). This was achieved by increasing synaptic currents in the PFC, which are mediated by NMDA and AMPA receptors, hence improving working memory. Similarly, fear relapsed in rats, and elevated platform stress-induced stress influenced the return of conditioned fear, suggesting that stress impacts multiple brain regions and types of memory, such as the PL and BLA, without involving the hippocampus (Xing et al., 2021). In addition, low levels of corticosterone have been shown to improve cognitive functions in mice (Sandi & Rose, 1994), however excessive levels of stress hormones can have detrimental effects on learning and memory (Meaney et al., 1988).

However, the effects of stress are not universally positive, and under certain conditions, such as the timing of stress exposure and whether stress is encountered before, immediately after, or during post-learning stages (Joëls et al., 2011), they may potentially interfere with learning. For example, acute stressors like as restraint or exposure to predator odour have been shown to increase the reinstatement of previously extinguished behaviours, including drug-seeking behaviours (Armstrong et al., 2023; Mantsch et al., 2016). While these stressors frequently enhance reinstatement, they can also impair learning performance due to stress-induced behaviour, such as conditioned freezing (Pizzimenti et al., 2017).

Moreover, acute stress can cause a lasting internal state that has been associated with acquired contingencies, potentially leading to relapse or reinstatement of behaviours when the original context is revisited (Schepers & Bouton, 2019; Self & Choi, 2004). This stress-induced inflexibility in behaviour, in which animals must adapt to new conditions. For example, the single prolonged stress paradigm, which includes intense stressors such as restraint and forced swimming, has resulted in long-term deficits in fear extinction (Souza et al., 2017). Similarly, the stress-enhanced fear-learning process shows that prolonged severe stress can cause exaggerated fear responses to mild stressors, with adverse long-term effects (Perusini et al., 2016; Pizzimenti et al., 2017).

The effects of acute stress on memory retention in humans, particularly in relation to its timing relative to learning, are complex. Stress triggers the release of glucocorticoids, which have been shown to impair long-term memory for neutral experiences but enhance memory for emotionally charged events compared to control conditions (Buchanan & Lovallo, 2001; Jelici et al., 2004; Payne et al., 2007). Stress negatively affects the retention of neutral information, enhancing the consolidation of emotional memories, and illustrating the nuanced impact of stress on memory processes (Sabia & Hupbach, 2020).

Similarly, stress experienced immediately after learning was found to strengthen the ability to recall neutral images, signifying an enhancement in recognition memory compared to a non-stress control condition (Yonelinas et al., 2010), particularly when it occurs immediately after learning, enhances long-term memory retention (Andreano & Cahill, 2006; Cahill et al., 2003). Also, exposure to stress following learning can have a detrimental effect on memory recall, especially for emotionally charged content (Buchanan et al., 2006; Kuhlmann et al., 2005; Schwabe & Wolf., 2014). The enduring impact of stress on associative learning, fear conditioning, and cognitive performance demonstrates the complexity of the stress response and implies that its effects are not always beneficial but vary depending on the context, nature, and timing of the stress.

The process by which acute stress influences learning involves stress mediators that progressively reach and alter brain regions (Joëls and Baram, 2009). Stress exerts a profound impact on learning and memory through its effects on the central nervous system, particularly by altering the functions of the hippocampus, PFC and amygdala.

Stress impacts the hippocampus by influencing levels of Brain-Derived Neurotrophic Factor (BDNF) and neurogenesis, both of which are critical for learning. Acute stress, for example, lowers BDNF levels and inhibits neurogenesis in the dentate gyrus, affecting the formation of new memories and LTP, a critical synaptic plasticity mechanism associated with learning and memory (Lakshminarasimhan & Chattarji, 2012; Schoenfeld & Gould, 2013). Also, stress inhibits LTP, particularly in the CA1 region of the hippocampus, preventing the formation and retrieval of new memories (Lindau et al., 2016). Furthermore, stress-induced decreases in hippocampal GRs, as shown in aged rats, are associated with reduced spatial learning, such as difficulties navigating the Morris water maze, a standard rodent spatial learning task. The administration of GR antagonists further affects learning, highlighting the significance of GR-mediated processes in spatial memory (Lindau et al., 2016).

As discussed, the amygdala is important for emotional learning and memory. Stress and glucocorticoids affect amygdala function, particularly in the basolateral nucleus, where GRs impair memory storage. Glucocorticoid agonists administered to this region following learning can improve the retention of acquired fear responses (McGaugh & Roozendaal, 2008).

The amygdala also interacts with other brain regions, including the hippocampus and cortex, to regulate stress hormone effects on learning processes. For instance, the release of noradrenaline into the amygdala during emotional arousal promotes learning by improving memory consolidation. This noradrenergic activity modulates memory processes in the hippocampus, affecting the consolidation of emotional memories (Lindau et al., 2016). However, excessive noradrenaline release impairs learning by causing hyperarousal or anxiety, which can interfere with cognitive processes. Furthermore, pharmacological inhibition of noradrenaline receptors in the amygdala has been found to disrupt LTP in the hippocampus, highlighting the amygdala's role in hippocampal function, learning and memory consolidation (McGaugh and Roozendaal, 2008).

3.2.2. Effect of acute stress on memory consolidation

The information encoded into memory during stressful experiences is generally well remembered (Kim and Diamond, 2002), particularly if the information is relevant to the stressor (Joëls et al., 2006; Sandi and Pinelo-Nava, 2007; Smeets et al., 2009). Although this phenomenon represents adaptive behavior, dysregulation of the underlying mechanism might lead to psychological trauma and potentially mental disorder (McEwen, 2004; de Kloet et al., 2005). It is widely believed that rapidly unfolding neurochemical events during the initial stress phase exert immediate effects on attentional, sensory, and mnemonic processes (de Kloet et al., 2005). Nevertheless, these possible effects of acute stress have been largely overlooked and are not well understood.

The effects of stress on memory, especially its immediate effects, have been extensively investigated in numerous rodent studies. Acute stress-induced increases in plasma corticosterone disrupted different stages of memory processing (Li et al., 2012). In particular, when acute restraint stress was applied immediately after memory acquisition, it impaired the consolidation of short-term (4 h) to long-term (24 h) memories. Moreover, rising levels of corticosterone in the blood due to stress are linked with impaired memory consolidation (Li et al., 2012). Also when stress applied during a brief interval between the retrieval test and the information acquisition, can affect various systems, including consolidation, short-term memory, storage and retrieval, typically lasting from 30 minutes to 4 hours (Baker and Kim, 2002; de Kloet et al., 1999; Diamond et al., 2005). In addition, stress hinders the recovery of previously learned information (retrograde amnesia) but does not affect the ability to form new memories (anterograde amnesia) (Diamond et al., 1996; Diamond et al., 1999; Sandi et al., 2005; Woodson et al., 2003). For instance, rats were placed on a 14-arm radial maze and allowed to explore for food in seven of their arms. After consuming the food in four of these arms, they were exposed to an unfamiliar environment, which caused stress, followed by a four-hour wait. Following this interval, they were reintroduced into the maze to search for food in the remaining three baited arms (Diamond et al., 1996). The results showed that stress hindered the recovery of previously learned information (retrograde amnesia) but had no effect on their ability to form new memories (anterograde amnesia) (Diamond et al., 1996).

Similarly, acute stress can either impair or enhance memory consolidation in humans, depending on the timing after learning (Sabia & Hupbach, 2020). For example, the impact on subjects' recognition of neutral and negative visuals after exposure to skydiving-induced stress immediately after learning strengthened their ability to their memory consolidation and recall neutral images, signifying an enhancement in recognition memory compared to a non-stress control condition (Yonelinas et al., 2010). In addition, participants were exposed to a series of slides, followed by either a non-stressful control task or an acute cold pressor stress task designed to elevate cortisol levels, exhibited significantly enhanced memory consolidation and long-term memory retention of the presented slides one week later compared to non-stressed individuals (Cahill et al., 2003). It is important to note that the influence on memory varies with the timing and intensity of stress exposure, highlighting that the impact of stress on memory consolidation is complex and not a one-size-fits-all scenario.

Memory consolidation and learning, both processes involve the hippocampus, amygdala, PFC and noradrenergic system. Memory consolidation primarily involves stabilizing and storing information after it has been learned, whereas learning is centred on acquiring new information. The neural mechanisms of acute stress on these processes overlap but differ in timing and specific pathways activated (Reul & Kloet, 1985). The output of the activated brain areas transmits to the hypothalamus, where it activates the fast-acting sympatho-adrenomedullar system and the slower-acting hypothalamus-pituitary-adrenal axis (Corbett et al., 2017). Both systems influence the function of peripheral organs while simultaneously feedback to the brain via adrenaline and corticosterone, respectively. Adrenaline can cause the central release of noradrenaline from the locus coeruleus via intermediate processes involving the nucleus tractus solitarius, which can then reach the amygdala, prefrontal cortex, and hippocampus. Corticosterone is distributed throughout the brain; however it only activates in receptor-rich areas (Corbett et al., 2017) and regulates memory consolidation. While the mechanisms by which stress or glucocorticoids decrease LTP and facilitate LTD remain unknown, NMDA-receptor activation during stress exposure and an active amygdala are essential (Morris, 1989).

Corticosterone's effects can be seen even in decreased hippocampal preparations that lack amygdala input (Ahmed et al., 2006). Several suggested mechanisms, including changes in after-hyperpolarization amplitude, calcium currents, or LTP-like variations in glutamate transmission, may interfere with LTP induction in a metaplastic manner.

LTP in limbic regions, which is mediated by NMDA-receptor processes, plays a critical role in memory consolidation. For example, acute stress, such as exposure to inescapable shock, has been shown to affect LTP induction in the CA1 hippocampal area—a finding that has been confirmed and linked to the ERK pathway (de Kloet et al., 2005). In addition, stress promotes the onset of long-term depression through a GR-dependent mechanism, with even acute stressors such as novelty changing the balance between LTP and LTD, implying a complicated, inverted U-shaped dose dependency and influence on memory retention. This complicated association suggests that severe or persistent stresses are particularly effective at suppressing LTP induction (Joëls et al., 2006).

3.2.3. Effect of acute stress on memory recall

The animal studies have significantly advanced our understanding of the effects of acute stress on memory recall. Acute stress can either impair or enhance memory recall, depending on several factors such as timing, the type of stressor, and the brain regions involved. For instance, administering stress before learning can enhance memory in humans. In this study, participants were given either cortisol (20mg) or a placebo one hour before being shown photographs. After a week, incidental memory for the photographs was tested, and the results discovered that high cortisol levels during memory acquisition significantly improved the long-term recall ability of emotionally stimulating pictures compared to neutral pictures, signifying that elevated cortisol levels during stimulating situations can lead to better memory retention in individuals (Buchanan and Lovallo., 2001). In contrast, rats underwent 60 minutes of cold-water stress, followed by acquisition trials. Twenty-four hours after the initial test, this was repeated three times to examine the long-term effects of stress on the rats' performance. The results showed that two different species of rats displayed an immediate increase in latencies to enter the dark compartment following stress exposure (Klenerová et al., 2002). After facing subsequent stress their response became much enhanced. But the rats' ability to learn the task remained unaffected during the stress-free phase. The results showed that the recurrent cold-water stressor served as a potential stimulus to amnesia, impacting the rats' memory recall despite their retained ability to learn the task (Klenerová et al., 2002; Diamond et al., 2006).

In addition, subsequent treatment with corticosterone found to improve memory in rodents (Lupien & McEwen, 1997; McGaugh, 2004; Kloet et al., 1999; Roozendaal et al., 2006). Effects of a rapid post-training systemic injection of glucocorticoid corticosterone on object recognition memory revealed improved memory retention in rats administered corticosterone immediately after a 3-min training trial over a 24-h interval (Okuda et al., 2004). Overall, these studies suggest that acute stress enhances memory retrieval, particularly when stress or glucocorticoid administration occurs shortly after learning in rodent research but impairs retrieval in all other instances (Andreano & Cahill, 2006; Cahill et al., 2003; Roozendaal et al., 2006).

4. Hypotheses and Objectives

To date, the available evidence suggests that stress has been found to exert profound effects on memory processes, influencing both encoding and retrieval stages. Understanding how stress impacts memory formation, consolidation, and retrieval is essential for elucidating the mechanisms underlying human cognition. However, there has been minimal research examining the effects of stress on recalling previously acquired fear memory at different time points. This paper aims to address the gap in the literature regarding the timing of stress exposure and its impact on fear memory retrieval in rats. It also seeks to investigate whether reelin can potentially mediate stress-induced memory impairment. As acute stress is a common occurrence in daily life, these findings could have significant implications for our understanding of the complex effects of acute stress on memory.

Overall, this thesis will address the impact of acute stress on previously acquired contextual fear memory using rats. Therefore, we proposed two main objectives:

4.1 Objective 1

Acute stress can impact fear learning and recall in various ways (Arnsten et al., 2015; Bhatia et al., 2011; Brosens et al., 2024). For instance, acute stress can impair the recalling of fear memories (McEwen & Morrison, 2013) as well as enhance fear memory recall depending on the timing of stress exposure (Fukushima et al., 2014). This complexity can be attributed to the timing of stress exposure in relation to the learning phase. The objective is to examine how exposure to acute elevated platform stress at various time points affects previously learned fear memory. To achieve this goal, the experiment compared freezing behavior between stressed and non-stressed rats (controls) during retention testing of a contextual fear memory at several time periods, including before and after elevated platform stress exposure. From here, the paper will also examine how acute stress impacts recalling the previous fear memory at 3 different time points. Two times points are: Stress-exposure two days after fear memory acquisition, and a week after fear memory acquisition. Previous studies have found that post-learning stress can impair the memory even after 90 mins post-stress (Schwabe et al., 2014) but literature lacks knowledge on how long this stress-induced memory impairment persist. We hypothesize that rats exposed to stress recently will have impairment in retrieving the previously acquired fear memory compared to rats exposed to stress after a week interval, despite both groups having comparable acquisition prior to stress exposure.

