# Oxytocin Regulation of Psychological Resilience: Mechanisms of Action in the Hippocampus

**Authors:** Jun Gao, Xue Bing, Wang Xuejiao, Ma Ning, Gao Jun

**Date:** 2020-10-17T00:00:00+00:00

## Abstract

Psychological resilience refers to the ability of an individual to effectively and flexibly adapt to stressful situations such as adversity, setbacks, or major threats, thereby promoting the restoration of normal physiological and psychological functions. Research indicates that the hippocampus is a crucial brain region regulating psychological resilience, and oxytocin may enhance psychological resilience by acting on the hippocampus. The internal hippocampal circuit, the entorhinal cortex-dentate gyrus-CA3 pathway, may regulate the generalization and extinction of fear memories to enhance psychological resilience; the external hippocampal circuits, including the dentate gyrus-amygdala-nucleus accumbens and hippocampus-nucleus accumbens pathways, regulate emotion and may respectively enhance or reduce psychological resilience by promoting reward or inducing aversion. Possible pathways through which oxytocin acts on the hippocampus to enhance psychological resilience include: oxytocin promotes hippocampal neurogenesis, reduces the stress sensitivity of mature neurons in the ventral hippocampus, enhances the "pattern separation" function of the hippocampus, and decreases the generalization of stress memories; oxytocin restores long-term potentiation at Schaffer collateral-CA1 synapses in the hippocampus, promoting adaptation to stress; oxytocin reduces glucocorticoid receptor levels in the hippocampus, re-establishing homeostasis.

## Full Text

### Oxytocin Modulates Psychological Resilience: Mechanisms of Action in the Hippocampus

**XUE Bing[1], WANG Xuejiao[2], MA Ning[2], GAO Jun[1]***

[1]Faculty of Psychology, Southwest University; Key Laboratory of Cognition and Personality, Ministry of Education, Chongqing 400715, China

[2]Faculty of Psychology, Southwest University; Key Laboratory of Cognition and Personality, Ministry of Education, Chongqing 400715, China

**Abstract:** Psychological resilience refers to the capacity for effective and flexible adaptation in the face of adversity, trauma, tragedy, threats, and other significant sources of stress, which helps restore normal physiological and psychological functioning. Previous studies have shown that the hippocampus plays a crucial role in psychological resilience, and oxytocin may enhance resilience by modulating hippocampal function. Within the hippocampus, the entorhinal cortex-dentate gyrus-CA3 circuit may regulate fear memory generalization and extinction to enhance resilience. Externally, the dentate gyrus-amygdala-nucleus accumbens and hippocampus-nucleus accumbens circuits regulate emotion, potentially enhancing or reducing resilience by promoting reward or aversion, respectively. Oxytocin may enhance psychological resilience through several hippocampal mechanisms: (1) promoting hippocampal neurogenesis, reducing stress sensitivity of ventral hippocampal mature neurons, and enhancing hippocampal "pattern separation" function to reduce stress memory generalization; (2) restoring Schaffer collateral-CA1 synaptic long-term potentiation to promote stress adaptation; and (3) reducing hippocampal glucocorticoid receptor levels to re-establish homeostasis.

**Keywords:** psychological resilience; stress; stress adaptation; oxytocin; hippocampus

---

Psychological resilience, also termed stress resilience, generally refers to the capacity for effective and flexible adaptation when individuals confront adversity, setbacks, or major threats, thereby promoting recovery of normal physiological and psychological function [1-4]. Research on psychological resilience spans diverse domains, and due to varying emphases, it has also been translated as psychological elasticity, recovery, resistance, toughness, and stress resilience [1,5-7]. Resilience levels serve as a primary mediating factor in the development of post-traumatic mental illness, can predict negative emotions following stress, determine the degree of stress adaptation, and significantly impact physical and mental health [8-9]. Clinically, scholars have proposed two subsets of psychological resilience—stress vulnerability and post-traumatic growth—using a Venn diagram model and employing multi-factor assessment to measure resilience [9], reflecting a developmental measurement approach. In animal research, traditional methods involve measuring molecular and behavioral changes in stress response circuits following trauma [9]. From a physiological psychology perspective, resilience further depends on effective activation and termination of stress responses, with buffering effects against stress and trauma manifested through cognitive reappraisal and generation of positive emotions [3].

Commonly used animal models for studying psychological resilience include chronic social defeat stress (CSDS), unpredictable chronic mild stress (UCMS), early life stress, learned helplessness (LH), and acute stress [1]. Evaluation

indices encompass post-stress anxiety states, learning, memory, and reward behaviors, with resilient animals demonstrating adaptation to stress and fewer negative reactions [1]. Investigating the neural basis and mechanisms of psychological resilience facilitates deeper understanding of its functional mechanisms and helps reduce the occurrence of post-traumatic mental illness. Both human and animal studies indicate that hippocampal activity differences influence psychological resilience, relating to hippocampal volume, projection connections, receptor types, and neurogenesis [1,10-11]. These studies demonstrate close relationships between hippocampal changes and resilience, but they only reflect correlations at the macro level, with micro-level regulatory mechanisms remaining unclear. Given that stress can alter hippocampal structure and impair hippocampus-dependent memory function [12], examining factors influencing stress-induced hippocampal structural and functional changes may reveal micro-level factors and mechanisms through which the hippocampus regulates resilience.

Oxytocin is a nine-amino-acid endogenous neurohormone synthesized in the hypothalamic paraventricular nucleus (PVN) and supraoptic nucleus (SON) and secreted into peripheral circulation by the posterior pituitary [13]. Oxytocin has attracted widespread attention for modulating stress responses, promoting positive social behaviors, and serving as a potential therapeutic agent for stress-related disorders [14-19]. The hippocampus receives direct oxytocinergic input from the hypothalamus [20-21], and oxytocin treatment can protect spatial memory and hippocampal synaptic plasticity in rats under uncontrollable stress, attenuating the impact of stress on physiological and psychological function [22-23], suggesting that oxytocin is one of the factors influencing stress-induced hippocampal structural and functional changes. Human and animal studies also indicate that oxytocin modulates psychological resilience [24-25]. In summary, the hippocampus is a critical brain region regulating psychological resilience, oxytocin is a modulatory factor for resilience, and oxytocin may regulate resilience through actions on the hippocampus. However, systematic reviews of these specific regulatory mechanisms are lacking. This article integrates existing data from animal and human studies, briefly elaborates on hippocampal internal and external circuits regulating resilience, and focuses on the effects and mechanisms of oxytocin acting on the hippocampus to modulate resilience. This review clarifies research on oxytocin' s hippocampal actions in regulating resilience, elucidates its mechanisms and significance, provides references for researchers, and offers important insights for the prevention and treatment of posttraumatic stress disorder (PTSD), anxiety disorders, and depression.

