Oxytocin and Vasopressin in Emotional Memory and "Face Reading": a Neurobiological Approach and Clinical Aspects

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Abstract

The ability to adequately perceive and recognize emotions is a key and universal tool in interpersonal communication, which allows people to understand feelings, intentions, and emotional reactions of themselves and others. Throughout their life, people have to make inferences about mental state of others by interpreting subtle social signals, such as facial expressions, to understand or predict others' behavior, which is crucial in constructive social interactions. Therefore, emotional memory associated with the ability to identify emotions based on one's life experience is the cornerstone of social cognition and interpersonal relationships. Oxytocin and vasopressin are neurohypophysial peptides that have attracted scientific attention due to their role in the emotional and social aspects of behavior. Variable and contrasting effects of oxytocin and vasopressin may be related to the sites of the brain where they exert their activity.

Aim. *This review aimed to evaluate neural mechanisms underlying oxytocin-mediated and vasopressin-mediated modulation of emotional memory; to assess how cerebral oxytocin-signal and vasopressin-signal transduction mediates emotional and social behavior; to discuss the role of the two neuropeptides in non-verbal interpersonal communication; and to present their cerebral effects in relation to an ability for "face reading" in patients with mental disorders.*

Keywords: *oxytocin; vasopressin; emotions; memory*

Source of funding. The article was prepared based on the study "Perceived quality of communication in real-world and computer-mediated meetings and its objective measurements using oxytocin and facial markers" conducted as part of Program 2030 Strategic Projects by Mirror Laboratories of National Research University Higher School of Economics.

Conflict of interest. The authors declare no apparent or potential conflicts of interest related to the publication of this article.

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For citation: Gorina Ya.V., Lopatina O.L., Mararitsa L.V. The role of oxytocin and vasopressin in emotional memory and "face reading": a neurobiological approach and clinical aspects. *Annals of Clinical and Experimental Neurology.* 2024;18(3):58–71.

DOI: https://doi.org/10.17816/ACEN.1047

Received 04.10.2023 / Accepted 27.10.2024 / Published 30.09.2024

Роль окситоцина и вазопрессина в эмоциональной памяти и «чтении мыслей по лицу»: нейробиологический подход и клинические аспекты

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Аннотация

Способность правильно воспринять и распознать эмоции является ключевым и универсальным инструментом в межличностном общении, который позволяет понять чувства, намерения и эмоциональные реакции – свои и другого человека. На протяжении всей жизни людям приходится делать выводы о психическом состоянии путём интерпретации тонких социальных сигналов, таких как выражение лица, чтобы осознать или предсказать поведение другого человека, что, несомненно, имеет решающее значение в выстраивании конструктивных социальных взаимодействий. В этой связи эмоциональная память, сопряжённая со способностью идентифицировать эмоции, базируясь на приобретённом жизненном опыте, является краеугольным камнем социального познания и межличностных отношений. Окситоцин и вазопрессин – два нейрогипофизарных пептида, которые привлекают внимание учёных за счёт их роли в реализации эмоциональных и социальных аспектов поведения. Установленные разнообразные и контрастирующие эффекты окситоцина и вазопрессина могут быть связаны с местом их активности в головном мозге.

***Цель** обзора – рассмотреть нейронные механизмы, лежащие в основе окситоцин- и вазопрессин-опосредованной модуляции эмоциональных воспоминаний, как церебральная окситоцин- и вазопрессин-сигнальная трансдукция опосредует эмоциональное и социальное поведение; обсудить роль двух нейропептидов в невербальном межличностном общении, а также представить их церебральные эффекты в отношении способности «чтения мысли по лицу» в контексте развития психоэмоциональных расстройств.*

***Ключевые слова:** окситоцин; вазопрессин; эмоции; память*

Источник финансирования. Статья подготовлена в результате проведения исследования по проекту «Воспринимаемое качество общения в реальных и компьютерно-опосредованных встречах и его объективные измерения на примере окситоцина и мимических маркеров» «Зеркальные лаборатории» НИУ ВШЭ в рамках стратегических проектов Программы 2030 НИУ ВШЭ.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Для цитирования: Горина Я.В., Лопатина О.Л., Мараница Л.В. Роль окситоцина и вазопрессина в эмоциональной памяти и «чтении мыслей по лицу»: нейробиологический подход и клинические аспекты. *Анналы клинической и экспериментальной неврологии.* 2024;18(3):58–71.