4.2 Objective 2

Various studies have established that in response to stress, c-Fos expression is activated in different regions of the brain (Kononen in 1992). Additionally, research has shown that chronic exposure to stress leads to a reduction in c-Fos expression in various parts of the brain (Cohen et al. in 2020; Kononen in 1992). However, there is a lack of studies that investigate cFos gene expression in both acute stress and repeated exposure to acute stressors. The first study is looking to examine the impact of repeated stress on cFos expression. For this, rats were exposed to stress for one day versus three days, and a control group with no stress exposure was also included. The hypothesis is that there will be no difference in cFos expression between rats exposed to stress for one day versus three days, and cFos expression will decrease in mPFC in stressed rats compared to non-stressed rats. To further investigate the neural mechanism behind the impairment in fear memory retrieval, the second study examined freezing behavior between stressed and no-stressed control rats during retention testing of a contextual fear memory following stress exposure. Consistent with the rationale for the previous objective, the first hypothesis for this objective is that stressed rats will freeze less during retention tests than controls. Next, to investigate the effects of stress on reelin mRNA expression that may drive differences in freezing behavior, we will perform RT-PCR to assess the differences in mRNA expression within the mPFC. It was determined in a study that the impact of chronic corticosterone on depression-like behavior was inversely associated with low reelin mRNA expression in the mPFC between groups (Fournier et al., 2009). Therefore, we hypothesize that the stressed rats will have lower levels of reelin mRNA expression than controls within the mPFC. Also, it was proposed that intravenous reelin administration could reverse stress-induced memory impairment.

CHAPTER II

The Effect of Stress on Fear Memory Retrieval: A Behavioral Experimental Study

1. Introduction

Stress is widely recognized as having a major impact on behavior and cognition (Yaribeygi et al., 2017). Chronic and acute stress can cause a variety of behavioral and cognitive problems, including increased fear and anxiety, post-traumatic stress disorder (PTSD), and memory deficits (Campeau et al., 2011; Sandi and Pinelo-Nava, 2007). These comorbid illnesses significantly decrease the quality of life and provide significant issues for patients. Given the frequency of acute stress in everyday life, it has been demonstrated to have serious consequences for numerous aspects of physical and mental health (Schneiderman, 2005). Further study in this field has revealed that acute stress can have a significant impact on decision-making and problem-solving abilities (Starcke and Brand, 2012). Aside from the immediate physical and emotional responses, acute stress has been shown to affect the prefrontal cortex, which is responsible for executive functions such as planning, decision-making, and self-control (Cerqueira et al., 2007). However, the diversity and heterogeneity of patient groups make understanding the impact of stress on behavioral changes in memory studies difficult (Sandi & Pinelo-Nava, 2007). To address these issues, researchers have turned to animal models, which provide a more controlled environment for investigating these subjects. Among these models, the elevated platform stress model stands out as a notable example (Patchev & Patchev, 2006; Pesarico et al., 2021).

The elevated platform stress model is often used to imitate psychological stress in animals (Pesarico et al., 2021). Following context fear acquisition training, this model uses an elevated plexiglass platform in a well-lit room. This model, which consists of two parts—the tower and the platform itself, has been shown to induce behavioral responses such as anxiety and fear in animal subjects, as well as physiological changes that provide valuable insights into the behaviors associated with acute stress (Campos et al., 2013; Lezak et al., 2017). Exposure to acute stress rapidly activates the HPA axis, causing physiological changes in the brain and body via glucocorticoid release. The activation of CRH in the PVH stimulates the secretion of ACTH in the anterior pituitary gland, promoting and synthesis and releasing glucocorticoids from the adrenal cortex (Herman et al., 2016).

Glucocorticoids, including corticosterone, influence the brain by controlling gene expression and activating cellular signaling pathways quickly. They also have slower-acting effects on cellular adaptability (Evanson et al., 2010; Joels et al., 2012). Because glucocorticoids have distinct methods of action, they can impact neuronal circuits rapidly during stress exposure and over time, leading to structural or functional plasticity (McEwen, 2017). These alterations in brain activity can have a major effect on an organism's behavioral response to stress (McEwen, 2017; McEwen et al., 2015). Although the effects of acute stress on memory have been extensively studied, little is known about how it affects learned fear memory.

Several studies have found that acute stress can accelerate the formation of fear memories while impairing their extinction (Miracle et al., 2006; Suvrathan et al., 2014). However, in most of this research, stress exposure comes before fear and extinction learning. Therefore, little is known about how stress affects memories that have already been established before stress exposure. The present study aimed to fill the gap by examining whether repeated exposure to acute stress impacts the retrieval of contextual fear memories.

Contextual fear memory is an important component of adaptive behavior because it allows humans to retain and respond to contextual cues linked with prospective risks (Xing et al., 2021). According to Suvrathan et al. (2014), stress is a known modulator of memory processes that can either improve or worsen memory retrieval, depending on time and how intense stress is experienced. According to research, memory outcomes can be significantly impacted by the timing of stress exposure in relation to the learning event (Joëls & Baram, 2009). According to Joëls & Baram (2009), memory retrieval can be hindered by chronic stress or stress exposure that occurs for an extended period after the learning event, whereas acute stress that is administered immediately before or after learning can improve memory consolidation (Joëls & Baram, 2009). It is an interesting topic of research, even though the precise effects of timing on the recovery of contextual fear memory after fear training are not well studied. It is crucial to comprehend how the timing of stress exposure may affect the recall of contextual fear memories that have already been learned. As the ability to retrieve fear memories linked to potential danger is crucial for adaptation, difficulties in retrieval can contribute to the development of generalized anxiety disorder.

The purpose of this study is to investigate the impact of stress exposure at three different time periods after fear memory acquisition, using EPS as an unconditioned stressor, in order to better understand the effect of stress on the retrieval of previously acquired contextual fear memory. To condition fear memory in rats, this experiment employed Pavlovian fear conditioning. Animals trained in Pavlovian fear conditioning are frequently employed to examine the etiology, treatment, and stress-induced recurrence of mental disorders including post-traumatic stress disorder (PTSD). Fear conditioning is a type of Pavlovian conditioning in which a neutral conditioned signal (such as a context; CS) is combined with an unpleasant unconditioned stimulus (such as a footshock) (LeDoux, 1995). When the CS and US are presented together, the CS predicts an unpleasant result and causes a conditioned response (CR), which may result in tachycardia, defecation, piloerection, and freezing behavior (LeDoux, 1995).

In the process of inducing conditioned fear, an aversive unconditional stimulus (US) is paired with a neutral stimulus (conditioned stimulus, CS) (LeDoux, 1995). Subsequently, presenting the CS alone repeatedly leads to fear extinction, where the fear response is mitigated. However, it's important to note that extinction doesn't erase the original fear memory (Bouton, 2004). Instead, it results in the acquisition of a distinct extinction memory, which temporarily suppresses fear expression (Bouton, 2004).

Humans are constantly exposed to stressors and pressures that are unrelated to the cues and environments of their initial (pathogenic) conditioning episodes. Therefore, the goal of this study is to better understand the effect of stress on fear memory retrieval by conducting two behavioral experiments that manipulate stress between the fear memory acquisition and retrieval sessions.

2. Materials and Methods

2.1 Subjects

The study followed the Canadian Council of Animal Care guidelines and received approval from the Trent University Animal Care Committee. The experiments used adult male Long-Evans or Sprague Dawley rats which were around 3 months old at the start of behavioral training from the Charles Rivers Laboratory in Québec, Canada. Rats, weighing approximately 260-310 g, were housed individually in a temperature-controlled room (21°C ± 2°C) with a light schedule of 07:00 h on and 19:00 h off. The behavioral tests were conducted during the light phases of the cycle, and the rats had food and water available ad libitum throughout the entire study.

2.1.1 Behavioral Test

2.1.1.1 Apparatus

Context-fear conditioning was conducted in two standard Ugo Basile (Varese, Italy) conditioning chambers housed in sound-attenuating cabinets. The Plexiglas-made boxes had dimensions of 25.4 x 25.4 x 36.5 cm with a circular front opening door. The floor was made of 21 metal rods (3 mm in diameter), each spaced 1.2 cm from center to center. Each conditioning box was kept in a soundproof room (54.3 x 46.4 x 55.1 cm). The floor's metal rods were connected to a shock generator and a scrambler, which were used to administer the shocks (Ugo Basile, Varese, Italy). Before and after each rat performed conditioning or retention testing, the boxes were cleaned with Oxivar Five 16 concentrate (1:16 dilution). A USB 2.0 Monochrome Industrial Camera (DMK 22AUC03, Imaging Source, Charlotte, NC) linked to a Dell laptop and set above the conditioning chamber was used to video record each conditioning and retention test session.

Context fear assessment, behavioral scoring, and ANY-MAZE software (Stoelting, Wood Dale, IL) were employed. During training and testing, ANY-MAZE was programmed to keep the internal box light level at 100 lux and the fan intensity at 100%. Each rat's freezing time, which is defined as the absence of movement except for breathing, was also measured by the software every 60 s. After 250 ms of continuous freezing, a rat was considered freezing. Each rat's duration of freezing state was calculated and utilized as a measure of memory.

2.1.1.2 Context Fear Conditioning (Acquisition)

Rats were trained on a robust context fear learning procedure to create a fear memory that would be resistant to extinction from repeated testing. Each rat was subjected to a sequence of 5 pairings of context shock, wherein each instance of aversive stimulation consisted of a 1.2 mA shock administered for a duration of 2 seconds, with an inter-stimulus interval of 60 seconds. These contextual-shock pairings were administered during 8-minute sessions, separated by intervals of 24 hours. The grouping of rats into either Control or Stress cohorts was determined by their freezing percentage observed throughout the entirety of the acquisition session.

2.1.1.3 Elevated Platform Stress (EPS)

Forty-eight hours after the conditioning, a subset of rats was exposed to EPS for three consecutive days. Rats were gently placed on an elevated Plexiglas platform (10 cm x 10 cm, 100 cm tall) in a brightly lit room following context fear acquisition training. The platform was composed of two parts: the tower (10cm×10cm×100cm) and the platform itself. In the first session, the platform was (10cm×10cm); however, to accommodate the rats' growth, it was replaced by a larger platform (15cm×15cm) in the following sessions if required. The apparatus was placed inside an open field arena (150cm diameter) which was filled with corn bedding (4cm in height) to ensure the animals' safety if they were to fall or jump off the platform. The rats were placed in the center of the platform for 60 minutes. Any rats that fell or jumped from the platform were immediately returned to the platform and testing resumed. At the end of their session, the rats were transported back to their home cages. Rats within the stress-exposed cohort were subjected to a regimen comprising three elevated platform stress exposure sessions, commencing 48 hours subsequent to the last acquisition session.

2.1.1.4 Context Fear Conditioning (Retention Tests)

Retention tests were conducted by returning rats to their respective conditioning chambers 48 hours after the last elevated platform stress exposure and allowing them to freely explore for 5 minutes. No shocks were administered. Subsequently, the second and third retention tests were conducted at intervals of 48 hours following the completion of the final elevated platform. Conditioned fear was assessed at multiple time points after exposure to EPS by measuring the amount of defensive freezing the animal exhibited during a 5-minute test session. The chambers were cleaned between rats using an Oxivar cleaning solution, to minimize potential olfactory cues.

2.1.1.5 Perfusion and Tissue Preparation

Animals were euthanized 90 minutes after the completion of the last retention test. The experimental procedure involved the administration of anesthesia to the rats through an intraperitoneal injection of sodium pentobarbital (0.5 mL; 340 mg/ml) (Euthansol; Merck Animal Health Canada). Following this, the rats were intracardially perfused with 200 mL of 0.1M phosphate buffer saline (PBS) and subsequently with 200 mL of a 4% histological fixative paraformaldehyde (Kalinina et al., 2019). This procedure was conducted approximately ninety minutes after the completion of the last retention test. Subsequently, the brains were removed and placed in 4% paraformaldehyde for a 48-hour preservation period. The brain tissue was then transferred into PBS containing 0.1% sodium azide and stored at 4°C, ensuring its preservation for future histological analysis.