## 1. Hippocampal Circuitry Mechanisms Underlying Psychological Resilience

Mechanisms regulating psychological resilience with the hippocampus as the primary brain region involve both internal and external projection circuits. The hippocampus comprises three main subfields—CA1, CA2, and CA3—along with

other regions including the dentate gyrus (DG), hippocampal subicular complex, and entorhinal cortex [26]. Major excitatory inputs from cortical and subcortical areas converge on the entorhinal cortex, which projects to the DG as the primary pathway for information entering the hippocampus [27]. Internal hippocampal signaling pathways include: (1) entorhinal cortex layer II projections to DG and CA3, with CA3 pyramidal neurons projecting to CA1 stratum radiatum and dorsolateral septum; and (2) entorhinal cortex layer III projections to CA1, with CA1 pyramidal neurons projecting to cortex and subiculum [28]. After hippocampal processing, these two pathways transmit signals from dorsal and ventral hippocampus to form external circuits [28]. The dorsal hippocampus primarily projects to retrosplenial cortex, subiculum, and medial/lateral septum, whereas the ventral hippocampus (vHIP) mainly projects to hypothalamus, nucleus accumbens (NAc), amygdala, prefrontal cortex (PFC), bed nucleus of stria terminalis, subiculum, and medial/lateral septum [28]. Stress affects memory, emotion, and other cognitive functions regulated by these circuits [28].

Hippocampal internal circuits may regulate resilience by modulating memory function. The DG, a critical region influencing hippocampal pathway excitability, is directly affected by stress hormones such as glucocorticoids and corticotropin-releasing hormone (CRH), which disrupt DG-CA3 signal transmission and cause behavioral abnormalities [29]. Elevated glucocorticoids or systemic corticosterone administration reduce DG neurogenesis and increase anxiety-related behaviors [30-31]. DG signal transmission and neurogenesis are affected by stress, leading to stress responses, but the DG can also modulate its own activity to attenuate stress effects and regulate resilience. Good resilience requires avoiding excessive fear response generalization [10]. Mouse studies show that dorsal DG participates in encoding stress-related memories and their retrieval and extinction, with signal connections to entorhinal cortex, CA3, and amygdala [32]. Inhibiting dorsal DG activity disrupts fear acquisition, increases fear generalization, and impairs fear extinction [32]. Research suggests dorsal DG reduces fear memory generalization by encoding fear context information and forming precise memories. When encountering similar contexts, dorsal DG reduces interference by discriminating contextual details, though the mechanism for DG modulation of fear extinction remains unclear [32]. These findings indicate that the entorhinal cortex-DG-CA3 internal circuit may enhance resilience by reducing fear generalization and promoting fear extinction.

Hippocampal external circuits may regulate resilience by modulating emotional function. First, the DG projection to basolateral amygdala (BLA)-NAc regulates resilience by modulating reward seeking. Mouse studies show that activating DG cells encoding positive memories reduces depression-like behaviors induced by chronic restraint stress [33]. The mechanism involves activating hippocampal DG cells, which further activates BLA glutamatergic projections to NAc, enhancing NAc-regulated reward-seeking behavior, weakening stress responses [34], and regulating resilience. This suggests that under stress, resilience promotes stress adaptation possibly through activating the DG-BLA-NAc pathway to enhance reward-seeking behavior, allowing organisms to adjust emotional

and behavioral responses and reduce the impact of stress on physiological and psychological function. Second, the hippocampal projection to NAc regulates resilience by modulating psychological aversion. Optogenetic studies in CSDS mice show that prolonged inhibition of the vHIP-NAc circuit enhances resilience, whereas brief activation of vHIP glutamate neurons projecting to NAc reduces resilience, while other circuits such as medial prefrontal cortex (mPFC)-NAc or BLA-NAc do not participate in this function [35]. Rat studies further demonstrate that aversive experiences from psychological stress can directly activate the vHIP-NAc circuit via monosynaptic connections, with stressed groups showing greater activation of medium spiny neurons in NAc and more depression-like behaviors [35-36]. These studies indicate that stress activation of the vHIP-NAc circuit reduces resilience and increases stress responses.

In summary, hippocampal involvement in resilience regulation includes internal and external circuits: (1) hippocampal DG neurogenesis improves entorhinal cortex-DG-CA3 signal transmission, modulates memory function, and reduces fear memory generalization; and (2) glutamatergic activity in hippocampal DG-BLA-NAc and hippocampus-NAc circuits regulates emotion, inhibiting or activating stress responses. Further findings show that NAc receives direct or indirect hippocampal projections with opposite effects, and BLA may play a key role. Studies indicate that stress causes complex interactions among BLA, hippocampus, and NAc [37-38], necessitating further research to better understand the specific mechanisms.

## 2. Oxytocin Enhances Psychological Resilience by Promoting Hippocampal Neurogenesis

Throughout life, hippocampal neurogenesis persists, primarily manifesting as the addition of new functional neurons in the hippocampal DG [39]. Adult hippocampal neurogenesis plays important roles in regulating learning, memory, negative emotions, and stress [40-42]. Stress activates the hypothalamic-pituitary-adrenal (HPA) axis and increases stress hormone levels. Low and high concentrations of glucocorticoids regulate signaling processes through hippocampal mineralocorticoid and glucocorticoid receptors, respectively, to inhibit hippocampal neurogenesis [43-44]. From the perspective of stress inhibiting hippocampal neurogenesis, micro-level mechanisms of oxytocin acting on the hippocampus to regulate resilience may be discovered.

### 2.1 Oxytocin Promotes Hippocampal Neurogenesis

Oxytocin promotes hippocampal neurogenesis under normal conditions. Systemic administration studies show that acute oxytocin promotes cell proliferation in ventral DG, while chronic oxytocin increases the number of granule neurons and glial cells in ventral DG, and central administration via hippocampal microinjection similarly promotes neurogenesis [45], suggesting that oxytocin regulates neurogenesis by acting on the hippocampus. PVN oxytocin signals can

activate oxytocin receptors in hippocampal CA3 pyramidal neurons, thereby promoting DG neurogenesis, which partially explains why long-term oxytocin treatment promotes cell proliferation and dendritic maturation of new neurons in adult rat hippocampus [46-47].

Oxytocin also promotes hippocampal neurogenesis under stress conditions. Oxytocin can promote cell proliferation in the hippocampus even when glucocorticoids are elevated, preventing stress hormones from inhibiting neurogenesis [45]. Oxytocin can also increase hippocampal neurogenesis to promote stress adaptation and improve stress symptoms. In rat studies, neonatal maternal deprivation stress caused depression-like behaviors in adulthood, and long-term intranasal oxytocin administration alleviated depressive behaviors behaviorally and improved stress-reduced hippocampal neurogenesis mechanistically [48]. These studies suggest that oxytocin may reduce stress-induced damage and increase stress adaptability by increasing hippocampal neurogenesis, thereby enhancing resilience. Specifically, oxytocin may regulate resilience through different approaches to promoting hippocampal neurogenesis.

### 2.2 Oxytocin Specifically Reduces Stress Sensitivity of Mature Neurons in Ventral Hippocampus

Oxytocin receptor distribution in the hippocampus shows cell-type and regional specificity. In most rodents, oxytocin receptor expression and binding can be detected in all hippocampal subfields (CA1, CA2, CA3, DG, entorhinal cortex) [14]. Studies show that oxytocin receptors in DG are more highly expressed in interneurons, with granule cells expressing almost no oxytocin receptors, while CA2/CA3 oxytocin receptors are more highly expressed in excitatory neurons [20,49-50]. This distribution pattern suggests that oxytocin may influence hippocampal function and regulate resilience through specific mechanisms.