DOI: https://doi.org/10.17816/ACEN.1047

Поступила 04.10.2023 / Принята в печать 27.10.2023 / Опубликована 30.09.2024

Until the XX century, the emotional domain was the subject of close attention of philosophers. However, over the last few decades, new highly informative methods to investigate brain structure and function have emerged, in particular, powerful neuroimaging tools to study local brain functions during well-defined tasks. This significantly improved current understanding of the neural substrates involved in emotion processing [1, 2]. From the neurobiological perspective, emotions are a program of complex actions that are triggered by certain external or internal stimuli that activate the nervous system [3]. Emotion as a basic biological program implies an innately programmed mechanism that connects the processing of a sensory stimulus with the development of a coordinated behavioral response pattern [4]. These emotional processes are mediated and transmitted by certain hormones, such as oxytocin (OXT) and vasopressin (VP), which can be considered key ones [5, 6].

From the evolutionary perspective, OXT and VP are highly conserved neuropeptides. They are of high scientific interest due to the discovery of the fascinating behavioral functions they regulate, especially in the context of social

interactions. For example, OXT was shown to modulate a gamut of behavior types such as maternal care [7] and aggression [8], pair bonding [9], sexual behavior [10], social memory [11] and support [12], anxiety behavior and coping with stress [13, 14].

In contrast, VP was shown to have a strong influence on complex social behavior and emotional states that are more typical for men, such as aggression, fear, and anxiety [15], as well as hypervigilance and arousal [16].

Initially considered as a "prosocial" neuropeptide that enhances social closeness, attachment, and affiliative behavior, OXT has been recently shown to be an effective regulator of social and emotional behavior aspects such as social fear, anger, and envy [17, 18]. It is of interest that only few studies investigated the influence of OXT and VP on the development of emotional memory and, in particular, fear memory [19–22]. However, memory is a fundamental cognitive function that allows people to have constant access to relevant information and appropriately adjust our behavior after encoding our experience.

Emotions are known to reflect our internal emotional state, and an emotional reaction allows us to connect current events with our individual specific previous experience. In this context, emotional memory, which is associated with the ability to identify emotions, plays an important role in interpersonal relationships [23, 24]. "Face reading", i. e. the ability to infer mental state of others, which is also called cognitive empathy, is a cornerstone of all social interactions. The ability to track other people's emotional state over time and draw conclusions about their internal state based on external signals, such as facial expressions, allows us to predict corresponding behavioral responses [25].

OXT and VP effects on social cognition have received considerable attention over the past two decades. In particular, several studies showed that OXT administration improved the ability to identify a wide range of emotions [26–28], while the effects of VP were selective for emotional perception with a pronounced predominance in recognizing negative emotions over positive ones [29].

These important discoveries raised the question on how the local release of OXT and VP and subsequent effects mediated by their receptors in the target brain regions are reflected in the emotional and social aspects of brain function with an emphasis on emotion recognition and perception and memorization of emotionally salient signals.

Aim. This review aimed to examine the neural mechanisms underlying OXT-mediated and VP-mediated modulation of emotional memory and how OXT and VP signaling in specific neural circuits of certain brain regions mediates emotional and social behavior. We also presented the role of OXT and VP in non-verbal interpersonal communication and reviewed recent cutting-edge studies that evaluate OXT and VP local effects in different brain regions on "face reading" in the development of mental disorders.

Neural mechanisms underlying oxytocinergic modulation of emotional memory

The ability of OXT to modulate higher brain functions such as prosocial behavior, social recognition, reward, learning and memory, is determined by the neural network in the hypothalamic nuclei, an important structural basis for coordinated activity of OXT neurons in response to external stimuli. Moreover, the extrahypothalamic regions of the forebrain such as the amygdala, the bed nucleus of the stria terminalis, and the nucleus accumbens of the septum pellucidum also contain OXT-expressing neurons, which mediates local OXT-ergic regulatory effects [30]. OXT receptors are found in brain regions that are crucial for processing and encoding of information and formation of memory, such as hippocampus, striatum, amygdala, hypothalamus, nucleus accumbens, and midbrain [31].

In a clinical study by A.J. Guastella et al., OXT was shown to enhance encoding for predominantly positive social stimuli (happy faces), making the information more meaningful and therefore more memorable, with reducing memory consolidation for angry or neutral faces [32]. A subsequent study showed that salivary OXT levels correlated with formation of memory about specific social events with other people. Mothers with high salivary OXT levels recalled previous positive social events related to their children with great detail, which contributes to formation of warm and trustful relationship between parents and their children and helps foster positive attachment with children [33].

According to a comprehensive study by G. Plasencia et al. [34], women had higher plasma OXT levels than men, and older adults had higher plasma VP levels than younger adults. Functionally, higher VP levels were associated with severe anxiety, while increased OXT levels and low VP levels correlated with more rapid processing of sensorimotor information and formation of verbal memory, with these effects being especially pronounced in young men. Differences in plasma levels of the endogenous neuropeptides depending on gender and age demonstrated their significant opposite effects on affection expression and formation of social cognition (Figure 1).