Experimental Design 1

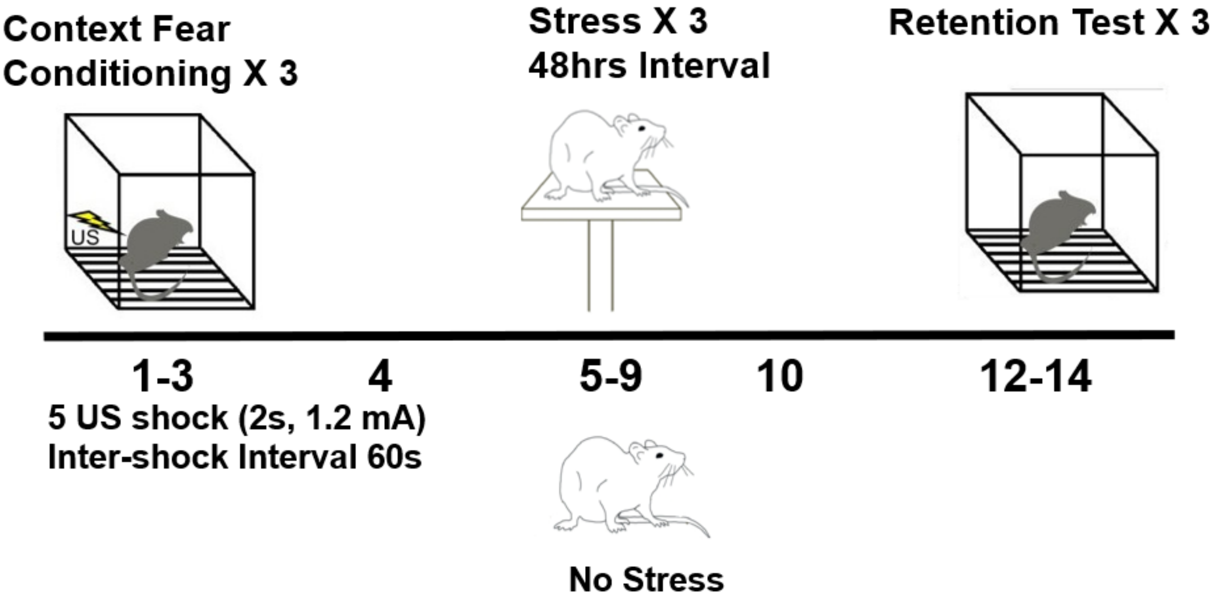


Figure 1. Illustrates the experimental design. Exposure to elevated platform stress, 48 hours after fear memory conditioning

2.2. Experiment 1

Sixteen male Long Evans rats, weighing approximately 260-310 g, were housed under the same conditions as in Chapter 2, page 47. The number of animals per group for memory testing in context fear retention testing 1,2 and 3 was as follows: No Stress; N = 8 and Stressed; N = 8.

2.2.1 Behavioral Test

2.2.1.1 Context Fear Conditioning (Acquisition)

The methodology employed in this experiment corresponds to the previous procedure detailed in Chapter 2 on page 55 for three consecutive days.

2.2.1.2 Elevated Platform Stress (EPS)

The presentation of elevated platform stress followed the procedure outlined in Chapter 2, page 55.

2.2.1.3 Context Fear Conditioning (Retention Tests)

Retention tests followed the procedures detailed in Chapter 2's methodology, page 55.

2.2.1.4 Perfusion and Tissue Preparation

Ninety minutes after the final retention test, animals were euthanized, and tissue processing was carried out using a similar method detailed in the study by Kalinina et al. (2019), page 55.

2.2.1.6 Statistical Analysis

All values are reported as means ± SEM. Statistical analysis was performed using two-way mixed-design ANOVA. All statistical analyses were conducted using the software Prism GraphPad 2017. An Alpha level of 0.05 was used to determine statistical significance.

To determine the impact of stress exposure on fear memory recall, two-way mixed-design ANOVA were conducted to compare the freezing levels between the stress group and the non-stressed group on each of the three retention testing days. These tests assessed whether there were significant differences in freezing levels between the two groups after stress exposure.

A two-way mixed-design ANOVA was applied to assess changes in freezing levels during the three days of retention testing. The within-subjects factor was the three retention testing days. This analysis is used to identify any within-group variations over time in both the stress and non-stressed groups two-way mixed-design ANOVA yielded significant results for changes in freezing levels during retention testing days, post-hoc tests (Bonferroni tests) were used to perform pairwise comparisons to identify which specific days exhibit significant differences.

Experimental Design 2

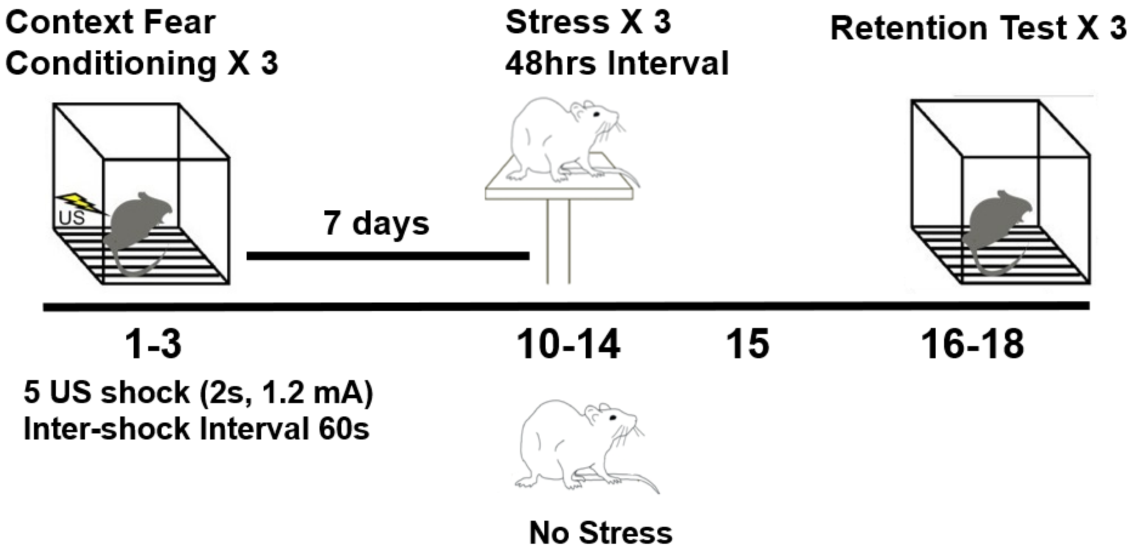


Figure 2. Illustrates the experimental design. Exposure to elevated platform stress, 7 days after fear memory conditioning.

2.3. Experiment 2

Eight male Sprague-Dawley rats weighing approximately 180-210 g were housed under the same conditions as in Chapter 2, page 47. The number of animals per group for memory testing in context fear retention testing 1,2 and 3 was as follows: No Stress; N = 4 and Stressed; N = 4.

2.3.1 Behavioral Tests

2.3.1.1 Context Fear Conditioning

The methodology employed in this experiment corresponds to the previous procedure detailed in Chapter 2 on page 55 for three consecutive days.

2.3.1.2 Elevated Platform

The presentation of elevated platform stress followed the procedure outlined in Chapter 2, page 55, with the exception of the initial stress exposure. This initial exposure took place seven days after the last acquisition session. During each stress session, the rats were positioned at the center of the platform for a duration of 60 minutes, repeated over 3 consecutive sessions with a 48-hour gap in between. After each session, the rats were returned to their respective home cages.

2.3.1.3 Retention Tests

Retention tests followed the procedures detailed in Chapter 2's methodology. The first retention test took place 48 hours after the final session of elevated platform stress. Following this, the second and third retention tests were administered at an interval of 24 hours. Each retention test lasted for five minutes.

2.3.1.4 Perfusion and Tissue Preparation

Ninety minutes after the final retention test, animals were euthanized, and tissue processing was carried out using a similar method detailed in the study by Kalinina et al. (2019). The experimental design is depicted in Figure 1.

2.3.1.5 Statistical Analysis

All statistical analyses were conducted using the software Prism GraphPad 2017 Statistics. The criterion for statistical significance was set at $P < .05$.

To assess the changes in freezing levels over the three days of fear context conditioning training after 7 days, two-way mixed design ANOVA was employed. The within-subjects factor will be the three days of conditioning, and the analysis will examine the changes in freezing levels across these days.

Additionally, two-way mixed design ANOVA was applied to assess changes in freezing levels during the three days of retention testing, with the within-subjects factor being the three retention testing days. This analysis will help identify any within-group variations over time in both the stress-exposed and non-stressed groups. A significance level (alpha) of 0.05 was used for all statistical tests to determine statistical significance.

3. Results

3.1 Exposure to EPS impairs recently acquired context fear memory

To assess the impact of stress exposure on the retrieval of fear memory, 16 rats were divided into two groups (No stress and Stress), each consisting of 8 rats. All animals underwent fear context conditioning sessions for three days each with 48-hour intervals, during which their percentage of freezing levels were measured. Subsequently, one group was exposed to elevated platform stress while the other group served as a control. Following the stress exposure, the animals were tested for their ability to retrieve fear memory over a period of three days, with the percentage of freezing levels measured during every session lasting 5 minutes. Statistical analysis was conducted to evaluate the effects of stress exposure on fear memory recall.

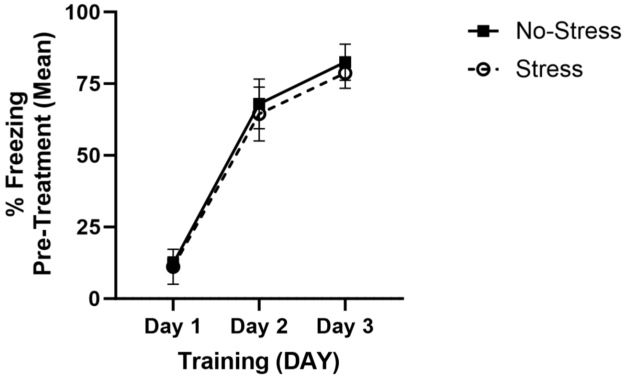
In this experiment, we explored the impact of stress on the retrieval of fear memory recently acquired prior to exposure to elevated platform stress. Figure 1 illustrates the experimental design and timeline. As expected, freezing levels increased significantly across the three days of conditioning [two-way mixed-design ANOVA, Day: $F(2,32) = 57.98$, $p < 0.001$, see Figure 5]. There was no significant main effect for Group [$F<1.00$, $p = 0.61$], nor was the interaction between Group and Day of conditioning significant [$F<1.00$, $= 0.02$, $p = 0.97$]. These results suggest that the acquisition of context fear memory was similar across both groups before exposure to stress.

Forty-eight hours after conditioning, animals were randomly assigned to either the stress (n=8) or no-stress (n=8) conditions. A two-way mixed-design ANOVA was conducted with Recall Test Day (Days 1 through 3) as the within-subject factor and Group (stress vs. no-stress) as the between-subject factor. The results showed a significant main effect of Day [$F(2,32) = 14.92$, $p < 0.001$] and Group [$F(1,14) = 11.21$, $p = 0.002$, see Figure 5] , indicating that freezing levels varied significantly across the retention test days between groups. Post-hoc tests with Bonferroni correction revealed significant decreases in freezing levels from Day 1 to Day 2 and from Day 2 to Day 3.

There was no significant main effect interaction between Group and Day significant [F (2,32) = 1.75, p = 0.18]. However, an independent samples t-test was used to compare the mean freezing levels between the no-stress group and the stress group. The analysis was non-significant for the freezing levels between the two groups on Day 1 (t(14) = 1.570, p = 0.139). But the analysis was significant between the two groups on Day 2 (t(14) = 2.254, p = 0.041), and Day 3 (t(14) = 2.212, p = 0.044). The stress-exposed group exhibited lower freezing levels on Day 2 and Day 3, indicating impaired fear memory retrieval compared to the control group.

These findings suggest that exposure to stress forty-eight hours after training significantly impaired the retrieval of fear memory. Both groups exhibited significant decrease in freezing behavior across the retention test days, indicating differential impact of stress on memory recall.

(A) Acquisition



(B) Post-Stress Retention

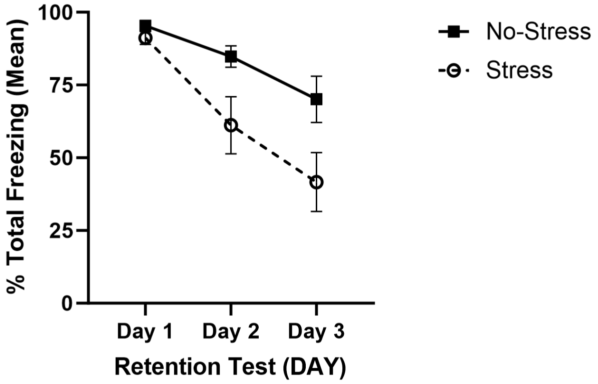


Figure 5. Illustration of the acquisition curve and post-stress retention test. Repeated exposure to acute stress impairs memory retrieval of recently acquired fear memory.

(A) Acquisition curve displaying an increase in freezing behavior (mean and SEM) across three training days during the pre-shock phase (p <.001), with no significant group differences (p =.61). The learning experiences of all the rats in the experiment were comparable. (B) Freezing behavior in the post-stress retention test (mean and SEM). Regarding the freezing levels on Day 1 in the two groups, the analysis was non-significant p = 0.14. However, Day 2 (t(14) = 2.254, p = 0.041), and Day 3 (t(14) = 2.212, p = 0.044), the analysis revealed a significant difference between the two groups. In comparison to the control group, the stress-exposed group showed lower freezing levels on Days 2 and 3, suggesting impaired fear memory retrieval.

3.2 Exposure to EPS does not impair context fear memory acquired one week ago

In this experiment, we explored the effect of EPS on the recall of context fear memory acquired one week earlier. Figure 2 illustrates the experimental design and timeline. The animals were divided into two groups: the Stress group and the No Stress group, with four animals in each group. All animals in both groups underwent context fear conditioning over a period of 3 days. During the conditioning phase, the animals were placed in a distinct context and received a mild foot shock as an aversive stimulus. The sessions aimed to establish fear memories associated with the conditioning context. Following the context fear conditioning phase, the animals were left undisturbed for a period of 7 days. Then the animals were exposed to an elevated platform stress. During the sessions, each animal was individually placed on an elevated platform for 60 mins (3 sessions, 48-hour intervals between each session). A final retention test was performed by placing each animal back into the fear conditioning chambers without delivering the shock. During the 5-minute test, freezing levels were recorded every minute.

As expected, defensive freezing increased significantly across the three days of conditioning [two-way mixed-design ANOVA, Day: $F(2,16) = 43.96$, $p < 0.001$, see Figure 6]. There was no significant main effect for Group [$F<1.00$, $p = 0.83$], and the interaction between Group and Day of conditioning was not significant [$F<1.00$, $p = 0.76$]. These results suggest that the acquisition of context fear memory was similar across both groups before exposure to stress.