Oxytocin modulates fast-spiking interneurons in the hippocampus, enhancing CA1 spike transmission and improving brain information processing, which is particularly important for regulating psychiatric or neurological disorders [51-52]. Oxytocin, via Gq/11-coupled oxytocin receptors, reduces dendritic branching and function of hippocampal glutamatergic neurons [53], which may maintain the balance between excitation and inhibition to ensure normal neurobehavioral development. These studies suggest that oxytocin may indirectly regulate resilience by modulating the firing of different hippocampal neuron types and regulating organism excitability.

Oxytocin can activate hippocampal pyramidal neuron excitation to promote neurogenesis and enhance resilience. Since neural progenitor cells in the adult DG subgranular zone or mature granule cells do not express oxytocin receptors, and only a small portion of GABAergic neurons in the polymorphic cell layer express oxytocin receptors, oxytocin is unlikely to directly act on DG to promote neurogenesis [46]. Further research shows that oxytocin acts in a non-cell-autonomous manner on oxytocin receptors in CA3 pyramidal neurons,

activating these neurons and promoting excitatory transmission. These signals project to DG, promoting neurogenesis in ventral DG [46]. Calcium imaging reveals that these new neurons inhibit activity of mature cells in ventral DG, reducing ventral DG stress sensitivity [54], promoting stress adaptation, and thereby enhancing resilience.

### 2.3 Oxytocin Reduces Stress Memory Generalization by Enhancing Hippocampal Pattern Separation Function

The hippocampus is a key brain region regulating learning and memory. When encoding stimuli similar to original stimuli, the hippocampus can transform representations or memories of similar stimuli into highly distinct, non-overlapping representations—a process termed "pattern separation" that is crucial for stimulus discrimination. The hippocampal DG-CA3 pathway plays an important role in pattern separation during memory [55-56]. Hippocampal neurogenesis participates in pattern separation, and increased neurogenesis can enhance this function [57-59]. In studies investigating PTSD and anxiety mechanisms, fear generalization—characterized by excessive fear responses to similar stress stimuli —is associated with lower pattern separation function [28]. Research shows that based on prior experience, hippocampal neurogenesis can regulate brain encoding and response processes to two different or identical contexts via the DG-CA3 pathway [60]. Lower neurogenesis impedes encoding of new memories, increases interference with original memories, and causes reallocation of encoding between old and new memories, accelerating transfer of post-traumatic stress memory elements and causing fear generalization. In contrast, high neurogenesis encodes old and new memories through different neuronal populations, reducing interference between them [28], thereby reducing stress memory generalization and promoting stress adaptation. Therefore, oxytocin may enhance resilience by acting on the hippocampal DG-CA3 internal circuit to promote neurogenesis, reduce stress sensitivity, and improve pattern separation function for stress stimuli.

## 3. Oxytocin Enhances Psychological Resilience by Restoring Abnormal Hippocampal Synaptic Plasticity

With experience, neural activity changes nervous system and circuit function, affecting synaptic transmission strength or efficacy of existing synapses. This activity-dependent synaptic modifiability constitutes synaptic plasticity, which is crucial for functional refinement of the nervous system and brain learning and memory processes [49,61]. Stress disrupts normal hippocampal synaptic plasticity [62]. Chronic stress reduces the number of apical dendritic terminals in hippocampal CA3, decreases long-term potentiation (LTP) in CA1 synapses, and increases anxiety-like behaviors and impairs working memory [63-64]. Acute stress also inhibits LTP in CA1 [65-67] and CA1-CA3 regions [68-69], producing long-lasting effects. Thus, stress affects hippocampal synaptic plasticity and causes behavioral changes, likely due to reduced resilience. From the perspec-

tive of stress-induced hippocampal synaptic plasticity abnormalities, micro-level mechanisms of oxytocin acting on the hippocampus to regulate resilience may be identified.

### 3.1 Oxytocin Influences Hippocampal Synaptic Plasticity

Oxytocin promotes hippocampal synaptic plasticity. In hippocampal slices from unmated female mice perfused with oxytocin, oxytocin induces persistent LTP and CREB phosphorylation through the MAPK cascade, promoting Schaffer collateral-CA1 synaptic LTP formation in the CA3-CA1 pathway [60,70]. Intracerebroventricular oxytocin injection promotes long-term spatial memory in nulliparous female mice, while oxytocin receptor antagonist injection inhibits these effects and disrupts spatial memory [70], indicating that oxytocin can regulate synaptic plasticity and improve hippocampus-dependent cognitive function in female mice. Activation of oxytocin receptors on pyramidal layer interneurons in hippocampal CA1 can regulate GABAergic activity of inhibitory interneurons, increase inhibitory postsynaptic transmission, and modulate downstream pyramidal neurons to improve signal-to-noise ratio and promote plasticity [52,71], which may be one mechanism by which oxytocin regulates hippocampal synaptic plasticity. Additionally, since oxytocin receptors are predominantly expressed in hippocampal CA2 and CA3 regions, studies using oxytocin receptor knockout mice have investigated oxytocin' s effects on CA2 and CA3 synaptic plasticity. Related research has revealed the critical role of oxytocin signaling in inducing LTP at synapses between entorhinal cortex and CA2 pyramidal neurons, and shows that oxytocin receptors promote long-term social recognition memory formation in hippocampal CA2/anterior CA3 (aCA3) by inducing LTP [49-50], demonstrating the importance of oxytocin in regulating social behavior through hippocampal synaptic LTP modulation.

### 3.2 Oxytocin Restores Stress-Suppressed Hippocampal Long-Term Potentiation

Oxytocin can restore stress-induced abnormalities in hippocampal synaptic plasticity. Under uncontrollable stress, rats without oxytocin treatment show impaired LTP, enhanced long-term depression (LTD), and poor spatial memory in hippocampal Schaffer collateral-CA1 synapses, whereas oxytocin-treated rats do not exhibit these changes. Oxytocin antagonist L-368899 inhibits oxytocin' s protective effects on the hippocampus [22], confirming that oxytocin attenuates stress effects by protecting hippocampal synaptic plasticity, which may represent a neural mechanism for oxytocin regulation of resilience. This study also found that stress reduces phosphorylated extracellular signal-regulated kinase (pERK) levels in the hippocampus, affecting synaptic plasticity. It is hypothesized that oxytocin acts on oxytocin receptors on non-pyramidal neurons, increasing their excitability and thereby inhibiting pyramidal neurons, which attenuates stress-induced changes in pERK and regulates stress adaptation [22]. Further research demonstrates that oxytocin treatment after stress can also res-

cue stress-induced impairments in hippocampal synaptic plasticity and recognition memory [23]. Although different oxytocin regulatory signaling mechanisms may exist between these two stages, no clear evidence is yet available and requires further investigation. Nevertheless, this demonstrates the possibility and importance of oxytocin enhancing resilience by restoring abnormal hippocampal synaptic plasticity. Oxytocin may promote stress adaptation and enhance resilience by increasing kinase levels in Schaffer collateral-CA1 synapses of the CA3-CA1 pathway, restoring abnormal LTP processes caused by stress. Regarding oxytocin restoring stress-suppressed hippocampal LTP to improve resilience, this may be achieved through the hippocampus-BLA circuit. Research shows that BLA activation is one manifestation of acute stress response, which is related to impaired DG synaptic LTP [37]. Therefore, oxytocin restoration of hippocampal LTP abnormalities may reduce excessive amygdala activation, thereby mitigating adverse effects of stress on cognition-related functions.

