Cognitive Neural Mechanisms of Oxytocin in Fear Acquisition and Extinction

Authors: Feng Pan, Feng Tingyong, Feng Tingyong

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Abstract

Fear is a fundamental emotion that plays a crucial role in human survival and adaptation. Previous research has demonstrated that brain regions such as the amygdala, dorsal anterior cingulate cortex, and insula constitute the cognitive neural basis of conditioned fear acquisition, while the amygdala, hippocampus, and ventromedial prefrontal cortex play important roles in fear extinction. Studies have revealed that oxytocin is closely associated with both fear acquisition and fear extinction processes. During fear acquisition, oxytocin influences the activity of the amygdala and dorsal anterior cingulate cortex, affects the functional connectivity between the amygdala and the dorsal anterior cingulate cortex and brainstem, thereby promoting or inhibiting the fear acquisition process; during fear extinction, oxytocin affects the activity of the amygdala and ventromedial prefrontal cortex, and influences the functional connectivity between the amygdala and the medial prefrontal cortex and hippocampus, thereby promoting or inhibiting the fear extinction process. Future research should be conducted from perspectives including sex differences, neural network models, somatic and psychological development, and pathological studies, striving to achieve a deeper understanding of the cognitive neural mechanisms through which oxytocin influences fear emotion processing.

Full Text

Cognitive Neural Mechanisms Underlying the Impact of Oxytocin on Fear Acquisition and Extinction

FENG Pan, FENG Tingyong
(Faculty of Psychology, Southwest University, Chongqing, 400715, China)

Abstract

Fear is a fundamental emotion that plays a crucial role in human survival and adaptation. Previous research has demonstrated that brain regions including the amygdala, dorsal anterior cingulate cortex (dACC), and insula constitute the cognitive neural basis of conditioned fear acquisition, while the amygdala, hippocampus, and ventromedial prefrontal cortex (vmPFC) are essential for fear extinction. Studies have revealed that oxytocin is intimately involved in both fear acquisition and extinction processes. During fear acquisition, oxytocin influences the activity of the amygdala and dACC, modulates functional connectivity between the amygdala and both the dACC and brainstem, thereby either facilitating or inhibiting the acquisition process. During fear extinction, oxytocin affects the activity of the amygdala and vmPFC, and influences functional connectivity between the amygdala and both the medial prefrontal cortex and hippocampus, thus promoting or suppressing fear extinction. Future research should investigate these mechanisms from perspectives of gender differences, neural network models, psychophysical development, and pathological studies to achieve a deeper understanding of the cognitive neural mechanisms through which oxytocin influences fear emotion processing.

Keywords: Oxytocin, Fear Acquisition, Fear Extinction, Amygdala, Ventromedial Prefrontal Cortex

Fear is an evolutionarily conserved emotion that triggers a series of defensive mechanisms and plays a vital role in human survival and adaptation. However, when animals or humans remain in a prolonged state of fear, they may develop related emotional disorders such as phobias, anxiety disorders, and posttraumatic stress disorder (PTSD), causing severe negative impacts on their physical and mental health and development. Conditioned fear, based on Pavlovian classical conditioning, serves as a classic animal model for investigating mental disorders including phobias, anxiety disorders, and PTSD. The conditioned fear model encompasses four distinct processes: conditioned fear acquisition, fear memory consolidation, fear memory reconsolidation, and fear extinction (冯攀 et al., 2018; Feng et al., 2014; Feng, Zheng, & Feng, 2016; Monfils et al., 2009; Schiller et al., 2010).