One week after conditioning, rats were randomly assigned to either the EPS ($n = 4$) or non-stress ($n = 4$) conditions. Recall tests were conducted twenty-four hours after the last stress session to assess the impact of EPS on the retention of the previously acquired context fear memory. A two-way mixed-design ANOVA was used to examine conditioned freezing, with

Recall Test Day (Recall Test Days 1 through 3) as the within-subject factor and Group (EPS vs. non-stressed controls) as the between-subject factor.

There were no significant main effects for Recall Test [Two-way mixed-design ANOVA: F (2,16) = 3.13, p = 0.07] or Group [F<1.00, p = 0.64], and the interaction between Recall Test and Group was not significant [F<1.00, p = 0.66]. These results indicate that exposure to EPS one week after training does not significantly impair the retrieval of context fear memory.

No additional post-hoc analyses were necessary, as the omnibus tests did not reveal any significant effects. The results suggest that animals subjected to stress did not exhibit a significantly different memory recall compared to animals in the non-stressed group.

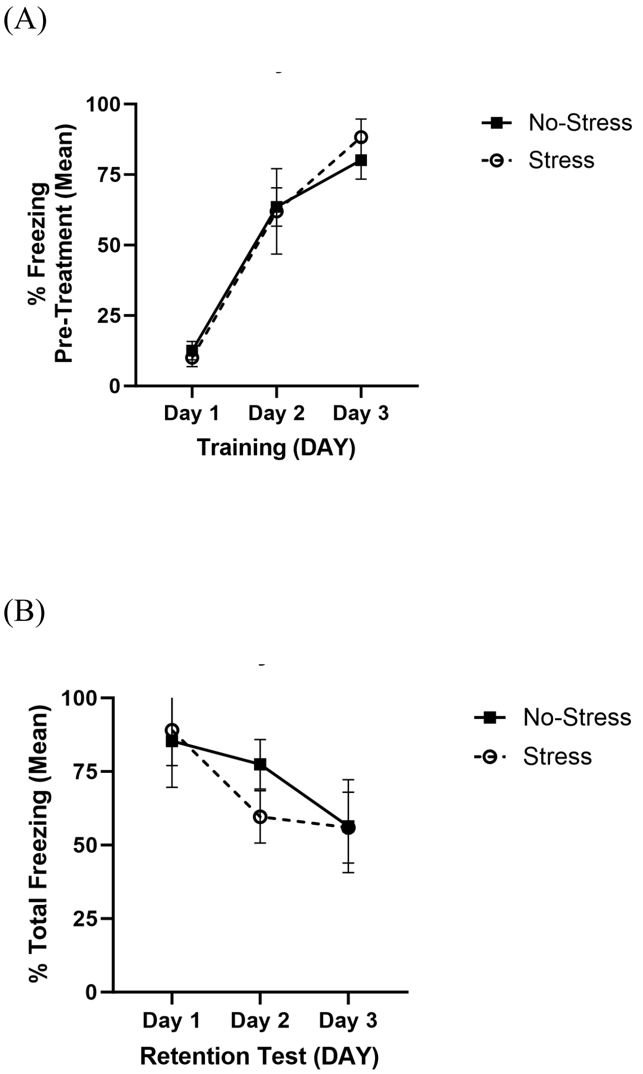


Figure 6. Illustration of the acquisition curve and post-stress retention test. Repeated exposure to acute stress did not impair fear memory acquired a week earlier.

(A) The acquisition curve shows no significant group differences (P =.83), but there is an increase in freezing behavior (mean and SEM) over the course of three training days during the pre-shock phase (P <.001). The learning experiences of all the rats in the experiment were comparable. (B) The mean and SEM of the post-stress retention test's freezing behavior. A two-way mixed-design ANOVA was used to examine the data from the three days of memory recall testing in order to compare the impact of stress. The findings revealed that the main impact of time was not significant ($F<1.00$, $p = 0.68$), meaning that there was no difference in freezing levels between the two groups over the course of the retention test's three sessions.

4. Discussion

The experiments were conducted to study the impact of acute stress on the fear memory of rats. The study comprised four experiments that were conducted to evaluate the effect of acute stress on fear memory retrieval at different time points following the acquisition of fear memory.

4.1 Repeated exposure to acute stress impairs memory retrieval of recently acquired fear memory but does not impair fear memory acquired a week ago.

The experiment evaluated the impact of stress exposure on the retrieval of fear memory. The study included two groups - No Stress and Stress, with each group consisting of 8 animals. All animals underwent fear context conditioning sessions for three days, with 48-hour intervals during which their percentage of freezing levels were measured. Subsequently, one group was exposed to elevated platform stress while the other group served as a control. Following the stress exposure, the animals were tested for their ability to retrieve fear memory over a period of three days. We hypothesized that stress after 48 hours will show impairment in the memory retrieval and delayed retrieval will not show any differences similar to Schwabe et al. (2014). The results showed that repeated exposure to acute stress impairs memory retrieval of recently acquired fear memory. The stress-exposed group exhibited lower freezing levels on Day 2 and Day 3, indicating impaired fear memory retrieval compared to the control group.

In the next experiment, we explored the impact of stress on the retrieval of fear memory acquired seven days prior to exposure to the elevated platform stress. The animals were divided into two groups - the Stress group and the No-Stress group, with four animals in each group. All animals underwent context fear conditioning over a period of three days. During the conditioning phase, the animals were placed in a context fear conditioning chambers and received a mild foot shock as an aversive stimulus. The sessions aimed to establish fear memories associated with the conditioning context. Following the context fear conditioning phase, the animals were left undisturbed for a period of seven days. The results showed that repeated exposure to acute stress did not impair fear memory acquired a week ago.

The impact of stress on memory retrieval has been a longstanding focus within the field, as evidenced by prior research (Roozendaal et al., 2009; Schwabe et al., 2012). Early investigations, which assessed memory retrieval approximately 30 minutes post-stress—corresponding to the peak of cortisol levels—initially suggested a decline in retrieval efficiency following stress exposure (Kuhlmann et al., 2005; Smeets et al., 2008). However, uncertainties persisted regarding the duration of this impairment beyond the corticosterone elevation and the potential influence of stress exposure timing.

To address these questions, the current study examines the effects of recurrent acute stressors administered 48 hours and 7 days post-fear conditioning on fear memory retrieval. Rats were subjected to stressors at these time points preceding a memory test for previously acquired fear memory. The findings revealed impaired retrieval 48 hours after stress exposure, whereas no significant impact on retrieval performance was observed 7 days post-stress exposure.

A previous investigation by Schwabe and Wolf (2014) in humans found that stress impeded memory retrieval only when cortisol levels were elevated. Once cortisol levels rose, retrieval efficiency decreased at 25 minutes and 90 minutes after stress exposure, persisting even after cortisol levels normalized (Schwabe et al., 2014). This suggests that stress-induced retrieval impairment might endure beyond the cortisol increase. Nonetheless, another research suggests that stress-induced arousal may improve memory retrieval provided stress is present in the retrieval context and cortisol levels stay low (Schönfeld et al., 2014). Thus, this shows that stress-induced memory retrieval appears to be time-dependent (Schönfeld et al., 2014).

Conversely, stress during retrieval can be distracting and lead to diminished performance, perhaps due to dual-task interference effects (Pashler, 1994). Dual-task interference effect known as simultaneous completion of two activities frequently results in performance losses in the component tasks (Pashler, 1994). This is assumed to be evidence of cognitive capacity limitations, with the lateral prefrontal cortex (LPFC) identified as a potential neural substrate (Pashler, 1994). As time elapses following stress exposure, facilitating cortisol elevation, memory retrieval is compromised due to the swift, non-genomic actions of corticosterone, potentially interacting with noradrenaline (Joëls et al., 2011; Roozendaal et al., 2004).

According to the dual-mode model of stress effects on memory proposed by Schwabe et al. (2012), retrieval impairments observed 48 hours after stress exposure may stem from the memory formation mode prompted by noradrenaline and rapid corticosterone actions. During this stage, cognition is focused on processing and remembering stressful experiences, and the ability to remember irrelevant information is reduced. Subsequently, as the brain stores the memories, certain effects of corticosterone inhibit the information processing that helps ensure that stressful events are consolidated, making it more difficult to recall those memories later.

The study's outcomes hold implications for comprehending memory processes in mental disorders like phobias or PTSD, where aberrant memory processes are prevalent (American Psychiatric Association, 2013). If stress or cortisol can impede memory retrieval, there may be potential to exploit these effects to hinder the retrieval of dysfunctional memories such as stressful memories (De Quervain & Margraf, 2008). Indeed, previous studies suggest that patients with PTSD or phobias may benefit from cortisol treatment (Soravia et al., 2006). The study underscores the notion that stress may impair memory retrieval, with effects persisting longer than previously assumed.

Future research could explore the correlation between fear memory retrieval and corticosterone levels in rodent models to enhance our understanding of the retrieval process. Additionally, investigating the duration of stress-induced impairments beyond the normalization of cortisol levels would shed light on the persistence of these effects.

CHAPTER III

Impact of Single and Repeated Stress Exposure on c-Fos Expression and Effect of Elevated Platform Stress on Reelin Expression in the Medial Prefrontal Cortex

1. Introduction

Acute stress causes rapid increases in neuronal activation, neurotransmission and hormone release, leading to significant physiological changes in the brain (Joëls & Baram, 2009). When exposed to a stress, specific brain areas are activated, with the PFC emerging as a region with greater susceptibility to stress (Arnsten, 2009). The PFC is engaged in a number of cognitive activities, including attention (Milham et al., 2001), decision-making (Woo et al., 2021), and working memory (Woodcock et al., 2019).

Studying the cellular activity associated with stress effects on the PFC and other brain areas often involves analyzing the expression of the c-Fos protein. This protein, encoded by the proto-oncogene c-Fos, serves as a marker for cellular activation (Tulchinsky, 2000). This immediate early gene (IEG) has the ability to regulate the expression of target genes (TGs) (Sheng & Greenberg, 1990), and it functions as a component of several inducible enhancer pathways (Tulchinsky, 2000). The low baseline expression of c-Fos in the absence of stimulation makes it a reliable marker to assess neuronal activation in response to different stimuli (Bullitt, 1990). As a result, the identification of its nuclear protein has been widely used to study central nervous system (CNS) activation and neural pathways (Hoffman et al., 1993; Herdegen & Leah, 1998). These results highlight the potential of c-Fos and its proteins as a useful method to study gene transcription in response to external stimuli and understand brain networks involved in stress responses (Hoffman et al., 1993). c-Fos is a protein that acts as a marker for neuronal activity, and its expression can help us understand the functional changes that occur in various brain regions during stress. Chronic stress has been found in studies to affect the expression of c-Fos in many areas of the brain (Cohen et al., 2020). However, there has been a lack of research into acute stress exposure at both single and short-term repeated stress exposure. This study looks at the effect of repetitive acute stress on cFos expression. Rats were subjected to stress for one or three days, with a control group receiving no stress exposure. The hypothesis suggests that there will be no disparity in cFos expression between rats subjected to stress for one day versus three days. Additionally, we predict an decrease in cFos expression in stressed rats compared to their non-stressed counterparts.

Accumulating evidence suggests that the amygdala and medial prefrontal cortex play important roles in the etiology of acute stress (Liu et al., 2022). The mPFC and amygdala are intricately linked in the brain and collaborate to regulate the expression of emotions including fear and anxiety (Fukushima et al., 2021; Sotres-Bayon & Quirk, 2010). The mPFC exerts top-down inhibitory control over amygdala activity under physiological conditions. This limits its output and preventing inappropriate emotional expression (Rosenkranz et al., 2004). Under physiological conditions, the mPFC exerts top-down inhibitory control over amygdala activity, limiting its output and preventing inappropriate emotional expression.

Nevertheless, under adverse circumstances, such as prolonged exposure to unavoidable stress that triggers the development of psychiatric disorders such as anxiety and depression, difficulties in prefrontal control led to abnormal activation of the amygdala, resulting in deficits in emotion, memory, learning, and behavior (Rauch et al., 2006; Quirk & Gehlert, 2003). This deficit is known to be the main neurobiological feature of stress-related neuropsychiatric disorders and has often been documented in both human and non-human models (Myers-Schulz & Koenigs, 2011; Shin et al., 2005).

Among molecular possibilities involved in the development psychopathology, reelin appears to be a significant link between cellular and physiological changes found in depression and chronic stress (Jossin, 2020). Reelin is a glycoprotein found in the extracellular matrix that plays a role in neuronal migration, spine formation, synapse formation and plasticity during brain development (Jossin, 2020; Wasser and Herz, 2017) and plays a role in adult neurogenesis (Bosch et al 2016). Reelin is produced primarily in Cajal-Retzius neurons during development and in interneurons of the cerebral cortex and hippocampus after birth (Wasser and Herz, 2017). Previous research has revealed that hippocampus reelin may be diminished in both depressed patients (Fatemi et al., 2000) and chronically stressed rodents with depression-like behaviors (Lussier et al., 2009). However, chronic antidepressant treatment has been shown in the literature to successfully reverse the negative effects of cortisol on reelin expression and depressed behavior (Fenton et al., 2015). Previous research has suggested that stress may have an adverse effect on reelin expression (Fenton et al., 2015; Fournier et al., 2009). However, studies have demonstrated that administering recombinant reelin via peripheral or intrahippocampal injections can successfully counteract cortisol's detrimental effects on reelin production and alleviate depression symptoms (Brymer et al., 2020). In light of this, the purpose of this study was to investigate the impact of elevated platform stress on the expression of reelin in the medial prefrontal cortex (mPFC) and the potential benefit of intravenous reelin treatment for the mitigation of stress-induced memory impairment. This experiment will provide information on the neurological basis of memory impairment and possible ways to mitigate its consequences.