## 4. Oxytocin Enhances Psychological Resilience by Reducing Hippocampal Glucocorticoid Receptor Levels

Glucocorticoids are the most important regulatory hormones in the stress response. Glucocorticoid receptors are highly expressed in the brain hippocampus, primarily distributed in pyramidal cells of hippocampal CA1, CA2, and DG [72]. The high expression level of glucocorticoid receptors in the hippocampus determines their impact on the hippocampus and the hippocampus' s role in stress response.

### 4.1 Stress Increases Hippocampal Glucocorticoid Receptor Expression

Stress affects hippocampal function through glucocorticoid receptors. Early stress can increase glucocorticoid receptor expression in the hippocampus of adult male and female mice and increase anxiety-like behaviors. Early gestational stress in rats not only increases glucocorticoid receptors but also affects hippocampal neurogenesis [73-74]. Stress-induced glucocorticoids act on hippocampal glucocorticoid receptors, affecting synaptic plasticity, reducing hippocampal neurogenesis, and inducing PTSD-like memory impairments [12]. Elevated corticosterone levels from stress, similar to acute systemic injection of high-concentration corticosterone, reduce hippocampal synaptic plasticity by activating glucocorticoid receptors, possibly by blocking N-methyl-D-aspartate (NMDA) receptor-dependent synaptic plasticity [75-76]. Glucocorticoid dysregulation also inhibits adult hippocampal neurogenesis, increases depression-like behaviors, and causes hippocampal neuronal apoptosis [42-43,77]. These studies demonstrate that stress affects hippocampus and behavior through glucocorticoid receptors, and from this perspective, micro-level mechanisms of hippocampal oxytocin regulation of resilience may be discovered.

### 4.2 Oxytocin Reduces Stress-Elevated Hippocampal Glucocorticoid Receptor Levels

Oxytocin affects hippocampal glucocorticoid receptor expression. Systemic oxytocin administration reduces glucocorticoid receptor mRNA expression in rat hippocampal CA1, CA2, and DG, while increasing mineralocorticoid receptor mRNA expression in DG [78]. Oxytocin may regulate resilience by reducing hippocampal glucocorticoid receptor expression and thereby attenuating stress effects on the hippocampus.

Oxytocin modulates stress-induced glucocorticoid and hippocampal glucocorticoid receptor levels to regulate resilience. As a neuropeptide originating from the hypothalamic-neurohypophyseal system, oxytocin participates in and modulates HPA axis activity under stress [79]. Human intranasal oxytocin treatment can reduce stress-induced cortisol elevation, an effect more pronounced in psychiatric patients [80-81]. PVN oxytocin treatment in rodents also reduces post-stress corticosterone levels and buffers stress responses through promoting social interaction, reducing anxiety-related behaviors [82]. This suggests that oxytocin may enhance resilience by regulating positive social behaviors and social interaction. The hypothalamus and hippocampus play key roles in oxytocin modulation of stress. Particularly, the hippocampus is important in regulating emotion and anxiety. Under stress conditions, oxytocin regulates stress through the hippocampus and protects the hippocampus from adverse stress effects [83]. Oxytocin also inhibits corticosterone-induced apoptosis in primary hippocampal neurons [84]. Microinjection of oxytocin into the rat hippocampus one hour or seven days after predator odor exposure stress reduces hippocampal glucocorticoid receptor expression and alleviates anxiety-related behaviors [85], which may indicate oxytocin' s role in stress memory formation. This study further found that oxytocin interacts with corticosterone and norepinephrine (NE) in regulating this process—only combined corticosterone and NE can induce plasma and hippocampal oxytocin release—demonstrating the complex relationship between glucocorticoids, catecholamines, and oxytocin, and partially revealing mechanisms by which oxytocin regulates stress-adaptive behavioral responses through the hippocampus [86]. Research has found that glucocorticoids regulate hippocampal oxytocin receptor binding, also demonstrating interactions between glucocorticoid and oxytocin systems [87]. We therefore hypothesize that under stress conditions, highly activated HPA axis increases corticosterone and NE levels, and their combination increases hippocampal oxytocin release, which subsequently inhibits HPA axis function and reduces hippocampal glucocorticoid receptor levels. On one hand, this may reduce stress-induced structural and functional hippocampal damage by affecting neurogenesis and synaptic plasticity; on the other hand, it may regulate stress response and stress memory formation processes, enabling the organism to re-establish homeostasis, promote stress adaptation, reduce anxiety-like behaviors, and weaken stress-related memories, thereby enhancing resilience.

## 5. Summary and Outlook

In summary, hippocampal circuits and oxytocin actions on the hippocampus play important roles in regulating psychological resilience. First, the entorhinal cortex-DG-CA3 internal circuit regulates fear memory generalization and extinction to enhance resilience, while DG-BLA-NAc and hippocampus-NAc external circuits regulate emotion, enhancing or reducing resilience by promoting reward or aversion, respectively. Second, oxytocin may: (1) act on oxytocin receptors in hippocampal CA3 pyramidal neurons to promote neurogenesis in ventral hippocampus and inhibit mature DG cell activity, thereby reducing stress sensitivity and enhancing resilience; (2) promote hippocampal neurogenesis and enhance "pattern separation" function in the DG-CA3 circuit to reduce stress memory generalization and promote stress adaptation; (3) increase kinase levels in NMDA receptor-dependent Schaffer collateral-CA1 synaptic signaling pathways in the CA3-CA1 circuit to restore abnormal synaptic LTP processes caused by stress, thereby adapting to stress and enhancing resilience; and (4) interact with glucocorticoid and catecholamine systems to increase release, inhibit HPA axis function, reduce hippocampal glucocorticoid receptor levels, protect hippocampal structure and function from glucocorticoid damage, re-establish brain homeostasis, and adjust hippocampal stress-related memory to enhance resilience.

Despite progress in understanding hippocampal and oxytocin regulation of resilience, several issues require attention and resolution. First, oxytocin' s regulation of resilience through hippocampal structure and function may differ across sexes and individual experiences. Chronic systemic oxytocin administration reduces ventral hippocampal neurogenesis in both adult male and female rats but only increases social interaction behavior in males [88]. This reduction in neurogenesis is inconsistent with most previous studies [45-46], and further investigation revealed that increased social behavior in males is associated with reduced neurogenesis, while reduced neurogenesis in females is influenced by decreased estradiol levels [88], demonstrating the complexity of oxytocin' s hippocampal effects and the need to consider sex differences in its behavioral regulation. Even when oxytocin' s hippocampal effects may be consistent, underlying mechanisms and mediated behaviors may differ, requiring in-depth analysis. Additionally, individual stress-related experiences affect oxytocin' s regulatory effects. Human studies show that oxytocin treatment under stress can attenuate HPA axis hormone responses in healthy individuals but produces opposite and harmful effects in those with abuse histories [89], indicating that individual diagnosis and treatment must incorporate these factors for rational therapeutic approaches.