Oxytocin (OXT), also known as the "love hormone," is a neuropeptide synthesized in the hypothalamus that acts on both the peripheral and central nervous systems (MacDonald & MacDonald, 2010). Oxytocin is primarily produced by magnocellular neurons in the paraventricular nucleus and supraoptic nucleus of the hypothalamus, which project to the posterior pituitary for release into the peripheral venous circulation; simultaneously, parvocellular neurons in the paraventricular nucleus project oxytocin to various brain regions (Ross & Young, 2009; Striepens et al., 2011). Hypothalamic oxytocinergic neurons project to the amygdala, hippocampus, midbrain, and frontal lobe, while oxytocin also modulates the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system function, thereby regulating fear acquisition and extinction processes

(Hasan et al., 2014). Research has demonstrated that oxytocin plays important roles in social-cognitive emotional processing and memory (Bartz et al., 2011; Campbell, 2010), and holds significant therapeutic value in clinical treatment of mental disorders such as schizophrenia and anxiety disorders (De Berardis et al., 2013; MacDonald & Feifel, 2014; Rich & Caldwell, 2015). Studies indicate that oxytocin can both facilitate and inhibit fear acquisition by influencing activity in the amygdala and dorsal anterior cingulate cortex (Cavalli et al., 2017; Eckstein et al., 2016; Huber et al., 2005; Viviani et al., 2011), while also promoting or suppressing fear extinction through modulating activity in the amygdala and medial prefrontal cortex (Lahoud & Maroun, 2013; Ninan, 2011; Sripada et al., 2012; Viviani et al., 2011). Given oxytocin' s intimate involvement in fear acquisition and extinction, elucidating its cognitive neural mechanisms in conditioned fear processing holds significant scientific value for constructing and refining neural network models of fear memory processing, while also offering clear clinical applications for understanding the etiology and treatment of fear-related emotional disorders such as phobias, anxiety disorders, and PTSD.

In recent years, researchers have systematically investigated the cognitive neural mechanisms through which oxytocin influences fear acquisition and extinction from animal, healthy human, and clinical perspectives. Building upon a synthesis of recent findings, this paper first delineates the research paradigms for fear acquisition and extinction, and provides an overview of their cognitive neural mechanisms based on relevant meta-analytic results. Second, we systematically examine the cognitive neural mechanisms of oxytocin's effects on fear acquisition and extinction by integrating evidence from animal studies, healthy human research, and clinical populations. Third, we elaborate on the neurobiological circuits through which oxytocin influences fear emotion processing by synthesizing previous literature. Finally, we offer perspectives on future research directions in the field of oxytocin and fear.

1.1 Fear Acquisition Research Paradigm and Neural Mechanisms

[Figure 1: see original paper] illustrates the research paradigms for fear acquisition and extinction. Conditioned fear acquisition in animals and humans is based on Pavlovian classical conditioning, wherein a conditioned stimulus (CS, such as geometric shapes, sounds, or odors) is paired with an unconditioned stimulus (US, such as electric shock). Following multiple pairing trials, presentation of the CS alone elicits fear responses (e.g., freezing behavior in animals and skin conductance responses in humans) (Agren et al., 2012; Linnman et al., 2012; Monfils et al., 2009; Schiller et al., 2013; Schiller et al., 2010). Milad and colleagues found that cortical thickness of the dorsal anterior cingulate cortex (dACC) showed a significant positive correlation with fear levels during acquisition, and dACC activation during fear acquisition also positively correlated with fear expression (M. R. Milad, Quirk, et al., 2007). Linnman et al. (2012) demonstrated that fear acquisition activates a fear network comprising the amygdala, insula, dACC, and midbrain, with activation levels in the insula and midbrain

showing significant positive correlations with fear intensity. Taken together, these findings indicate that the fear network—including the amygdala, insula, midbrain, and dACC—plays a crucial role in fear acquisition. Consistently, numerous meta-analytic studies have identified the amygdala, dorsal anterior cingulate gyrus (dACC), insula, and thalamus as key regions involved in fear acquisition (冯攀 & 冯廷勇, 2013; Etkin & Wager, 2007; M. A. Fullana et al., 2016; Mechias et al., 2010).