Experimental Design 1

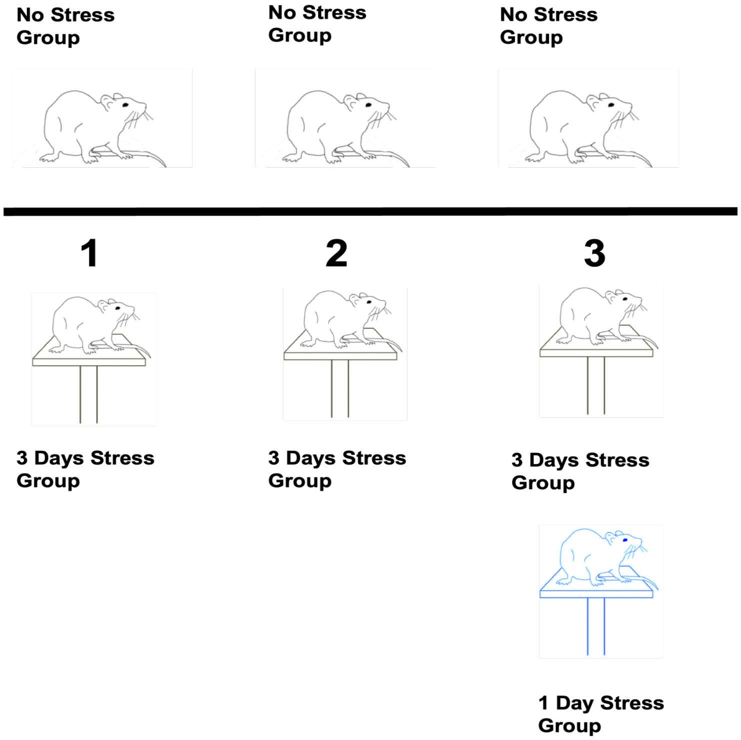


Figure 9. Illustrates the experimental design. Impact of single and repeated stress exposure on c-Fos expression.

2. Materials and Methods

2.1 Subjects

Eight male Long Evans rats, weighing approximately 180-210g, were housed under the same conditions as the ones described in Chapter 2, pg. 35. The number of animals per group for stress training was as follows: No-stress group N=4, 1-day Stress group N=4, and 3-day Stress group N=4.

2.1.1 Behavioral Tests

2.1.1.1 Elevated Platform

The elevated platform stress experiment adhered to the protocol described on page 37 of Chapter 2. It involved 12 animals, which were divided into three groups of four animals each. One group was designated as the control and did not receive any stress during the experiment. The second group received stress exposure for three consecutive days, while the third group was exposed to stress only on the third day. After the last stress exposure, the entire cohort of animals underwent perfusion around 90 minutes later.

2.1.1.2 Perfusion and Tissue Preparation

Ninety minutes after the final retention test, animals were euthanized, and tissue processing was carried out using a similar method detailed in the study by Kalinina et al. (2019). The experimental design is depicted in Figure 4. Immunostaining was performed on free-floating coronal sections (1 in 12 series for Cg1, Prl, IL, and BLA).

2.1.1.3 Immunohistological Procedures

The brains were sectioned at a thickness of 50 µm in coronal sections as part of a 1:12 series using a Vibrating Microtome, VMT-400. To preserve their integrity, these sections were stored in a 0.1 M phosphate buffer (PB) solution containing 0.1% sodium azide. Subsequently, the sections underwent thorough de-cryoprotection, involving six sequential washes in 1X phosphate-buffered saline (PBS), each lasting 10 minutes, all under gentle agitation.

For immunohistochemical staining, the sections were first incubated in a 0.3% v/v hydrogen peroxide solution in 1X PBS for 30 minutes, followed by another six rinses in 1X PBS to eliminate any residual bubbles.

The tissue sections were then subjected to a blocking step in a PBS solution containing 5% v/v normal goat serum, 1% w/v bovine serum albumin, and 0.3% v/v Triton X-100. Following this, they were incubated with a primary anti-rabbit cFos polyclonal antibody, appropriately diluted in the same mixture as mentioned above. The tissues were incubated for 1 hour at room temperature, followed by 48 hours at 4°C, with the antibody concentration set at 1:10000. Subsequently, the sections were rinsed six times with 1X PBS, each rinse lasting 10 minutes, all performed at room temperature.

The tissue sections were then incubated for 2 hours at room temperature with a biotinylated (goat anti-rabbit, Vector Laboratories) secondary antibody, diluted at 1:500 in 1X PBS containing 0.3% Triton X-100. The sections underwent another six rinses in 1X PBS, each lasting 10 minutes, at room temperature.

To further amplify the signal, the sections were subjected to a 1-hour incubation at room temperature with an A/B solution (from the Vectastain Elite ABC Kit Standard), diluted at 1:500 in 1X PBS containing 0.3% Triton X-100. Subsequently, the sections were rinsed three times, each lasting 5 minutes, in 1X PBS, followed by three additional rinses, each lasting 5 minutes, in 0.175 M sodium acetate (pH 7.0).

For the development of color, the sections were immersed in NIDAB chromogen solution, consisting of 0.020% w/v 3,3'-diaminobenzidine (DAB), 2.5% w/v nickel (II) sulfate hexahydrate, and 0.083% v/v hydrogen peroxide (H2O2) in 0.175 M sodium acetate (pH 7.0), for 20 minutes. After this incubation, the sections underwent three rinses, each lasting 5 minutes, with 0.175 M sodium acetate to halt the enzymatic reaction, followed by another three rinses, each lasting 5 minutes, in 1X PBS.

The processed sections were then mounted onto glass slides, electrostatically charged (Fisher Superfrost Plus), and allowed to air-dry overnight. The mounted tissue sections were subsequently dehydrated and cleared by sequential immersion in distilled water (5 minutes), 50% ethanol (5 minutes), 70% ethanol (5 minutes), 95% ethanol (5 minutes), 100% ethanol (10 minutes), 100% ethanol (10 minutes), xylene (10 minutes), and xylene again (10 minutes).

2.1.1.4 c-Fos Expression Quantification

To enable quantification of the c-Fos protein expression, digital images of each segment were subsequently captured at 10X magnification using a light microscope (Nikon H600L), camera (DS-Qi1Mc), and Nikon Element software (Nikon Instruments Inc., Melville, NY). Then, the images were processed using Fiji ImageJ (Version 2.0.0-rc-69/1.52p). Two new FIJI plugins developed by the Kopec lab—Warp Image and Batch Counter—as well as two sets of coordinate files, were used to warp the images onto atlas figures and designate ROIs for analysis (Bourgeois et al., 2021). Subsequently, semi-automated brain atlas-based analysis counts c-Fos positive cells inside predefined ROI coordinates derived from the atlas (Bourgeois et al., 2021).

2.1.1.5 Statistical Analysis

All statistical analyses were performed using Prism GraphPad 2017 and SPSS Statistics to compare c-Fos expression quantified data among all three groups. One-way ANOVA was used to compare the c-Fos expression between groups. P values <0.05 were considered statistically significant.

Experimental Design 2

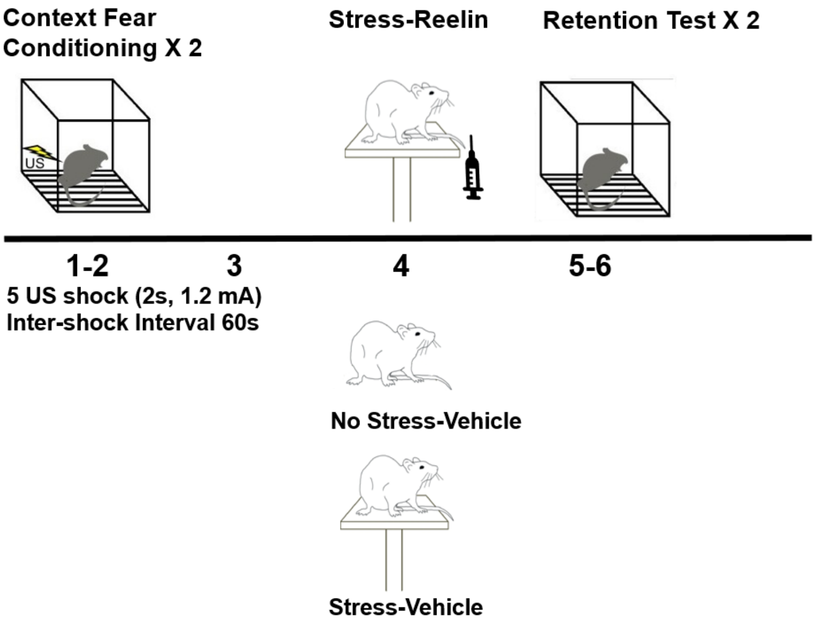


Figure 10. Illustrates the experimental design. Effect of elevated platform stress on reelin expression in the medial prefrontal cortex.

2.2 Subjects

Sixteen male Sprague-Dawley rats weighing approximately 270-315 g were maintained under the same conditions as described in Chapter 2, page 55. The number of animals per group for memory testing in context fear retention testing 1 and 2 was as follows: Non-stressed-vehicle N=5, Stressed-vehicle N=4, and Stress-reelin N=6.

2.2.1 Behavioral Tests

2.2.1.1 Context Fear Conditioning

The methodology utilized the similar procedure described in Chapter 2 on page 55. However, in this experiment, fear conditioning training was conducted over a period of two days, with each training session spaced 24 hours apart. During the experiment, each rat experienced a sequence of 5 pairings of context shock, where the unconditioned stimulus was administered as a 1.2 mA shock lasting for 2 seconds, with an inter-stimulus interval of 60 seconds. At the end of the second acquisition session, the rats were divided into three groups: Control-Vehicle, Stress-Vehicle, and Stress-Reelin cohorts.

2.2.1.2 Treatment

Rats were administered either peripheral recombinant reelin (3820-MR-025/CR, R&D Systems) or a vehicle solution (PBS) following the fear acquisition sessions. The rats were subsequently categorized into three distinct groups: 1) control group receiving the vehicle (C-V, n = 6); 2) stress group receiving the vehicle (S-V, n = 4); and 3) stress group receiving reelin (S-R, n = 6). The intravenous administration of peripheral recombinant reelin (3820-MR-025/CR, R&D Systems) was administered at a dosage of 5 ug/m. The vehicle used was physiological saline containing 0.9% w/v NaCl, and it was intravenously injected at the same dosage of 5 ug/ml. These injections were carried out for a duration of one day, 48 hours after acquisition and with a time interval of thirty minutes before the beginning of the stress regimen.

2.2.1.3 Elevated Platform

The elevated platform stress protocol adhered to the steps detailed in Chapter 2, page 35, except for the first elevated platform stress session. The elevated platform session was presented 48 hours after the final acquisition session. The rats were placed in the platform's center for a 30-minute period. Following the session, the rats were returned to their individual home cages.

2.2.1.4 Retention Tests

The initial retention test was performed 24 hours after the last elevated platform stress session, while the subsequent test took place 24 hours later. Each retention test had a duration of five minutes. No shocks were administered. The total percentage of freezing, as well as the percentage of freezing for each minute of retention, was recorded using an automated scoring system (AnyMaze, Stoelting).

2.2.1.5 Perfusion and Tissue Preparation

A procedure similar to that described in the methodology was followed to euthanize the animals ninety minutes after the final retention test. The tissues were processed and prepared for further analysis. The graphical representation of the experimental design can be seen in Figure 9.

2.2.1.6 Statistical Analysis

All statistical analyses were conducted using the software Prism GraphPad 2017 and SPSS Statistics.

To assess the pre-shock freezing levels in all animals after fear conditioning, a two-way mixed design ANOVA was conducted using the two consecutive days of pre-shock measurements as the within-subjects factor. The freezing levels between the control group and each of the two experimental groups (Stress-Vehicle and Stress-Reelin) were compared to identify any initial differences in freezing levels among the groups before stress exposure.

To assess differences in freezing levels during the two days of retention testing after stress exposure, a two-way mixed design ANOVA was applied using the two retention testing days as the within-subjects factor. The two-way mixed design ANOVA yield significant results for changes in freezing levels during retention testing, post-hoc tests (Bonferroni test) were used to perform pairwise comparisons to identify which specific days exhibit significant differences.

All statistical tests will be performed at a significance level (alpha) of 0.05 to determine statistical significance.

2.2.1.7 RNA Extraction and Quantitative RT-PCR

Twenty-four hours after exposure to the final EPS or no-stress session, rats were anesthesized briefly 5% isoflurane before decapitation. The brain was removed and the medial prefrontal cortex rapidly dissected on ice. The tissue was placed in nuclease freeze tubes and then flash frozen in liquid nitrogen and stored at -80 degree C until RNA extract and quantatitative RT-PCR.

Total RNA was extracted using QIAzol Lysis reagent (Qiagen, CA) and was further purified with RNeasy mini kit (Qiagen, CA) according to the manufacture's protocol. The quantity and quality of RNA was determined by measuring the absorbance at 260 nm (A260) using a NanoDrop spectrophotometer. The purity of RNA was determined based on the $A260/A280$ ratio, which was 2.00–2.10 for all RNA preparations used for subsequent expression analyses. First-strand cDNA was generated with random primers using the QuantiTect Reverse Transcription (Qiagen, CA) kit.