Second, oxytocin' s regulation of resilience through the hippocampus must consider gene-environment interactions. Some studies suggest that oxytocin' s hippocampal regulation of resilience involves a potential mechanism highlighting the importance of gene-environment interactions. Reduced hippocampal volume is associated with high susceptibility to affective disorders, while larger hippocampal volume is considered a marker of post-stress resilience [90]. Oxy-

tocin gene polymorphisms affect hippocampal volume and resilience [91-93], suggesting a possible role for oxytocin in regulating resilience through hippocampal volume. However, this effect is also influenced by environment. For example, when adolescent girls were divided into low and high emotional trauma exposure groups, both carrying the oxytocin rs53576 AA allele associated with lower resilience, the low-trauma group showed larger left hippocampal volume, which positively correlated with perceived social support from friends [94]. This indicates that oxytocin gene polymorphisms interact with individual psychological environment and social support to jointly affect hippocampal volume and resilience. This genotype also interacts with family environment, with positive family environments contributing to enhanced resilience [91]. Therefore, investigating oxytocin' s hippocampal regulation of resilience must account for individual differences and external environmental factors. Treating stress-related mental illness requires not only medication but also attention to individual characteristics, interpersonal relationships, and emotional support to targetedly enhance resilience.

Third, investigating resilience neural mechanisms must closely integrate human and animal studies to compensate for respective limitations. Animal models themselves may have potential factors affecting results. Different animal strains, sexes, life experiences, genetic backgrounds, stress susceptibility, and variations in stress intensity, duration, and testing environments can all affect resilience measurement [95]. Therefore, studies may employ multiple models for replication or use the same models and procedures as previous research to obtain stable results and increase comparability and integrability among conclusions. Human studies lack depth in investigating resilience neural mechanisms and coordination with animal studies [96]. Future research should combine human brain imaging with animal neural circuit techniques to identify precise brain structures and circuits regulating resilience. Achieving model integration requires deeper understanding of genetic and epigenetic, neurobiological, and neuroendocrine foundations to better comprehend complex interactions between individual differences and environmental factors affecting resilience, providing effective prevention and treatment approaches for human post-traumatic mental illness susceptibility and pathogenesis.

## References

[1] 刘浩然, 张晨风, 杨莉. (2019). 心理韧性及其神经机制: 来自非人类动物模型的证据. 心理科学进展, 27(02), 126-135. (LIU Haoran, ZHANG Chenfeng, & YANG Li. (2019). The neural mechanism underlying resilience. Advances in Psychological Science, 27(02), 126-135.)

[2] Horn, S. R., Charney, D. S., & Feder, A. (2016). Understanding resilience: New approaches for preventing and treating PTSD. Experimental Neurology, 284(Pt B), 119-132.

[3] Horn, S. R., & Feder, A. (2018). Understanding Resilience and Preventing

and Treating PTSD. Harvard Review of Psychiatry, 26(3), 158-174.

[4] Hornor, G. (2017). Resilience. Journal of Pediatric Health Care : Official Publication of National Association of Pediatric Nurse Associates & Practitioners, 31(3), 384-390.

[5] 刘伟伟, 汪海彬, 李梅, 黄丽. (2017). 心理弹性的国内外研究回顾及展望. 宁波大学学报 (教育科学版), 39(01), 18-23. (LIU Wei-wei, WANG Hai-bin, LI Mei, & HUANG Li. (2017). A Review of Current Status and Prospects of Research on Resilience. Journal of Ningbo University(Educational Science Edition)(01), 18-23.)

[6] 席居哲, 左志宏, Wei, W. U. (2012). 心理韧性研究诸进路. 心理科学进展, 20(009), 1426-1447. (XI Ju-Zhe, ZUO Zhi-Hong, & WU Wei. (2012). Approaches to Research on Resilience. Advances in Psychological Science, 20(009), 1426-1447.)

[7] 诸彦含, 赵玉兰, 周意勇, 吴江. (2019). 组织中的韧性：基于心理路径和系统路径的保护性资源建构. 心理科学进展, 27(2), 357-369. (ZHU Yanhan, ZHAO Yulan, ZHOU Yiyong, & WU Jiang. (2019). Resilience in organizations: Construction of protective resources from psychological and systematic perspective. Advances in Psychological Science, 027(002), 357-369.)

[8] 林思婷, 罗梦娜, 汪丹, 李泽楷. (2019). 心理韧性测量工具的研究现状. 解放军护理杂志, 36(04), 54-57. (LIN Siting, LUO Mengna, WANG Dan, & LI Zekai. (2019). Research Status of Psychological Resilience Measurement Tools:A Review. Nursing Journal of Chinese People' s Liberation Army, 36(04), 54-57.)

[9] Rakesh, G., Morey, R. A., Zannas, A. S., Malik, Z., Marx, C. E., Clausen, A. N., . . . Szabo, S. T. (2019). Resilience as a translational endpoint in the treatment of PTSD. Molecular Psychiatry, 24(9), 1268-1283.

[10] 杨婧, 王詠, 宋莉莉. (2019). 心理韧性的神经机制研究进展. 神经解剖学杂志, 35(01), 94-98. (Yang Jing, Wang Yong, & Song Lili. (2019). Neural mechanism of psychological resilience in neuroimaging. Chinese Journal of Neuroanatomy, 35(01), 94-98.)

[11] Levone, B. R., Cryan, J. F., & O' Leary, O. F. (2015). Role of adult hippocampal neurogenesis in stress resilience. Neurobiology of Stress, 1, 147-155.

[12] Kim, E. J., Pellman, B., & Kim, J. J. (2015). Stress effects on the hippocampus: A critical review. Learning & Memory (Cold Spring Harbor, N.Y.), 22(9), 411-416.

[13] King, C. E., Griffin, W. C., Luderman, L. N., Kates, M. M., McGinty, J. F., & Becker, H. C. (2017). Oxytocin Reduces Ethanol Self-Administration in Mice. Alcoholism, Clinical and Experimental Research, 41(5), 955-964.

[14] Jurek, B., & Neumann, I. D. (2018). The Oxytocin Receptor: From intracellular signaling to behavior. Physiological Reviews, 98(3), 1805-1908.

[15] Robinson, D. A., Wei, F., Wang, G. D., Li, P., Kim, S. J., Vogt, S. K., . . . Zhuo, M. (2002). Oxytocin mediates stress-induced analgesia in adult mice.

The Journal of Physiology, 540(Pt 2), 593–606.

[16] Sack, M., Spieler, D., Wizelman, L., Epple, G., Stich, J., Zaba, M., & Schmidt, U. (2017). Intranasal oxytocin reduces provoked symptoms in female patients with posttraumatic stress disorder despite exerting sympathomimetic and positive chronotropic effects in a randomized controlled trial. BMC Medicine, 15(1), 40.

[17] van Zuiden, M., Frijling, J. L., Nawijn, L., Koch, S. B. J., Goslings, J. C., Luitse, J. S., . . . Olff, M. (2017). Intranasal Oxytocin to Prevent Posttraumatic Stress Disorder Symptoms: A randomized controlled trial in emergency department patients. Biological Psychiatry, 81(12), 1030–1040.