1.2 Extinction Research Paradigm and Neural Mechanisms

Research paradigms for fear extinction include the traditional extinction paradigm (no reminder-extinction) and the reminder-extinction paradigm. Following conditioned fear acquisition, fear memory enters a reconsolidation state. In the traditional extinction paradigm, the CS is repeatedly presented alone under non-reactivation conditions, leading to gradual fear response reduction. However, extinction in this paradigm is not permanent, as the process does not directly modify the original memory but rather forms a new inhibitory memory trace; the suppressed fear memory remains highly susceptible to reinstatement (Bouton et al., 2006; LeDoux, 2000; Myers & Davis, 2007). In contrast, the reminder-extinction paradigm involves first presenting the CS once to reactivate the fear memory, followed by extinction training (CS presentation without the aversive stimulus) within the fear memory reconsolidation window (within one hour post-reactivation). Research demonstrates that extinction conducted during the reconsolidation window after memory reactivation yields superior outcomes compared to traditional extinction (孙楠 et al., 2012; Agren et al., 2012; Feng et al., 2016; Monfils et al., 2009; Schiller et al., 2013; Schiller et al., 2010). Phelps et al. (2004) found significant activation of the ventromedial prefrontal cortex (vmPFC) during extinction learning, with vmPFC activation levels showing a significant positive correlation with extinction efficacy. Milad and colleagues observed significant activation of both the amygdala and vmPFC during extinction learning; however, during extinction recall, the vmPFC and hippocampus showed significant activation, with activation levels in both regions positively correlating with extinction success. Moreover, vmPFC and hippocampal activation during extinction recall were significantly positively correlated (M. R. Milad et al., 2007). Additionally, Milad et al. (2005) found that vmPFC cortical thickness was significantly negatively correlated with fear levels during extinction recall. Collectively, these findings demonstrate that the vmPFC and hippocampus are critically involved in fear extinction. Consistently, numerous meta-analytic studies have identified the amygdala, hippocampus, ventromedial prefrontal cortex (vmPFC), dorsolateral prefrontal cortex (dlPFC), and ventrolateral prefrontal cortex (vlPFC) as key regions mediating fear extinction (Diekhof et al., 2011; Miquel A. Fullana et al., 2018; Gottfried & Dolan, 2004; Kalisch et al., 2006; Menz et al., 2016; Milad et al., 2007; Phelps et al., 2004).

2 Cognitive Neural Mechanisms of Oxytocin' s Effects on Fear Acquisition and Extinction

Research has shown that both exogenous and endogenous oxytocin influence fear acquisition and extinction processes, particularly in social contexts (Brill-Maoz & Maroun, 2016; Cavalli et al., 2017; Eckstein et al., 2015; Eckstein et al., 2019; Eckstein et al., 2016). Neuroimaging studies demonstrate that oxytocin modulates amygdala activation, affects anterior cingulate cortex and insula responses, and regulates functional connectivity between the amygdala and other brain regions, thereby either facilitating or inhibiting fear acquisition (Cavalli et al., 2017; Huber et al., 2005; Viviani et al., 2011). Additionally, oxytocin influences the activation of the amygdala and medial prefrontal cortex and their functional connectivity, promoting or suppressing fear extinction (Lahoud & Maroun, 2013; Ninan, 2011).

2.1 Cognitive Neural Mechanisms of Oxytocin' s Effects on Fear Acquisition and Expression

Numerous studies have demonstrated that oxytocin influences both the acquisition and expression of fear. Behaviorally, oxytocin suppresses fear expression and inhibits fear acquisition. At the neural level, oxytocin affects the amygdala, hypothalamus, brainstem, fusiform gyrus, cingulate cortex, and their functional connectivity, thereby inhibiting fear expression and acquisition. Evidence for these effects derives from animal research, studies of healthy humans, and clinical populations.