Quantitative reverse transcriptase PCR (RT-qPCR) was used to quantify the mRNA levels of reelin. All reactions were carried out using Quantitect SYBR Green PCR kit (Qiagen, CA). Each 50 uL reaction contained 5 uL (10 ng) cDNA, 300 nM forward and reverse primer for *Reln*, 25 ul SYBR Green qPCR Master Mix, and 10 uL of nuclease free water. Triplicate reactions were carried out for each experimental sample for each primer pair and for no reverse transcriptase and no template control reactions. Thermal cycling was performed on a CFX Connect (Bio Rad, California, US) real-time PCR system with the following conditions: hot-start activation of HotStart TaqDNA polymerase (94 °C) for 15 min and 40 cycles of denaturation (95 °C, 15 s, annealing 30 s, 55 °C), and extension (72 °C, 30 s). Melting curve analysis was performed according to the dissociation stage data and reactions with a single peak at expected temperature melting (Tm) were considered for further analysis. All primers were designed using Primer3 software and their specificity was verified using nucleotide blast software (BLAST Interface, www.ncbi.nlm.nih.gov/blast). Relative gene expression was determined using the 2−ΔΔCt method with GAPDH as the reference gene. The relative expression of each gene of interest in the EPS conditioned was determined by comparing it to the expression of the same gene in the non-stressed sample used as the calibrator.

The primers used in this study are listed below.

The primers were:

Reelin	F 5’-CCCAGCCCAGACAGACAGTT-3’
	R 3’-CCAGGTGATGCCATTGTTGA-5’

GAPDH	F: 5’-ACCACAGTCCATGCCATCAC-3’ R 3’- TCCACCACCCTGTTGCTGTA-5’

3. Results

3.1 Elevated platform stress exposure increases c-Fos expression in the medial prefrontal cortex following one and three days.

Male Long Evans rats were subjected to elevated platform stress for 30 minutes to examine the brain regions activated by single and three days of exposure to this stress. Following stress, rats underwent immunohistochemistry for c-Fos, a marker of neuronal activity in multiple brain regions associated with emotional regulation. Their c-Fos expression levels were assessed in three brain regions - Cg1, PrL, and IL - under different stress conditions (No Stress, 1 Day Stress, 3 Days Stress). Statistical analysis using one-way ANOVA was conducted to evaluate the differences in c-Fos expression between stress groups within each brain region. In this experiment, a control group, the naïve group, was also included, in which rats were left undisturbed in their home cages. This control group helped identify brain subregions that were selectively activated by elevated platform stress compared to the no-manipulation group.

Animals 004 and 007 were excluded from quantification due to tissue damage during sectioning, and their data were replaced with the mean values of their respective groups. A two-way mixed design ANOVA was conducted to examine freezing levels across the three groups over two time points. Figure 8 illustrates the experimental design and timeline. The results revealed significant interaction time × group effect [$F(2, 9) = 5.691$, $p = 0.008$, see Figure 10], indicating that the freezing levels varied differently across time between the groups. No significant main effect of group [$F(2, 9) = 0.41$, $p = 0.57$] and main effect of time [$F(1, 10) = 1.534$, $p = 0.236$] was observed, suggesting that freezing behavior did not differ significantly between the no-stress group (n=4), 1-day stress group (n=4), and 3-day stress group (n=4).

Post-hoc pairwise comparisons were conducted to further investigate the significant interaction effects. In the brain subregions tested, repeated acute stress over 3 days increased the number of c-Fos-positive cells compared to the no-stress group, though the increase was less pronounced than in the 1-day stress group. A significant difference was found in the cingulate cortex [Cg1; $p = 0.007$, $q(33) = 4.62$, see Figure 10], with more c-Fos-positive cells in the 3-day stress group compared to the no-stress group. However, no significant differences were observed between the No Stress and 1-Day Stress groups ($p = 0.06$), or between the 1-Day Stress and 3-Day Stress groups ($p = 0.64$). These results suggest that neurons in the Cg1 region, associated with emotion regulation, were selectively activated by 3 days of stress, while other regions such as the prelimbic cortex and infralimbic cortex did not show significant activation compared to the no-stress group.

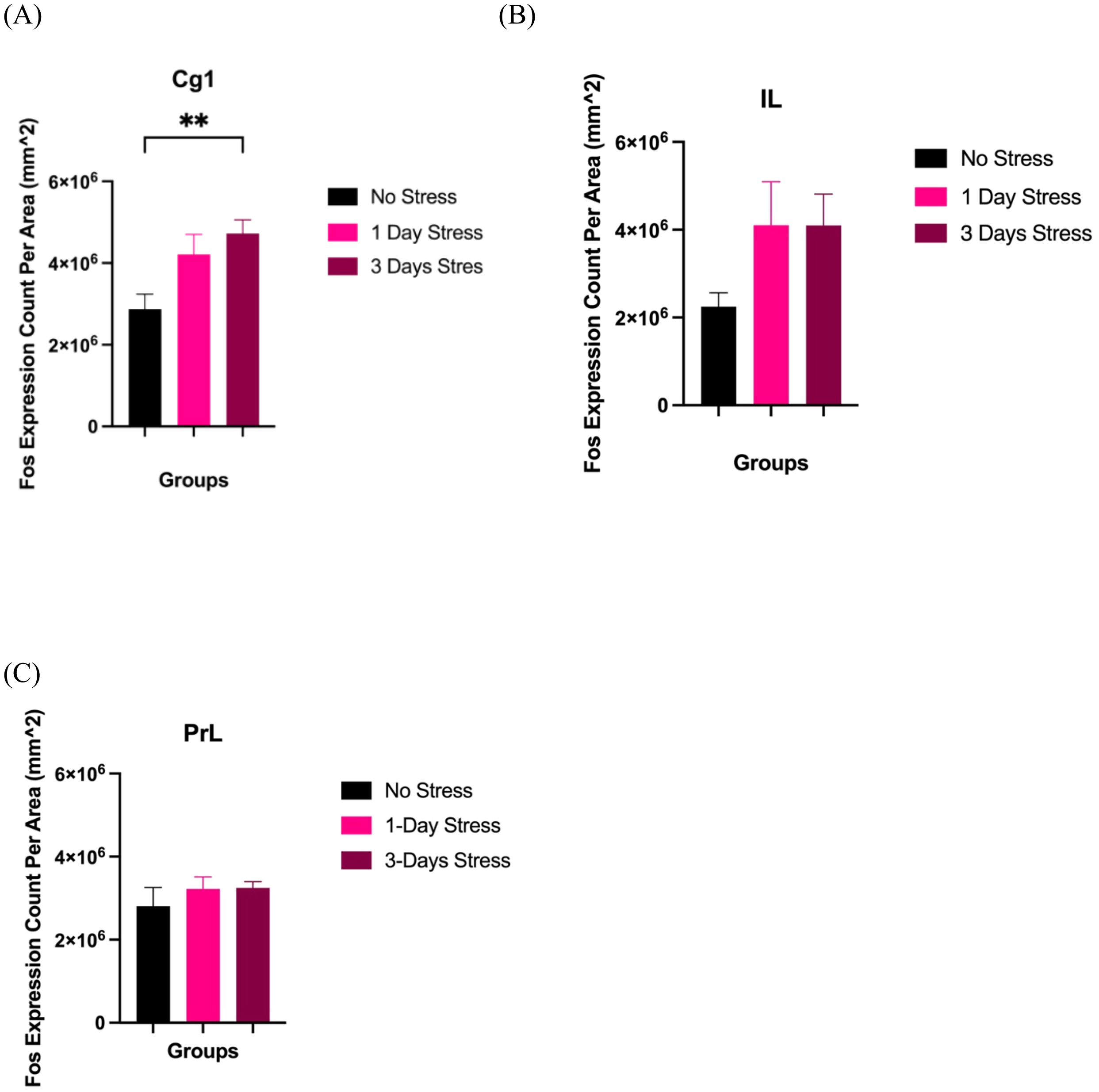


Figure 11. Illustrates the c-Fos expression in Cg1, IL, and PrL, respectively, in count per area (mm²), comparing 1 day and 3 days of stress vs. no stress groups.

3.2 Exposure to EPS reduces Reelin mRNA levels in the medial prefrontal cortex

To evaluate the effect of elevated platform stress on reelin expression in the mPFC, rats underwent two days of contextual fear conditioning (5 UCS, 1.2 mA, ISI 60 s). Forty-eight hours later, a subset of rats was exposed to elevated platform stress for 30 minutes each day for two days. Recall tests were conducted 24 hours later. We performed RT-qPCR to examine the expression of *Reelin* following exposure to 2 days of EPS (n=4-6 per group). We found that levels of *Reelin* mRNA in the medial prefrontal cortex were significantly reduced in stressed rats compared to non-stressed controls [non-stressed: 1.04 vs. stressed: 0.60; t(7.97)=2.49, p<.038, n=4-6 rats per group, see Figure 11].

3.3 Peripheral Reelin reverses the impact of stress on contextual fear memory

This experiment aimed to evaluate impact of acute stress in reelin expression and whether intravenous treatment with reelin could reverse the effects of prior stress on contextual fear conditioning. The experiment results involved three groups, No Stress-Vehicle, Stress-Vehicle, and Stress-Reelin groups. The experiment was conducted with a total of 15 animals. The freezing levels of one rat on both days of training were low on both days of training, indicating no conditioning (<20%). Therefore, this animal was removed from the analysis. The final group composition was non-stressed-vehicle (n=5), stressed-vehicle (n=4), and stress-reelin (n=6). All animals were trained for context fear conditioning. Freezing levels were measured over two days before the animals were exposed to stress and intravenous treatment. After the stress exposure, they were subjected to a fear memory retention test for two additional days. Figure 9 illustrates the experimental design and timeline.

The two-day initial fear context conditioning was analyzed using a two-way mixed design ANOVA. The results revealed a significant increase in freezing levels over the three-day period (F(2,24) = 60.987, $p < 0.001$), indicating successful fear conditioning across all groups. Additionally, there was no significant interaction effect between the group and day factors (F(2,24) = 5.656, $p = 0.019$), suggesting that the initial fear memory acquisition was comparable between the groups.

A one-way ANOVA was conducted to assess freezing levels during the first recall. The analysis revealed no significant differences in freezing levels among the stress-vehicle group, non-stressed-vehicle controls, and the stressed group treated with reelin [F(2,12) = 1.74, $p = 0.217$, see Figure 9].

However, a significant group difference was observed during the second retention test [F(2,12) = 8.17, $p < 0.006$, see Figure 9] between stress-vehicle group and control group. Rats that received peripheral reelin injections and stress showed no change in freezing levels. Post-hoc analyses using Fisher's LSD indicated that the stressed-vehicle group exhibited significantly lower freezing levels compared to the non-stressed-vehicle controls ($p < 0.010$) and the stress group treated with reelin ($p < 0.002$). These results suggest that peripheral reelin may mitigate the impact of stress on context fear memory.

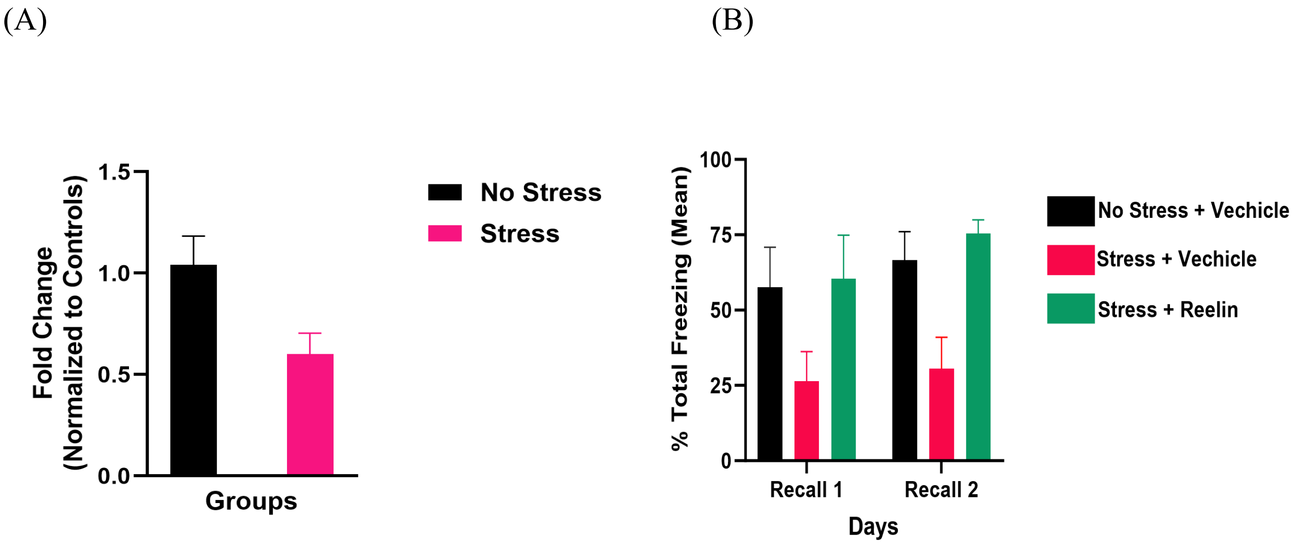


Figure 12. Illustration of the post-treatment retention test freezing percentages (mean and SEM) and measurement of reelin mRNA expression in mPFC. (A) The expression of Reelin mRNA in the mPFC was detected by RT-PCR (n=3-4 per group). There was a significant decrease in reelin mRNA expression for the stress group compared to controls [non-stressed: 1.04 vs. stressed: 0.60; t(7.97)=2.49, $p<.038$, n=4-6 rats per group]. (B) Post-treatment retention test did not reveal any group differences on the first recall test ($p = .217$). However, during the second retention test, a significant group difference observed ($p < 0.006$) between stress-vehicle group and control group. Rats that received peripheral reelin injections and stress showed no change in freezing levels. Post-hoc test revealed that the stress-vehicle group had significantly lower freezing levels than the non-stressed-vehicle controls ($p < 0.010$) and the reelin-treated stressed group ($p < 0.002$).