[18] Wang, S. C., Lin, C. C., Chen, C. C., Tzeng, N. S., & Liu, Y. P. (2018). Effects of Oxytocin on Fear Memory and Neuroinflammation in a Rodent Model of Posttraumatic Stress Disorder. International Journal of Molecular Sciences, 19(12), 3848.

[19] Winter, J., & Jurek, B. (2019). The interplay between oxytocin and the CRF system: Regulation of the stress response. Cell and Tissue Research, 375(1), 85–91.

[20] Cilz, N. I., Cymerblit-Sabba, A., & Young, W. S. (2019). Oxytocin and vasopressin in the rodent hippocampus. Genes, Brain, and Behavior, 18(1), e12535.

[21] Lee, M. R., Rohn, M. C., Tanda, G., & Leggio, L. (2016). Targeting the Oxytocin System to Treat Addictive Disorders: Rationale and Progress to Date. CNS Drugs, 30(2), 109–123.

[22] Lee, S. Y., Park, S. H., Chung, C., Kim, J. J., Choi, S. Y., & Han, J. S. (2015). Oxytocin Protects Hippocampal Memory and Plasticity from Uncontrollable Stress. Scientific Reports, 5, 18540.

[23] Park, S. H., Kim, Y. J., Park, J. C., Han, J. S., & Choi, S. Y. (2017). Intranasal Oxytocin following Uncontrollable Stress Blocks Impairments in Hippocampal Plasticity and Recognition Memory in Stressed Rats. The International Journal of Neuropsychopharmacology, 20(10), 861–866.

[24] Barrett, C. E., Arambula, S. E., & Young, L. J. (2015). The oxytocin system promotes resilience to the effects of neonatal isolation on adult social attachment in female prairie voles. Translational Psychiatry, 5(7), e606.

[25] Kim, H. W., Kang, J. I., An, S. K., & Kim, S. J. (2019). Oxytocin receptor gene variants are associated with emotion recognition and resilience, but not with false-belief reasoning performance in healthy young Korean volunteers. CNS Neuroscience & Therapeutics, 25(4), 519–526.

[26] Schultz, C., & Engelhardt, M. (2014). Anatomy of the hippocampal formation. Frontiers of Neurology and Neuroscience, 34, 6–17.

[27] Fa, M., Xia, L., Anunu, R., Kehat, O., Kriebel, M., Volkmer, H., & Richter-Levin, G. (2014). Stress modulation of hippocampal activity–spotlight on the dentate gyrus. Neurobiology of Learning and Memory, 112, 53–60.

[28] Besnard, A., & Sahay, A. (2016). Adult Hippocampal Neurogenesis, Fear Generalization, and Stress. Neuropsychopharmacology, 41(1), 24–44.

[29] Gunn, B. G., & Baram, T. Z. (2017). Stress and Seizures: Space, time and hippocampal circuits. Trends in neurosciences, 40(11), 667–679.

[30] Chetty, S., Friedman, A. R., Taravosh-Lahn, K., Kirby, E. D., Mirescu, C., Guo, F., . . . Kaufer, D. (2014). Stress and glucocorticoids promote oligodendrogenesis in the adult hippocampus. Molecular Psychiatry, 19(12), 1275–1283.

[31] Revest, J. M., Dupret, D., Koehl, M., Funk-Reiter, C., Grosjean, N., Piazza, P. V., & Abrous, D. N. (2009). Adult hippocampal neurogenesis is involved in anxiety-related behaviors. Molecular Psychiatry, 14(10), 959–967.

[32] Bernier, B. E., Lacagnina, A. F., Ayoub, A., Shue, F., Zemelman, B. V., Krasne, F. B., & Drew, M. R. (2017). Dentate Gyrus Contributes to Retrieval as well as Encoding: Evidence from context fear conditioning, recall, and extinction. The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 37(26), 6359–6371.

[33] Ramirez, S., Liu, X., MacDonald, C. J., Moffa, A., Zhou, J., Redondo, R. L., & Tonegawa, S. (2015). Activating positive memory engrams suppresses depression-like behaviour. Nature, 522(7556), 335–339.

[34] Stuber, G. D., Sparta, D. R., Stamatakis, A. M., van Leeuwen, W. A., Hardjoprajitno, J. E., Cho, S., . . . Bonci, A. (2011). Excitatory transmission from the amygdala to nucleus accumbens facilitates reward seeking. Nature, 475(7356), 377–380.

[35] Bagot, R. C., Parise, E. M., Peña, C. J., Zhang, H. X., Maze, I., Chaudhury, D., . . . Nestler, E. J. (2015). Ventral hippocampal afferents to the nucleus accumbens regulate susceptibility to depression. Nature Communications, 6, 7062.

[36] Lipski, W. J., Dibble, S. M., Rinaman, L., & Grace, A. A. (2017). Psychogenic Stress Activates C-Fos in Nucleus Accumbens-Projecting Neurons of the Hippocampal Ventral Subiculum. The International Journal of Neuropsychopharmacology, 20(10), 855-860.

[37] Saha, R., Kriebel, M., Volkmer, H., Richter-Levin, G., & Albrecht, A. (2018). Neurofascin Knock Down in the Basolateral Amygdala Mediates Resilience of Memory and Plasticity in the Dorsal Dentate Gyrus Under Stress. Molecular Neurobiology, 55(9), 7317–

[38] Segev, A., & Akirav, I. (2016). Cannabinoids and Glucocorticoids in the Basolateral Amygdala Modulate Hippocampal-Accumbens Plasticity After Stress.

Neuropsychopharmacology, 41(4), 1066–1079.

[39] Toda, T., & Gage, F. H. (2018). Review: Adult neurogenesis contributes to hippocampal plasticity. Cell and Tissue Research, 373(3), 693-709.

[40] Christian, K. M., Song, H., & Ming, G. L. (2014). Functions and dysfunctions of adult hippocampal neurogenesis. Annual Review of Neuroscience, 37, 243–262.

[41] Hill, A. S., Sahay, A., & Hen, R. (2015). Increasing Adult Hippocampal Neurogenesis is Sufficient to Reduce Anxiety and Depression-Like Behaviors. Neuropsychopharmacology, 40(10),

[42] Snyder, J. S., Soumier, A., Brewer, M., Pickel, J., & Cameron, H. A. (2011). Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. Nature, 476(7361), 458–461.

[43] Anacker, C., Cattaneo, A., Luoni, A., Musaelyan, K., Zunszain, P. A., Milanesi, E., . . . Pariante, C. M. (2013). Glucocorticoid-related molecular signaling pathways regulating hippocampal neurogenesis. Neuropsychopharmacology, 38(5), 872–883.

[44] Hueston, C. M., Cryan, J. F., & Nolan, Y. M. (2017). Stress and adolescent hippocampal neurogenesis: Diet and exercise as cognitive modulators. Translational psychiatry, 7(4), e1081.

[45] Leuner, B., Caponiti, J. M., & Gould, E. (2012). Oxytocin stimulates adult neurogenesis even under conditions of stress and elevated glucocorticoids. Hippocampus, 22(4), 861–868.