In animal studies of conditioned fear acquisition, oxytocin suppresses fear acquisition and expression by attenuating amygdala activity. Specifically, oxytocin exerts potent anxiolytic effects in the central amygdala (CeA) (Neumann, 2008), a core structure for fear responses. Local oxytocin injection inhibits GABAergic neurons in the medial CeA (CeM), the primary output region from CeA to the brainstem, thereby reducing fear responses (Viviani et al., 2011). In rat experiments, optogenetic stimulation-induced release of endogenous oxytocin in the CeA during conditioned fear acquisition significantly suppressed freezing behavior and attenuated fear responses. In the CeA, oxytocin weakened CS-US associations and reduced freezing levels, while injection of selective agonists (WAY-267474 and TGOT) similarly decreased freezing and impaired fear acquisition. In the basolateral amygdala (BLA), oxytocin administration prior to CS-US pairing slowed fear acquisition and suppressed fear expression (Campbell-Smith et al., 2015; Knobloch et al., 2012; Lahoud & Maroun, 2013). Both the BLA and CeA contribute to fear acquisition (Ciocchi et al., 2010; Kim & Davis, 1993), indicating that oxytocin attenuates fear acquisition by modulating amygdala activation. In a study by Modi et al. (2016), rats underwent fear acquisition training on day one with tone (CS)-shock (US) pairings. On day two, during fear acquisition, administration of the novel oxytocin receptor agonist PF-06655075 (PF1) via either central or peripheral routes significantly reduced freezing responses to fear stimuli. The authors speculated that PF1 may suppress fear

acquisition through direct peripheral actions or by activating central oxytocin receptors. Collectively, animal research demonstrates that oxytocin primarily inhibits fear acquisition and expression by attenuating amygdala activity.

In studies of healthy humans undergoing conditioned fear acquisition, oxytocin influences activity in the amygdala, nucleus accumbens, fusiform gyrus, anterior cingulate cortex, and hippocampus, as well as their functional connectivity, thereby affecting various stages of fear acquisition. Using facial stimuli as conditioned stimuli (direct gaze vs. averted gaze), Petrovic et al. (2008) found that oxytocin reduced post-acquisition emotional evaluation indices. More importantly, oxytocin decreased activity in the amygdala and fusiform gyrus, with this modulatory effect being particularly pronounced when the conditioned stimulus involved direct gaze. These findings suggest that oxytocin influences the evaluation of socially relevant stimuli following fear acquisition by modulating the amygdala and fusiform gyrus. Eckstein et al. (2016) employed social and non-social stimuli as conditioned stimuli and found that the oxytocin group exhibited faster reaction times and higher skin conductance levels to conditioned stimuli. Furthermore, oxytocin enhanced activation in the subgenual anterior cingulate cortex (sACC) during non-social conditioning and increased activation in the posterior midcingulate cortex (pMCC) during social conditioning. Simultaneously, oxytocin reduced skin conductance and neural responses to electric shocks. The study concluded that oxytocin facilitates fear learning, which may have important adaptive value but could also increase susceptibility to negative events, optimize social fear acquisition processes, and enhance social cognition (Eckstein et al., 2016). These findings contradict other studies showing oxytocin suppresses fear acquisition, possibly because the timing of oxytocin administration (pre- vs. during acquisition) represents a critical factor. In this study, oxytocin was administered 30 minutes before fear acquisition. Cavalli et al. (2017) found that 45 minutes after intranasal oxytocin administration, the oxytocin group showed higher arousal levels during late cue and contextual acquisition. Oxytocin reduced nucleus accumbens activation during early cue and contextual acquisition, decreased insula and anterior cingulate activation during early contextual acquisition, but enhanced hippocampal activation during late contextual acquisition. These results indicate that oxytocin exerts differential modulatory effects on cue and contextual fear acquisition at both neural and subjective report levels (Cavalli et al., 2017). Therefore, research in healthy humans demonstrates that oxytocin influences fear acquisition by modulating activity in the amygdala, anterior cingulate cortex, and hippocampus, and by regulating functional connectivity between these regions, thereby either facilitating or inhibiting the acquisition process.