Of interest are data showing that vaginocervical stimulation enhanced olfactory social recognition memory in female rats via oxytocin release in the olfactory bulb and modulatory actions on noradrenaline release [35].

Animal studies showed that exogenous OXT can have both promnestic and amnestic effects depending on gender, dose, and context [36]. In particular, intranasal OXT impaired

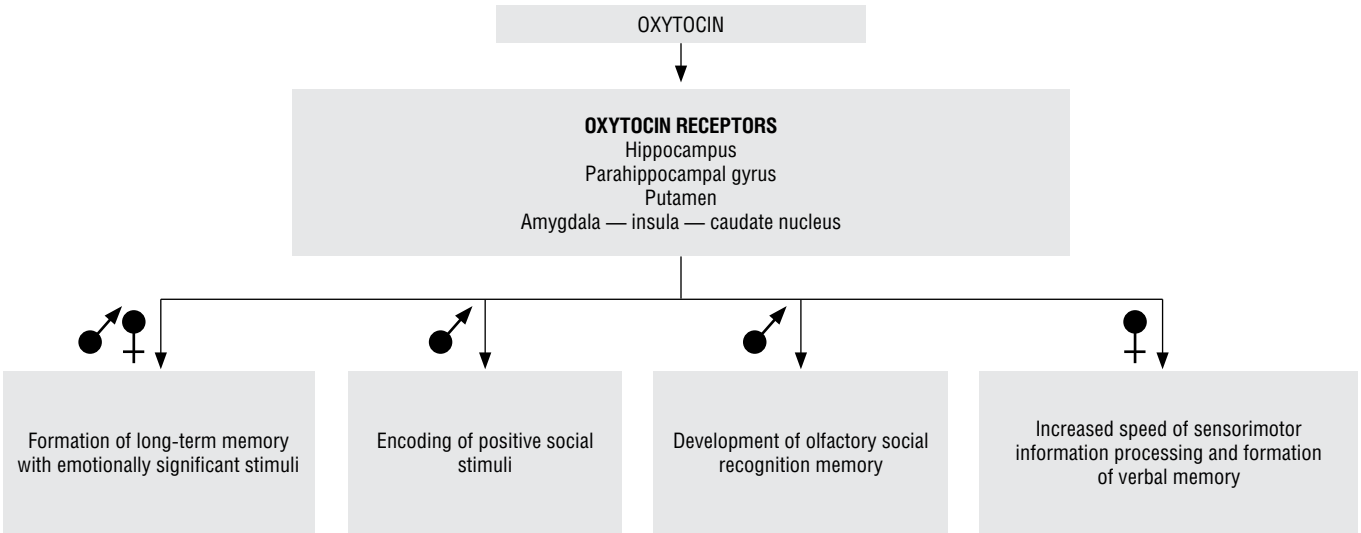

Fig. 1. Oxytocin-mediated modulation of emotional memory.

semantic association for words with reproduction-related but not neutral meaning, thus suggesting that OXT has selective effects on memory formation depending on the psychobiological salience of the stimuli [37]. Effects of intranasal OXT on human memory are ambiguous and depend on the OXT dose and its administration time, as well as the nature of the stimuli used (i. e. emotional or non-emotional). Specifically, data on the long-term memory of non-emotional stimuli showed either no effect or even worsening in memory, while studies using emotional stimuli showed an improvement in long-term memory performance with exogenous OXT [38].

Such a selective OXT-induced improvement in learning and memory triggered by emoticon stimuli was likely to be associated with increased activation and formation of functional connections in the brain regions that are responsible for the formation of emotional memory such as amygdala, hippocampus, parahippocampal gyrus and putamen, as well as between the amygdala and the insula and caudate [39].

Furthermore, in mice, OXT reversed β-amyloid-induced impairment of synaptic plasticity in the hippocampus via phosphorylation of extracellular regulated protein kinase-1 and protein kinase-2 (pERK1/2) and Ca2+-permeable receptors of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [40], which suggests that OXT can neutralize β-amyloid-mediated toxic effects on synapses. H.M. Latt et al. reported that OXT inhibited corticosteroid-induced apoptosis in hippocampal neurons by influencing OXT receptors, thus maintaining synaptic plasticity and memory during stress [41].