[46] Lin, Y. T., Chen, C. C., Huang, C. C., Nishimori, K., & Hsu, K. S. (2017). Oxytocin stimulates hippocampal neurogenesis via oxytocin receptor expressed in CA3 pyramidal neurons. Nature Communications, 8(1), 537.

[47] Sánchez-Vidaña, D. I., Chan, N. M., Chan, A. H., Hui, K. K., Lee, S., Chan, H. Y., . . . Lai, C. Y. (2016). Repeated treatment with oxytocin promotes hippocampal cell proliferation, dendritic maturation and affects socio-emotional behavior. Neuroscience, 333,

[48] Ji, H., Su, W., Zhou, R., Feng, J., Lin, Y., Zhang, Y., . . . Li, J. (2016). Intranasal oxytocin administration improves depression-like behaviors in adult rats that experienced neonatal maternal deprivation. Behavioural Pharmacology, 27(8), 689–696.

[49] Lin, Y. T., & Hsu, K. S. (2018). Oxytocin receptor signaling in the hippocampus: Role in regulating neuronal excitability, network oscillatory activity, synaptic plasticity and social memory. Progress in Neurobiology, 171, 1–14

[50] Raam, T., McAvoy, K. M., Besnard, A., Veenema, A. H., & Sahay, A. (2017). Hippocampal oxytocin receptors are necessary for discrimination of social stimuli. Nature Communications, 8(1), 2001.

[51] Owen, S. F., Tuncdemir, S. N., Bader, P. L., Tirko, N. N., Fishell, G., & Tsien, R. W. (2013). Oxytocin enhances hippocampal spike transmission by modulating fast-spiking interneurons. Nature, 500(7463), 458–462.

[52] Zaninetti, M., & Raggenbass, M. (2000). Oxytocin receptor agonists enhance inhibitory synaptic transmission in the rat hippocampus by activating interneurons in stratum pyramidale. The European Journal of Neuroscience, 12(11), 3975–3984.

[53] Ripamonti, S., Ambrozkiewicz, M. C., Guzzi, F., Gravati, M., Biella, G., Bormuth, I., . . . Rhee, J. (2017). Transient oxytocin signaling primes the development and function of excitatory hippocampal neurons. Elife, 6, e22466.

[54] Anacker, C., Luna, V. M., Stevens, G. S., Millette, A., Shores, R., Jimenez, J. C., . . . Hen, R. (2018). Hippocampal neurogenesis confers stress resilience by inhibiting the ventral dentate gyrus. Nature, 559(7712), 98–102.

[55] Bakker, A., Kirwan, C. B., Miller, M., & Stark, C. E. (2008). Pattern separation in the human hippocampal CA3 and dentate gyrus. Science, 319(5870), 1640–1642.

[56] Leal, S. L., Tighe, S. K., Jones, C. K., & Yassa, M. A. (2014). Pattern separation of emotional information in hippocampal dentate and CA3. Hippocampus, 24(9), 1146–1155.

[57] Clelland, C. D., Choi, M., Romberg, C., Clemenson, G. D., Fragniere, A., Tyers, P., . . . Bussey, T. J. (2009). A functional role for adult hippocampal neurogenesis in spatial pattern separation. Science, 325(5937), 210–213.

[58] França, T. F. A., Bitencourt, A. M., Maximilla, N. R., Barros, D. M., & Monserrat, J. M. (2017). Hippocampal neurogenesis and pattern separation: A meta-analysis of behavioral data. Hippocampus, 27(9), 937–950.

[59] Sahay, A., Scobie, K. N., Hill, A. S., O' Carroll, C. M., Kheirbek, M. A., Burghardt, N. S., . . . Hen, R. (2011). Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. Nature, 472(7344), 466–470.

[60] Lange, I., Goossens, L., Michielse, S., Bakker, J., Lissek, S., Papalini, S., . . . Schruers, K. (2017). Behavioral pattern separation and its link to the neural mechanisms of fear generalization. Social Cognitive and Affective Neuroscience, 12(11), 1720–1729.

[61] Citri, A., & Malenka, R. C. (2008). Synaptic plasticity: multiple forms, functions, and mechanisms. Neuropsychopharmacology, 33(1), 18–41.

[62] McEwen, B. S. (1999). Stress and hippocampal plasticity. Annual Review of Neuroscience, 22, 105–122.

[63] Aalling, N., Hageman, I., Miskowiak, K., Orlowski, D., Wegener, G., & Wortwein, G. (2018). Erythropoietin prevents the effect of chronic restraint

stress on the number of hippocampal CA3c dendritic terminals-relation to expression of genes involved in synaptic plasticity, angiogenesis, inflammation, and oxidative stress in male rats. Journal of Neuroscience Research, 96(1), 103–116.

[64] Bhagya, V. R., Srikumar, B. N., Veena, J., & Shankaranarayana Rao, B. S. (2017). Short-term exposure to enriched environment rescues chronic stress-induced impaired hippocampal synaptic plasticity, anxiety, and memory deficits. Journal of Neuroscience Research, 95(8),

[65] Hirata, R., Togashi, H., Matsumoto, M., Yamaguchi, T., Izumi, T., & Yoshioka, M. (2008). Characterization of stress-induced suppression of long-term potentiation in the hippocampal CA1 field of freely moving rats. Brain Research, 1226, 27–32.

[66] Li, C., Huang, P., Lu, Q., Zhou, M., Guo, L., & Xu, X. (2014). KCNQ/Kv7 channel activator flupirtine protects against acute stress-induced impairments of spatial memory retrieval and hippocampal LTP in rats. Neuroscience, 280, 19–30.

[67] Takeda, A., Suzuki, M., Tamano, H., Takada, S., Ide, K., & Oku, N. (2012). Involvement of glucocorticoid-mediated Zn2+ signaling in attenuation of hippocampal CA1 LTP by acute stress. Neurochemistry International, 60(4), 394–399.

[68] Pavlides, C., Nivón, L. G., & McEwen, B. S. (2002). Effects of chronic stress on hippocampal long-term potentiation. Hippocampus, 12(2), 245–257.

[69] Sousa, V. C., Vital, J., Costenla, A. R., Batalha, V. L., Sebastião, A. M., Ribeiro, J. A., & Lopes, L. V. (2014). Maternal separation impairs long term-potentiation in CA1-CA3 synapses and hippocampal-dependent memory in old rats. Neurobiology of Aging, 35(7), 1680–

[70] Tomizawa, K., Iga, N., Lu, Y. F., Moriwaki, A., Matsushita, M., Li, S. T., . . . Matsui, H. (2003). Oxytocin improves long-lasting spatial memory during motherhood through MAP kinase cascade. Nature Neuroscience, 6(4), 384–390.

[71] Maniezzi, C., Talpo, F., Spaiardi, P., Toselli, M., & Biella, G. (2019). Oxytocin Increases Phasic and Tonic GABAergic Transmission in CA1 Region of Mouse Hippocampus. Frontiers in Cellular Neuroscience, 13, 178.