In studies of fear face processing in healthy humans, oxytocin reduces amygdala activity in response to fearful faces. Tost et al. (2010) found that individuals carrying the rs53576 (A/A) oxytocin receptor gene polymorphism exhibited significantly lower amygdala activation to fearful faces and stronger functional connectivity between the amygdala and hypothalamus. Kirsch et al. (2005) demonstrated that during social fear processing, oxytocin decreased amygdala

activity and reduced functional connectivity between the amygdala and brainstem, suggesting that oxytocin lowers fear levels. Domes et al. (2007) found that oxytocin attenuated amygdala responses not only to fearful faces but also to happy and angry faces, indicating that oxytocin reduces uncertainty regarding the expected value of social stimuli, thereby promoting social approach behavior. Gamer et al. (2010) reported that oxytocin decreased activation in lateral and dorsal anterior amygdala subregions in response to fearful faces. Additionally, Kanat et al. (2015) found that oxytocin reduced amygdala activation to fearful eyes and decreased activity in the fusiform gyrus and brainstem, as well as functional connectivity between the amygdala and fusiform gyrus when processing threatening cues from the eyes.

Pathological studies of fear face processing also show that oxytocin reduces amygdala activity in response to fearful faces. In PTSD patients, left amygdala activation to fearful faces was significantly attenuated under oxytocin conditions, demonstrating that oxytocin weakens left amygdala responses to fear emotions in clinical populations. Moreover, in PTSD patients, the severity of childhood trauma exposure showed a significant negative correlation with the magnitude of oxytocin-induced changes in left amygdala activation (Flanagan et al., 2019). In generalized social anxiety disorder, oxytocin reduced excessive amygdala activation when processing fearful faces (Labuschagne et al., 2010). These pathological findings suggest that oxytocin may represent a potential therapeutic approach for anxiety disorders, phobias, and PTSD. However, it is crucial to note that higher doses of oxytocin do not necessarily produce better therapeutic outcomes. A recent neuroimaging study demonstrated that 24 IU of oxytocin suppressed amygdala responses to fearful faces, whereas 48 IU actually enhanced amygdala reactivity (Spengler et al., 2017).

In summary, during conditioned fear processing, oxytocin can either facilitate or inhibit fear acquisition. Oxytocin influences fear acquisition by modulating amygdala activation, affecting responses in the anterior cingulate cortex, insula, and hippocampus, and regulating functional connectivity between the amygdala and other brain regions.

2.2 Cognitive Neural Mechanisms of Oxytocin' s Effects on Fear Extinction

In animal studies of fear extinction, oxytocin influences the extinction process by modulating activity in the amygdala and prefrontal cortex. Specifically, Toth et al. (2012) found that oxytocin administration prior to conditioned fear acquisition reduced fear expression during extinction and facilitated fear extinction; however, oxytocin injection before extinction training actually impaired the extinction process. In contextual fear conditioning studies, oxytocin was infused into the infralimbic medial prefrontal cortex (IL-mPFC), basolateral amygdala (BLA), and central amygdala (CeA) of rats. Following fear memory reactivation, oxytocin injection into the IL-mPFC decreased freezing levels and accelerated extinction, while infusion of the non-peptide oxytocin receptor agonist