4. Discussion

4.1 Significant Increase in Medial Prefrontal Cortex c-Fos Expression Following One and Three Days of Elevated Platform Stress Exposure in Rats

This study aimed to investigate changes in c-Fos expression in the medial prefrontal cortex (mPFC) resulting from single and repeated acute stress exposure. We hypothesized that c-Fos expression will decrease in rats exposed to both single and repeated stress, compared to the no-stress group. However, no difference in c-Fos expression is expected between the two stressed groups. The results showed that repeated acute stress over 3 days increased the number of c-Fos-positive cells in the examined mPFC compared to the no-stress group, although to a lesser extent than the 1-day stress group. Notably, more c-Fos-positive cells were observed in the Cg1 brain region in the 3-day stressed group compared to the unstressed group. These results indicate that neurons in specific brain regions involved in emotion regulation, such as Cg1, are selectively activated after 3 days of stress exposure, whereas neurons in other subregions, such as PL and IL, are not significantly activated suggesting that it did not show significant activation compared to the no-stress group.

The prefrontal cortex (PFC), the most evolved brain region, is responsible for supporting higher-order cognitive abilities. However, it is particularly vulnerable to the negative effects of stress (Arnsten, 2009). Even minor acute uncontrollable stress can cause significant and immediate impairment of prefrontal cognitive functions, whilst continuous stress exposure can cause structural alterations in prefrontal dendrites (Arnsten, 2009). Recent research has begun to shed light on the intracellular signaling pathways that underpin the PFC's response to stress.

The expression of immediate-early genes (IEGs) indicates the activation of certain brain circuits involved in the processing and integration/ transcription of primary inputs by neural depolarization, as well as neuroendocrine, autonomic, and behavioral responses (de Medeiros et al., 2005). Previous studies have shown that 30-min immobilization stress can cause robust expression of c-Fos and other IEGs in various areas of the brain, including the allocortex and neocortex, the lateral septal region, the paraventricular and dorsomedial nuclei of the hypothalamus, the postchiasmatic region, medial and cortical nuclei of the amygdala, periaqueductal grey matter and locus coeruleus (LC) (Cullinan et al., 1995). This widespread and strong activation of the central nervous system (CNS) is associated with the complexity and diversity of stress responses (de Medeiros et al., 2005). Stress elicits complex, coordinated responses to stimuli that include motor, sensory, autonomic, and cognitive processes; the hypothalamic-pituitary-adrenal (HPA) axis and autonomic structures (Cullinan et al., 1995). These stimulation of different brain regions can have facilitatory or inhibitory effects on the HPA axis (Lachuer et al., 1994; Herman et al., 2003).

This supports that the observed increase in c-Fos gene expression in the medial prefrontal cortex (mPFC) is likely a consequence of HPA axis activation (Woo et al., 2021). Neurons in the prefrontal cortex (PFC) create top-down objectives via recurrent excitatory connections on spines, which underpin persistent firing and enable higher cognitive tasks like working memory and abstract cognition (Woo et al., 2021). However, acute unmanageable stress causes increased catecholamine release in the PFC, triggering feedforward calcium-cAMP signaling pathways that activate adjacent potassium channels, rapidly weakening synaptic connection and decreasing persistent firing. Chronic stress can increase these signaling processes, causing spine loss and substantial cognitive impairment (Woo et al., 2021). This can be also explained by neural depolarization, when certain channels, including NMDA and VSCCs, trigger signaling pathways that target response elements on the c-Fos promoter. These response elements include serum response elements (SREs) and cAMP response elements (CREs) (Aguilar-Delgadillo et al., 2023). Under stress conditions, additional signaling pathways associated with NMDA receptors, such as the CREB/CRE pathway and the ERK/MAPK/SER pathways, also participate in the upregulation of c-Fos expression. This pathway promotes further upregulation of c-Fos gene expression during stress due depolarization (Aguilar-Delgadillo et al., 2023).

4.2 Downregulation of Reelin mRNA Expression in the Medial Prefrontal Cortex following Stress Exposure

Numerous studies have examined the importance of Reelin signaling in synaptic plasticity, memory formation, and cognitive function. Reelin-expressing neurons are broadly dispersed throughout the adult brain, (Ramos-Moreno et al., 2006) even after Cajal-Retzius cells have deteriorated (Sarnat and Flores-Sarnat, 2002). Despite its extensive distribution, the functional significance of prolonged Reelin expression following cell migration completion remains unknown in most brain areas. Reelin and its lipoprotein receptors play an important role in synaptic transmission and plasticity in the hippocampus, impacting mammalian learning and memory behavior (Beffert et al., 2005; D'Arcangelo, 2005).

While substantial research has shown the neural circuitry directing the acquisition of fear memories via fear conditioning, less is known about the mechanism involved in memory retrieval. Thus, we sought to evaluate the effect of acute stress on Reelin expression during fear memory retrieval in the medial prefrontal cortex (mPFC). Therefore, this study is interested in learning about how acute stress impacts reelin during fear memory retrieval.

Our RT-PCR results showed a substantial reduction in Reelin mRNA expression in the mPFC of the stress group compared to controls. The rats were then divided into three groups:

Stress-Reelin, Stress-Vehicle, and No Stress-Vehicle. The Stress-Reelin group got an intravenous injection of recombinant Reelin 30 minutes before stress exposure and then performed retention testing.

Interestingly, while the post-treatment retention test found no group differences on the first memory test, but a significant difference developed on the second recall test. Stressed rats showed much less freezing behavior than stressed rats treated with Reelin and non-stressed controls, which did not vary significantly from one another.

These findings are consistent with prior studies showing the effect of stress on Reelin expression and the consequences for neuropsychiatric illnesses. For example, Fenton et al. (2015) discovered that corticosterone promotes depression-like behaviour while decreasing the amount of Reelin cells in the hippocampus's subgranular zone. Furthermore, several postmortem investigations have linked Reelin gene deficiencies to a variety of neuropsychiatric illnesses, including schizophrenia, bipolar disorder, autism, severe depression, lissencephaly, and Alzheimer's disease (Fatemi, 2011; Impagnatiello et al., 1998).

Fatemi (2005) conducted subsequent research that confirmed and expanded on these findings, extending the reported deficiencies in Reelin to individuals with non-psychotic bipolar illness, significant depression, and autism. Furthermore, research has shown that Reelin impairments are common in a variety of cognitive illnesses, including lissencephaly, Alzheimer's disease, and temporal lobe epilepsy.

Teixeira et al., (2011) investigated the effects of reelin overexpression in a transgenic mouse model on wild-type and heterozygous reeler mutant mice. They investigated the notion that, whereas downregulation of reelin synthesis may cause a variety of behavioral defects, overexpression of this molecule may be able to correct these deficiencies. This study found that heterozygous reelin mice have no behavioral abnormalities. Mice that overexpressed reelin had higher levels of reelin, which prevented the transgenic mice from developing depression-like behavior in the forced swim test. Stress-induced NMDA markers of depression-mediated synaptic transmission were also found low in transgenic mice. Finally, positive symptoms of schizophrenia were reduced (Teixeira et al., 2011). This shows reelin plays an important role in stress-induced behavior abnormalities.

The medial prefrontal cortex (mPFC) has also been identified as a brain region important for cognitive and emotional regulation (Goldman-Rakic, 1995). Previous studies have found a link between epigenetic regulation of gene expression and memory formation in the prefrontal cortex (Bredy et al., 2007; Goldman-Rakic, 1995). This study has found that H4 acetylation at the brain-derived neurotrophic factor (BDNF) promoter in the prefrontal cortex increases during the extinction of conditioned fear memories (Bredy et al., 2007). Additionally, cortical DNA methylation is required for the maintenance of fear memory (Bredy et al., 2007).

The medial prefrontal cortex (mPFC) plays an important role in the pathophysiology of different illnesses, notably stress-related ailments such as anxiety, depression, and PTSD (Moricia et al., 2015; Yang & Raine, 2009). The mPFC, which is associated with tasks such as cognition, working memory, and decision-making, is critical in regulating emotional and cognitive responses.

In our investigation, recombinant reelin was delivered intravenously into the mPFC cortex, yielding intriguing results during post-treatment retention tests. While no group differences were found after the first memory test, a significant difference developed on the second recall test. Stressed rats treated with reelin showed much less freezing behavior than stressed rats without treatment or non-stressed controls, who did not vary significantly from one another.

These findings are consistent with prior research showing that reelin prevents cognitive abnormalities caused by phencyclidine (PCP) noncompetitive NMDA receptors, as shown in mice following intracerebroventricular reelin injection (Ishii et al., 2015). Furthermore, our findings are supported by other research showing comparable effects (Hethorn et al., 2015; Rogers et al., 2013). However, the particular mechanism behind reelin's effect is mainly unclear.

Another study discovered that microinjecting recombinant reelin into the mPFC reversed MK-801 (blocker of the NMDA receptor) induced cognitive deficits, indicating that reelin may have a therapeutic function in cognitive impairments (Sawahata et al., 2021). This impact appears to be caused by changes in neuronal activity within the mPFC, where reelin binds to its receptor and activates downstream signaling pathways.

Previous research has emphasized Reelin's neuroprotective effects, as indicated by its capacity to restore cognitive and affective abnormalities in animal models exposed to prenatal inflammation (Ibi et al., 2020). Mechanistically, reelin modulates neuronal plasticity, affects glutamate-induced calcium influx, and increases dendritic spine density in the brain, all of which contribute to long-term potentiation and memory formation.

These findings collectively indicate that reelin play an important role in guarding against cognitive impairments and synaptic dysfunction, possibly opening up therapeutic options for the treatment of cognitive and emotional problems. In addition, findings help to clarify the intricate relationship between acute stress, reelin expression, and fear memory retrieval in the mPFC, offering light on neural mechanism driving stress-related neuropsychiatric diseases.

5. Conclusion

The findings from this comprehensive study shed light on the intricate relationship between stress exposure and fear memory retrieval. The study demonstrated that immediate stress following fear conditioning significantly impairs fear memory retrieval, highlighting the vulnerability of fear memories to acute stress. However, following study revealed that delayed stress exposure seven days post-conditioning did not affect fear memory retrieval, suggesting a time-dependent influence of stress on memory processes.

In addition to behavior paradigms, immunohistochemistry methods were also utilized to further elucidate the effects of stress on memory processes. Reelin treatment emerged as a promising intervention for reversing stress-induced memory impairment, suggesting potential therapeutic avenues for alleviating the detrimental effects of stress on memory retrieval. This promising outcome was supported by changes observed in mRNA reelin levels in RT-PCR analysis, which indicated stress-induced hormonal alterations and decreased reelin mRNA expression in the prefrontal cortex, respectively.

Moreover, another study identified specific brain regions, particularly the cingulate cortex (Cg1), that were selectively activated by prolonged stress exposure, highlighting the importance of considering regional neural responses in stress-related memory processes. These findings underscore the complexity of the neural mechanisms underlying the effects of stress on memory and provide valuable insights for future research aiming to develop targeted interventions for stress-related memory disorders.

In conclusion, this study provides valuable insights into the complex interactions between stress, fear memory, and neural mechanisms. Understanding these dynamics not only enhances our knowledge of stress-related memory disorders but also offers potential avenues for the development of targeted interventions aimed at alleviating the detrimental effects of stress on memory function.

CHAPTER IV

General Discussion

4.1. Summary

Numerous studies in both preclinical and clinical settings have demonstrated the negative effects of stress on cognitive function (Rosen et al., 2010). When stressors occur, specific neuronal populations rapidly increase the release of monoamines such as dopamine, norepinephrine, and serotonin. In addition, neurons in the hypothalamic nucleus activate the sympathetic nervous system, releasing adrenaline and noradrenaline from the adrenal medulla (Schwabe et al., 2022). At the same time, the hypothalamus triggers a slow HPA axis, resulting in the release of corticotropin-releasing factor, adrenocorticotropic hormone, and ultimately corticosteroids (Schwabe et al., 2022).

These different stress mediators are released in waves and reach the brain at different times. Although many regions of the brain are affected by one or more stress mediators, most studies have focused on the hippocampus and subregions of the prefrontal cortex, the amygdala nucleus, and to a lesser extent the nucleus accumbens and ventral tegmentum. focuses on a specific area, such as hypothalamus (Schwabe et al., 2022). Given that these structures are associated with learning and memory (Fanselow & Poulos, 2005), it is not surprising that stress has a profound impact on cognitive function in both humans and non-human animals.

We know that acute stress can affect fear learning and memory in various ways (Arnsten et al., 2015; Bhatia et al., 2011; Brosens et al., 2024). For example, acute stress can impair fear memory recall (McEwen & Morrison, 2013) and increase fear memory recall depending on the timing of stress exposure (Fukushima et al., 2014). However, how do these stress-related changes affect memories acquired before the onset of stress, memories that are thought to have undergone a process of cellular consolidation are important to assess (Kandel et al., 2014).

This study addressed the effects of repeated stress on the ability to retain previously acquired contextual fear memories in rats. These results from my paper demonstrate that stress-related dysfunction is time-dependent and persists for more than 48 hours, that the mPFC becomes hypersensitive after exposure to stress, and that stress promotes extinction learning. We contribute to the field of learning and memory research by providing evidence that stress-induced impairments are time-dependent and last longer than 48 hours mPFC gets hypersensitivity after stress exposure and stress enhances extinction learning.