[72] Van Eekelen, J. A., Jiang, W., De Kloet, E. R., & Bohn, M. C. (1988). Distribution of the mineralocorticoid and the glucocorticoid receptor mRNAs in the rat hippocampus. Journal of Neuroscience Research, 21(1), 88–94.

[73] Lin, Y. T., Hsieh, T. Y., Tsai, T. C., Chen, C. C., Huang, C. C., & Hsu, K. S. (2018). Conditional Deletion of Hippocampal CA2/CA3a Oxytocin Receptors Impairs the Persistence of Long-Term Social Recognition Memory in Mice. The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 38(5), 1218–1231.

[74] Brydges, N. M., Jin, R., Seckl, J., Holmes, M. C., Drake, A. J., & Hall,

J. (2014). Juvenile stress enhances anxiety and alters corticosteroid receptor expression in adulthood. Brain and Behavior, 4(1), 4–13.

[75] Pawluski, J. L., Császár, E., Savage, E., Martinez-Claros, M., Steinbusch, H. W., & van den Hove, D. (2015). Effects of stress early in gestation on hippocampal neurogenesis and glucocorticoid receptor density in pregnant rats. Neuroscience, 290, 379–388.

[76] Park, H. J., Lee, S., Jung, J. W., Kim, B. C., Ryu, J. H., & Kim, D. H. (2015). Glucocorticoid- and long-term stress-induced aberrant synaptic plasticity are mediated by activation of the glucocorticoid receptor. Archives of Pharmacal Research, 38(6), 1204–

[77] Wiegert, O., Pu, Z., Shor, S., Joëls, M., & Krugers, H. (2005). Glucocorticoid receptor activation selectively hampers N-methyl-D-aspartate receptor dependent hippocampal synaptic plasticity in vitro. Neuroscience, 135(2), 403–411.

[78] Lee, A. L., Ogle, W. O., & Sapolsky, R. M. (2002). Stress and depression: Possible links to neuron death in the hippocampus. Bipolar Disorders, 4(2), 117–128.

[79] Petersson, M., & Uvnäs-Moberg, K. (2003). Systemic oxytocin treatment modulates glucocorticoid and mineralocorticoid receptor mRNA in the rat hippocampus. Neuroscience Letters, 343(2), 97–100.

[80] Engelmann, M., Landgraf, R., & Wotjak, C. T. (2019). The hypothalamic-neurohypophysial system regulates the hypothalamic-pituitary-adrenal axis under stress: An old concept revisited. Frontiers in Neuroendocrinology, 25(3–4), 132–149.

[81] Cardoso, C., Ellenbogen, M. A., Orlando, M. A., Bacon, S. L., & Joober, R. (2013). Intranasal oxytocin attenuates the cortisol response to physical stress: A dose-response study. Psychoneuroendocrinology, 38(3), 399–407.

[82] Cardoso, C., Kingdon, D., & Ellenbogen, M. A. (2014). A meta-analytic review of the impact of intranasal oxytocin administration on cortisol concentrations during laboratory tasks: Moderation by method and mental health. Psychoneuroendocrinology, 49, 161–170.

[83] Smith, A. S., & Wang, Z. (2014). Hypothalamic oxytocin mediates social buffering of the stress response. Biological Psychiatry, 76(4), 281–288.

[84] Matsushita, H., Latt, H. M., Koga, Y., Nishiki, T., & Matsui, H. (2019). Oxytocin and Stress: Neural mechanisms, stress-related disorders, and therapeutic approaches. Neuroscience, 417, 1–10.

[85] Latt, H. M., Matsushita, H., Morino, M., Koga, Y., Michiue, H., Nishiki, T., . . . Matsui, H. (2018). Oxytocin Inhibits Corticosterone-induced Apoptosis in Primary Hippocampal Neurons. Neuroscience, 379, 383–389.

[86] Cohen, H., Kaplan, Z., Kozlovsky, N., Gidron, Y., Matar, M. A., & Zohar, J. (2010). Hippocampal microinfusion of oxytocin attenuates the behavioural response to stress by means of dynamic interplay with the glucocorticoid-catecholamine responses. Journal of Neuroendocrinology, 22(8), 889–904.

[87] Liberzon, I., Chalmers, D. T., Mansour, A., Lopez, J. F., Watson, S. J., & Young, E. A. (1994). Glucocorticoid regulation of hippocampal oxytocin receptor binding. Brain Research, 650(2), 317–322.

[88] Duarte-Guterman, P., Lieblich, S. E., Qiu, W., Splinter, J. E. J., Go, K. A., Casanueva-Reimon, L., & Galea, L. A. M. (2020). Oxytocin has sex-specific effects on social behaviour and hypothalamic oxytocin immunoreactive cells but not hippocampal neurogenesis in adult rats. Hormones and Behavior, 122, 104734.

[89] Grimm, S., Pestke, K., Feeser, M., Aust, S., Weigand, A., Wang, J., . . . Bajbouj, M. (2014). Early life stress modulates oxytocin effects on limbic system during acute psychosocial stress. Social Cognitive and Affective Neuroscience, 9(11), 1828–1835.

[90] Chan, S. W., Harmer, C. J., Norbury, R., O' Sullivan, U., Goodwin, G. M., & Portella, M. J. (2016). Hippocampal volume in vulnerability and resilience to depression. Journal of Affective Disorders, 189, 199–202.

[91] Bradley, B., Davis, T. A., Wingo, A. P., Mercer, K. B., & Ressler, K. J. (2013). Family environment and adult resilience: Contributions of positive parenting and the oxytocin receptor gene. European Journal of Psychotraumatology, 4.

[92] Riem, M. M. E., van Ijzendoorn, M. H., & Bakermans-Kranenburg, M. J. (2019). Hippocampal volume modulates salivary oxytocin level increases after intranasal oxytocin administration. Psychoneuroendocrinology, 101, 182–185.

[93] Womersley, J. S., Hemmings, S. M. J., Ziegler, C., Gutridge, A., Ahmed-Leitao, F., Rosenstein, D., . . . Seedat, S. (2019). Childhood emotional neglect and oxytocin receptor variants: Association with limbic brain volumes. The World Journal of Biological Psychiatry : The Official Journal of the World Federation of Societies of Biological Psychiatry, 1–16.

[94] Malhi, G. S., Das, P., Outhred, T., Dobson-Stone, C., Bell, E., Gessler, D., . . . Mannie, Z. (2020). Interactions of OXTR rs53576 and emotional trauma on hippocampal volumes and perceived social support in adolescent girls. Psychoneuroendocrinology, 115, 104635.

[95] Murthy, S., & Gould, E. (2018). Early Life Stress in Rodents: Animal Models of Illness or Resilience? Frontiers in Behavioral Neuroscience, 12, 157.

[96] Russo, S. J., Murrough, J. W., Han, M.-H., Charney, D. S., & Nestler, E. J. (2012). Neurobiology of resilience. Nature Neuroscience, 15(11), 1475–1484.

*Corresponding author: GAO Jun, E-mail: gaojunscience@126.com*

**Author Contributions Statement:**
XUE Bing: Proposed review framework and wrote content;
WANG Xuejiao, MA Ning: Revised content;
GAO Jun: Conceptual guidance and revision.

*Note: Figure translations are in progress. See original paper for figures.*