WAY-267464 into the BLA after fear reactivation also reduced freezing and promoted extinction. In contrast, oxytocin infusion into the CeA had no effect on extinction. Pre-conditioning infusion of oxytocin into the basal amygdala facilitated fear acquisition but impaired subsequent extinction (Brill-Maoz & Maroun, 2016; Campbell-Smith et al., 2015; Lahoud & Maroun, 2013). Administration of oxytocin into the amygdala prior to extinction training facilitated extinction and enhanced functional connectivity between the medial prefrontal cortex and amygdala (Ninan, 2011; Sripada et al., 2012; Viviani et al., 2011). These findings indicate that oxytocin promotes fear extinction by suppressing amygdala activation, enhancing medial prefrontal cortex activity, and strengthening functional connectivity between the amygdala and prefrontal cortex. These studies demonstrate that oxytocin influences fear extinction primarily by regulating activity in the prefrontal cortex and amygdala. Notably, both the timing and site of oxytocin administration produce differential effects on extinction. Specifically, injections before or after acquisition, before or after memory reactivation, or before or after extinction training, as well as infusions into different amygdala subregions or medial prefrontal areas, all yield distinct effects on extinction. Recent research by Kritman et al. (2017) revealed age-dependent differences in oxytocin' s effects on extinction: in juvenile mice, oxytocin agonist infusion into the medial prefrontal cortex had no effect on extinction, whereas infusion into the amygdala impaired extinction and increased fear. This highlights differences between adult and developing brains, reflecting distinct oxytocin effects in juvenile versus adult animals. Thus, age represents another critical factor influencing oxytocin' s impact on extinction. Additionally, studies have examined oxytocin' s role in fear extinction using PTSD animal models. Eskandarian et al. (2013) employed the single prolonged stress (SPS) model to simulate traumatic stress and investigated the effects of repeated systemic oxytocin injections on contextual fear extinction. They found that rats receiving systemic oxytocin exhibited higher freezing levels after extinction training compared to controls, suggesting that systemic oxytocin delayed extinction, possibly due to insufficient oxytocin concentrations from systemic administration. In cue fear conditioning, one study divided rats into control and SPS groups and administered intranasal oxytocin seven days after SPS and prior to extinction training. The SPS group showed significantly lower freezing levels than controls, indicating that intranasal oxytocin facilitated extinction and suggesting potential therapeutic value for PTSD (Wang et al., 2018). These findings again underscore injection site (systemic vs. local) as a key factor modulating oxytocin' s effects on extinction. Animal research demonstrates that oxytocin regulates medial prefrontal cortex and amygdala responses to promote fear extinction, providing guidance for therapeutic interventions in PTSD and other psychiatric conditions. Furthermore, oxytocin modulates social fear conditioning. Zoicas et al. (2014) investigated oxytocin' s effects on social fear conditioning (SFC) and found that oxytocin infusion into the dorsolateral septum of mice during extinction training significantly reduced social fear compared to controls.

In healthy human studies of fear extinction, oxytocin promotes extinction by in-

fluencing activity in the amygdala, cingulate cortex, frontal lobe, and precuneus, as well as their functional connectivity, particularly when extinction occurs after memory reactivation within the reconsolidation window. Specifically, Acheson et al. (2013) conducted a double-blind, placebo-controlled study with 44 healthy participants. On day one, participants underwent fear acquisition training. Following acquisition, they received intranasal oxytocin or placebo, then completed extinction training 45 minutes later. On day two, participants underwent an extinction recall test. Results showed similar fear levels between groups before extinction training. During extinction, the oxytocin group exhibited temporarily attenuated fear reduction, but by the end of extinction training, both groups showed comparable extinction levels. On day two, however, the oxytocin group demonstrated significantly greater extinction recall than the placebo group. Recent research by Hu et al. (2019) revealed that post-reactivation intranasal oxytocin produced superior extinction compared to both non-reactivation oxytocin and post-reactivation placebo groups, confirming that oxytocin facilitates extinction after memory reactivation. These findings underscore that the timing of oxytocin administration critically influences extinction efficacy. Human studies indicate that oxytocin enhances medial prefrontal cortex activity, suppresses amygdala activation, and strengthens functional connectivity between brain regions, thereby playing a positive facilitatory role in fear reactivation-extinction processes. Petrovic et al. (2008) found that after conditioned fear acquisition, oxytocin reduced activation in the amygdala and dorsal anterior cingulate cortex to conditioned facial stimuli and decreased subjective ratings of these faces. Eckstein et al. (2015) investigated the effects of post-acquisition intranasal oxytocin on extinction. Behaviorally, oxytocin enhanced skin conductance responses during early extinction but facilitated their decline during later phases, with the oxytocin group showing higher fear responses initially but significantly lower fear levels than placebo during later extinction stages, thereby promoting extinction recall. Neurally, oxytocin increased frontal lobe activation during early extinction, reduced amygdala activation during both early and late extinction, enhanced functional connectivity between frontal lobe and posterior cingulate cortex and between frontal lobe and precuneus during early extinction, and strengthened amygdala-precuneus connectivity during late extinction. These findings indicate that oxytocin promotes fear extinction by increasing frontal lobe activity, inhibiting amygdala activity, and enhancing functional connectivity between frontal lobe and amygdala and between amygdala and precuneus (Eckstein et al., 2015). A recent resting-state study revealed that oxytocin modulates the emotion regulation network (amygdala and frontal lobe). Specifically, oxytocin increased functional connectivity between central-medial and basal amygdala subregions and the cerebellum, and enhanced connectivity between basal amygdala and frontal lobe. Additionally, oxytocin reduced functional connectivity between central-medial amygdala and core regions of the neural network for emotional face processing (e.g., temporal, occipital, and parietal lobes). These results suggest that during fear extinction, oxytocin may influence activity and functional connectivity of the amygdala, frontal lobe, and cerebellum, thereby modulating extinction processes (Eckstein et al., 2017).