Furthermore, in Chapter 3, we revealed that stress reduces reelin mRNA in the mPFC, which is important for memory and behavioral disorders. Interestingly, we found that intravenously administered recombinant Reelin could alleviate stress-induced dysfunction. These results are consistent with the non-human study of Fenton et al., (2015). My experiments also revealed anxiety-like freezing behavior caused by repeated acute stress. This is consistent with previous studies showing immediate antidepressant effects and reversal of abnormal behaviors with repeated CORT treatment (Brymer et al., 2020).

Finally, in Chapter 3, we showed that during the post-stress retention test in stressed rats, cFos expression was significantly higher in the Cg1 brain region of the 3-day stress group compared to the no-stress group. These results indicate that neurons in specific brain regions involved in emotion regulation, such as Cg1, are selectively activated after 3 days of stress exposure, whereas neurons in other subregions, such as PL and IL, are not significantly activated suggesting that it did not show significant activation compared to no-stress.

Although I expected cFos expression in these regions to be lower in stressed rats than in controls (Cohen et al., 2020; Kononen, 1992), acute uncontrollable stress potential increases catecholamine release in the PFC to modulate stress responses in stressed rats could support these results.

4.2 Stress impairs memory retrieval of recently acquired fear memory but does not impair fear memory acquired a week ago.

Studies examining the effects of pre-learning stress have yielded inconsistent results. Some studies showed later improvement in memory (Schwabe et al., 2008; Smeets et al., 2007), and some studies showed impaired memory (Payne et al., 2007). However, stress applied immediately after learning has been shown to improve subsequent memory recall (Cahill et al., 2003; Smeets et al., 2008). Conversely, stress before a memory test appears to impair memory (Schwabe & Wolf., 2014; Kuhlmann et al., 2005). As an addition, we found that repeated exposure to acute stress impaired recall of recently acquired fear memories, but did not affect fear memories acquired a week earlier. Here we used a contextual fear conditioning paradigm to assess the effects of stress on fear memory retrieval.

Context is a crucial function in abstracting situational meaning from the world. In fact, the brain's ability to contextualize information greatly increases cognitive and behavioral flexibility. Pavlovian fear conditioning and extinction studies in non-human rodents and humans have shown that neural circuits including the hippocampus, amygdala, and medial prefrontal cortex are involved in the learning and memory processes that enable context-dependent behavior (Maren et al., 2013). Dysfunction of this network may be involved in various forms of psychopathology, such as post-traumatic stress disorder, schizophrenia, and substance use disorders (Maren et al., 2013; Lonsdorf., 2017).

For example, in Pavlovian fear conditioning, an environmental context (conditioning chamber) can be placed to signal the delivery of a foot shock (US), which triggers a conditioned response to the context such as freezing behaviour in rats (Maren et al., 2013). For context learning to occur, the animal must first form a representation of the context (Lonsdorf., 2017). These types of contextual representations are learned incidentally (simply by exposure to context) and are acquired very quickly (Lonsdorf., 2017). Once encoded, the context representation itself can be associated with other events, such as the occurrence of an aversive footshock.

Thus, during a typical contextual fear conditioning procedure, the animal first encodes a representation of the context (as the animal explores the context before the footshock) and then associates this representation with the US (Lonsdorf., 2017). These two learning processes are called context encoding and context conditioning, respectively. Contextual encoding is necessary for contextual conditioning. In fact, animals that were shocked immediately after being placed in the room showed no contextual conditioning, suggesting that for conditioning to occur, animals need to encode a contextual representation.

To ensure that conditioning worked well, our study included a 3-minute habituation period to expose the context and establish associations. This was followed by a conditioning protocol with five pairs of context shocks. Each aversive stimulus consisted of a 1.2 mA shock delivered for 2 s with a 60 s interstimulus interval. Our acquisition data provide evidence that the stressed and non-stressed groups showed similar levels of freezing on each day of acquisition/fear conditioning, evidence of successful fear memory learning. During our retention tests, rats were returned to the original same fear conditioning chambers allowing them to freely explore for 5 minutes. No shocks were administered. Then the freezing levels are repeated 1-3 times depending on the experiment.

On the other hand, testing memory impairment is similar to extinction, requiring rats to be repeatedly returned to the situation to measure reductions in freezing behavior (Ishikawa et al., 2016; Maren & Quirk, 2004). Therefore, there could be questions about whether the results in Chapter 2 may be more consistent with the results of extinction than with those of stress-induced memory impairment.

Extinction is when the unconditioned stimulus stops following the conditioned stimulus for a number of trials, and the conditioned behavior gradually disappears. In the extinction training, it is found that the original conditioned fear memory is not erased, but rather is suppressed by a competing extinction memory. This happens because each time the rat returns to the situation, the fear memory trace returns to a liable state, allowing it to add new information - in this case, the fact that the situation poses no threat of shock- and undergo reconsolidation to form a stable trace of memory (Alberini & Ledoux, 2013).

When conditioned stimulus in this case rats are returned to the fear conditioning chamber without shock at a later time this is called the fear retention test (Lonsdorf et al., 2019). When repeatedly exposed to the chamber without shock, the dominance of extinction learning over fear memory is known as extinction retention (Lonsdorf et al., 2019). To examine extinction retention, some studies have included two types of different conditioned stimuli during context fear training/acquisition (Lonsdorf., 2017), in which one conditioned stimulus is subsequently extinguished, and the second conditioned stimulus is not presented during the extinction training which allows to distinguish between retention of fear memory and extinction learning (Lonsdorf et al., 2017).

The term extinction retention is used to refer to a variety of procedural scenarios (Lonsdorf et al., 2017). The testing period after extinction training, for example, 24 hours after extinction training is typically referred to as the extinction retention period (Lonsdorf et al., 2017). Nevertheless, it is only fitting to use contextual manipulations that have the potential to lead to extinction rather than fear memory. For example, test stages that take place in the context of extinction learning, such as acquisition in context A and extinction and retention tests in context B. In the absence of such context manipulation for example, if acquisition, extinction, and retention are tested in the same context A, fear memories are more likely to be recalled than extinction learning memories. This is explained by the term "spontaneous recovery", which is often used for the same process as extinction maintenance (Lonsdorf et al., 2017). Spontaneous recovery is the delayed reappearance of a previously extinguished conditioned response. Therefore, according to the literature, more specifically, the post-extinction test phase is called a retention test (Lonsdorf et al., 2019), during which the re-emergence of the conditioned response or absence may be observed. Therefore, the processes underlying our observations are called fear retention. This is also supported by our findings in Chapter 2 of the study, a fear conditioning experiment on rats for three days, followed by elevated platform stress, and retention testing at different time points when rats were exposed to the conditioning chamber without the unconditioned stimulus shock.

If the results were due to extinction, then we would have observed spontaneous recovery during the repeated fear memory tests. However, the absence of spontaneous recovery highlights the influence of external factors, here stress on fear memory and suggests that this measure is more related to fear memory retention.

In addition, extinction also includes theories on renewal and reinstatement (Maren & Quirk, 2004). When using two different environments, the return of freezing behavior to the original context is called renewal (Maren & Quirk, 2004). On the other hand, reinstatement testing is when rats trained for context fear memory returned to the original context with a single footshock after extinction training is known as reinstatement (Maren & Quirk, 2004). Here when returned to the original context the next day, rats will show freezing levels associated with the original context (Maren & Quirk, 2004).

Additionally, when comparing the retention test data from Experiment 1 and Experiment 5, the findings highlight the importance of the duration of both conditioning and stress exposure in modulating the strength of conditioned fear responses. The 3-day contextual conditioning followed by 3 days of elevated platform stress facilitated more robust associative learning and stronger stress response, resulting in higher freezing levels during the first retention test (mean freezing of 80%). In contrast, the 2-day conditioning followed by 1 day of elevated platform stress produced lower freezing levels during the first retention test (mean freezing of 25%), indicating weaker memory formation.

4.3 Stress-Induced Molecular Changes

The PFC is important for controlling fear-related behaviors and encoding fear in various species (Gourley et al., 2016). The PFC is also involved in emotional regulation processes. The medial prefrontal cortex (mPFC) includes the IL, PrL, and Cg1, and regulates the balance between goal-directed, habitual behaviors (Gourley et al., 2016) and the integration of information about potential environmental threats (Miller, 2000).

It has been shown that stress has distinct impacts on different parts of the mPFC. In a study, bilateral lesions of the cortical PrL region were found to increase plasma adrenocorticotropic hormone (ACTH), corticosterone, and PVN c-Fos expression (Figueiredo et al., 2003). Corticosterone secretion, on the other hand, is reduced by damage to the infralimbic cortex (IL) (Sullivan and Gratton, 1999). These results suggest that PL and IL have opposing reactions to stress.

The molecules processes that underlie the fear of memory acquisition and extinction go all the way down to epigenetic, transcriptional, and translational changes. Research has uncovered that the way our cells learn to remember fear and extinction involves special changes in the genes of certain cells. These changes persist for weeks after the first conditioning session (Chen et al., 2020). A study found that inhibiting PARP-1, the gene plays a key role in ADP ribosylation and is essential for making RNA from DNA into the medial prefrontal cortex impairs fear extinction (Inaba et al., 2015).

Research has also found paradigms to induce stress while they're inside an fMRI machine to see how stress-induced changes. The studies used ScanSTRESS, an image stress test, aversive viewing paradigm (AVP) - showing movie clips, a social evaluation threat, or a cyberball - making participants think they were being judged (Henckens et al., 2009). The study uncovered bilateral activation in areas like the pretectum, insula, and inferior frontal gyrus. These areas are linked to the limbic areas that regulate emotions such as the anterior cingulate cortex, prefrontal cortex, amygdala, and ventral striatum (Berretz et al., 2021). It indicates that when a person feels stress from social or psychological sources, it triggers areas in the brain that deal with emotions and the body's stress response system (Berretz et al., 2021). Additionally, future research needs to explore different paradigms and focus on different facets of psychosocial stress.

4.4 Implications and Limitations

Stress-induced memory retrieval impairment has important practical implications in educational and pathological conditions. Stress during exams can affect learning ability, affect exam performance, and lead to impaired memory which is usually described as blackouts during exams.

Furthermore, the effects of stress on memory recall have important clinical implications, as some psychiatric disorders, such as phobias and post-traumatic stress disorder (PTSD), are characterized by abnormal memory processes (American Psychiatric Association, 2013). Abnormal memory is a common feature of these disorders and stress, or stress hormones are found to interfere with memory recall, this provides a significant direction toward using cortisol or stress-inducing situations to rectify the presence of abnormal memories (De Quervain & Margraf, 2008). Indeed, there are studies suggesting cortisol treatment for patients with PTSD or phobia (Soravia et al., 2006).

Our results highlight that stress can impair memory retrieval depending on the presence of cortisol. Specifically, our results show that the detrimental effects of stress on memory retrieval can persist long after cortisol levels are regulated.

This study also suggests that reelin is a possible agent in mitigating memory issues linked to stress. This is because reelin plays a crucial role in fear memory consolidation and the signalling pathways related to stress. These findings pave the way for more in-depth investigations into how reelin could be advantageous and contribute to an expanding collection of studies indicating the involvement of reelin in mental health conditions like depression (Fenton et al., 2015; Ishii et al., 2016). Furthermore, the study sheds light on how reelin could serve as a possible treatment option aiming to improve the harmful impacts of stress thereby reducing the symptoms seen in mental health conditions (Ishii et al. 2016). It has also been shown that reelin dysfunction is found in people with alzheimer's disease known for its impact on memory (Bothwell & Giniger 2000). Perhaps, reelin might be used to reverse memory loss in people who have Alzheimer's disease, schizophrenia or epilepsy.

Given the exploratory nature of this study, the small sample size may limit statistical power and prevent subtle differences from being observed. Therefore, using a larger sample may have reduced variability and yielded stronger effects, which may have made the results of the first-day retention test significant. Another limitation of this study is that intravenous injection was not specifically targeted. Research by Sawahata et al.(2021), showed that direct microinjection of reelin into the mPFC can prevent antagonist-induced recognition memory impairment. The study showed that impairment is prevented by acting on receptors and suppressing neuronal activity in mice. In addition, my experiment included only male rats, here gender differences were also not investigated in this study, therefore generalizability to female rats is limited. Future studies should include both male and female rats to determine whether there are sex differences in memory retention following stress exposure.

Future studies also should extend these preliminary findings and evaluate the immediate effects of reelin using a broader range of animal models. In this study, low doses of reelin were administered to upregulate reelin signaling and improve behaviors associated with acute stress, but significant increases in reelin expression may be associated with certain cancers and liver fibrosis (Khialeeva and Carpenter, 2016). Therefore, it may be beneficial to review the recommended dosage of reelin administration. Additionally, it is important to determine reelin's time frame of action, as ketamine which is a rapid-acting antidepressant treatment is known to act within 1 hour and up to 2 weeks after administration (Kishimoto et al., 2016). Future studies could examine the duration of action in stress models.

Conclusion

This thesis aimed to examine the effects of acute stress on the retrieval of previously acquired fear memories. We found that exposure to stress significantly impairs recently acquired fear memory recall. In contrast, delayed stress exposure does not affect fear memory recall, indicating that fear memories are time-dependently vulnerable to stress. Futhermore, when examining the c-Fos gene and reelin mRNA expression we found that c-Fos expression was upregulated in rats exposed to stress and decreased in reelin mRNA expression. This is primarily seen in the mPFC, indicating increased neural activity in response to stress however it impacts the reelin levels. Interestingly, we found that the administration of recombinant reelin reversed stress-related memory deficits, as evidenced by improved fear memory recall.

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