Collectively, oxytocin is intimately linked with the amygdala and prefrontal cortex in mediating fear extinction. Oxytocin influences activity and functional connectivity of the amygdala and medial prefrontal cortex while also modulating activity in other fear-related brain regions, thereby affecting extinction processes. In specific studies, oxytocin' s effects on fear extinction may be influenced by experimental procedures and methodologies, with differential effects observed during early versus middle-to-late stages of experiments. Furthermore, specific parameters including injection timing, site and region of administration, dosage, as well as participant age and gender may all influence final outcomes.

In summary, oxytocin reduces activation in the amygdala and dorsal anterior cingulate cortex, thereby decreasing subjective anxiety levels while enhancing adaptive endocrine and autonomic fear responses. More importantly, oxytocin improves emotional regulation and top-down control capabilities. Oxytocin attenuates amygdala and dACC activation, enhances insula activity, and alters functional connectivity within salience network nodes. Oxytocin reduces functional connectivity between the amygdala and brainstem, thereby diminishing fear expression, yet enhances connectivity between the vmPFC and amygdala, indicating strengthened top-down regulatory control of the amygdala by the vmPFC (Koch et al., 2014).

Therefore, oxytocin may exert modulatory effects on fear, manifesting as time-dependent and brain region-dependent bidirectional actions on fear memory acquisition and elimination, while potentially altering the valence and salience of emotions in social versus non-social contexts (Guzman et al., 2013). Furthermore, animal approach-avoidance neural network models propose that approach and avoidance behaviors are determined by activity in various amygdala subregions (lateral, basal, central, and medial amygdala), with the medial prefrontal cortex and oxytocin exerting modulatory influences on these subregions. Consequently, oxytocin may offer therapeutic insights for atypical social and fear-related behaviors (Maroun & Wagner, 2016).

3 Summary and Outlook

Fear acquisition and extinction represent two critical components of conditioned fear processing. Extensive research in animals, healthy humans, and clinical populations has investigated the cognitive neural mechanisms underlying these processes. During fear acquisition and extinction, the amygdala, medial prefrontal cortex, and anterior cingulate cortex constitute essential neural substrates, with the amygdala playing a particularly pivotal role. Oxytocin modulates activity in the amygdala, prefrontal cortex, anterior cingulate cortex, insula, hippocampus, and other related brain regions, thereby influencing fear processing. Oxytocin primarily affects fear acquisition by modulating activation in the amygdala and cingulate cortex, while influencing fear extinction through its effects on amygdala activation, medial prefrontal cortex activity, and functional connectivity between the amygdala and medial prefrontal cortex. Additionally, oxytocin regulates activity in fear-related regions including the anterior cingulate cortex,

insula, and hippocampus, thereby impacting both fear acquisition and extinction. It is important to note that in experimental studies, specific parameters such as oxytocin dosage, injection timing, and administration site all influence fear acquisition and extinction processes.

Although substantial research has examined oxytocin' s effects on the cognitive neural mechanisms of fear acquisition and extinction, the inherent complexity of oxytocin' s influence on fear emotion processing leaves numerous questions for future exploration. Key research directions include:

First, investigating gender differences in the cognitive neural mechanisms through which oxytocin influences fear emotion processing warrants attention. Gender differences are widely observed in fear emotion processing (Schwabe et al., 2013; Williams et al., 2005). Specifically, significant sex differences exist in the lateralization and temporal dynamics of fear perception: right amygdala activity in males decreased during the latter half of experiments, whereas females maintained bilateral amygdala activation throughout, with left amygdala activity showing an increasing trend in the second half (Williams et al., 2005). Recent research indicates that noradrenergic arousal produces opposite effects on fear processing in male versus female participants, enhancing amygdala activity in women while reducing it in men (Schwabe et al., 2013). Additionally, the female menstrual cycle influences fear acquisition and extinction, with women in the premenstrual phase showing facilitated acquisition but impaired extinction of contextual fear, suggesting that sex hormones during this phase affect brain emotion regulation functions (金艳 & 郑希付, 2015). Future research should examine how gender differences moderate oxytocin' s effects on fear emotion processing.

Second, future research should investigate neural network models of oxytocin' s effects on fear emotion processing. While numerous studies have examined oxytocin' s neural mechanisms in fear acquisition and extinction, the mechanisms underlying fear memory consolidation and reconsolidation remain unclear. To construct and refine neural network models of oxytocin' s influence on fear emotion processing, future studies should focus on developing comprehensive models that incorporate oxytocin' s effects on fear acquisition, consolidation, reconsolidation, and extinction to achieve deeper understanding of the neural circuits involved. Therefore, future research needs to explore the cognitive neural mechanisms through which oxytocin influences fear memory consolidation and reconsolidation. Additionally, since previous research has identified memory reactivation and the reconsolidation time window as essential conditions for persistent extinction effects (Agren et al., 2012; Feng et al., 2015; Feng et al., 2016; Schiller et al., 2013; Schiller et al., 2010), future studies should integrate these two conditions into investigations of oxytocin' s effects on fear reconsolidation and extinction.

Third, examining psychophysical development in relation to the cognitive neural mechanisms of oxytocin' s effects on fear emotion processing represents an important perspective. Kritman et al. (2017) found differential effects of oxytocin

agonist administration in juvenile mice: infusion into the medial prefrontal cortex had no effect on extinction, whereas amygdala infusion impaired extinction and increased fear. Therefore, investigating the neural mechanisms of oxytocin' s influence on fear emotion processing from a developmental cognitive neuroscience perspective is crucial for comprehensively understanding the relevant neural circuits and holds significant scientific value and practical implications.

Finally, future research should conduct pathological studies on oxytocin's effects on fear emotion processing. Meta-analyses indicate that compared to healthy controls, patients with PTSD, specific phobia, and generalized anxiety disorder show greater activation in the amygdala and insula, while PTSD patients exhibit reduced activation in the dorsal and rostral anterior cingulate cortices (dACC and rACC) and vmPFC (Etkin & Wager, 2007). Additionally, personality trait factors should be considered. Research has shown that state anxiety influences conditioned fear acquisition and extinction: specifically, state anxiety reduces subjective expectancy values for CS+ while increasing them for CS-, and inhibits extinction of conditioned stimuli during the extinction phase. State anxiety also affects evaluative conditioning, with anxious individuals showing more negative valence ratings for conditioned stimuli during habituation and extinction phases compared to controls (张予贺 et al., 2013). Therefore, future research from a pathological perspective should aim to systematically understand the cognitive neural mechanisms through which oxytocin influences fear emotion processing and develop effective intervention methods.

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