Vasopressin-mediated memory modulation

The hippocampus is a critical center for memory formation and a key structural target for VP because of high VP receptor density [42, 43]. The activation of vasopressin V1a receptors increased the functional activity of both pyramidal neurons in the subiculum (i. e. the base of the hippocampus with a branched neural network that processes sensory and motor signals to form a cognitive map that encodes spatial, contextual and emotional information) [44] and interneurons in the CA1-region of the hippocampus [45]. However, the highest density of VP receptors, especially V1a, was found in the dentate gyrus of the hyppocampus, which serves as a gate or filter at the entrance to the hippocampus, blocking or filtering incoming information [46]. At the cellular level, nanomolar VP levels were shown to cause a long-lasting increase in the amplitude of field excitatory postsynaptic potentials in neurons of the dentate gyrus in the hippocampus mediated by V1a receptors [47]. Moreover, intracerebroventricular administration of VP increased long-term potentiation in the dentate gyrus of intact anesthetized rats [48], which suggests that VP can increase neural excitability. This was confirmed by a recent study by X. Zhang et al., who showed that the intranasal administration of VP effectively improved the synaptic plasticity and related working and long-term memory in the APP/PS1 mouse model of Alzheimer's disease [49]. Non-clinical and clinical studies showed that VP was directly involved in the regulation of memory consolidation during sleep, which is mediated by activation of V1a receptors in the hippocampus [50].

Besides VP effects on hippocampal neurons in remodeling synaptic plasticity and long-term memory formation, a possible relationship between VP and the perception of emotional information, memory, and activation was reported (Fig. 2).

In particular, A.J. Guastella et al. showed that VP significantly enhanced the encoding of happy and angry male faces in comparison with neutral ones, which suggests that emotionally expressed stimuli are the most significant and priority

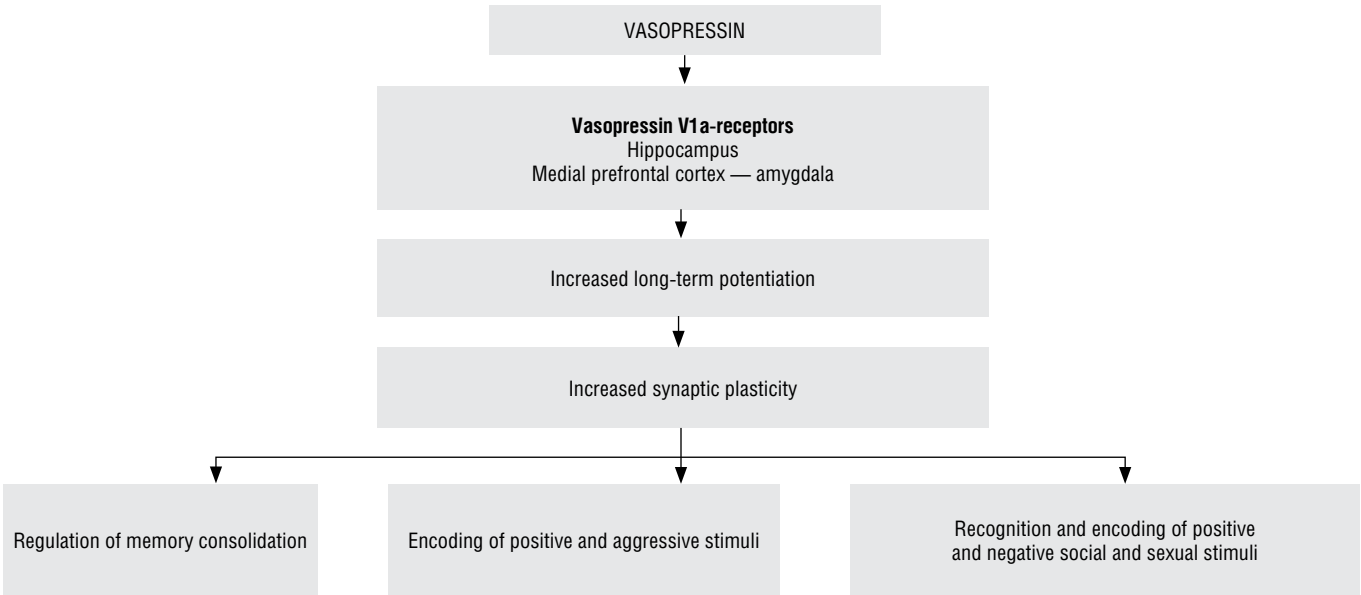

Fig. 2. Vasopressinergic memory modulation.

for memorization [51]. This specific effect of VP on social cognition, which is manifested by increased encoding of both positive and aggressive signals, may represent a mechanism by which VP may increase the variability and plasticity of behavioral responses in interpersonal relationships [52]. In a related study, exogenous VP facilitated recognition of positive and negative social and sexual stimuli over non-social stimuli, which demonstrated the possible participation of VP in cognitive mechanisms aimed at improving the perception and implementation of complex social behavior [53].

As suggested by several authors, these social and emotional VP effects are mediated by V1a receptors in target brain structures such as the lateral septum, hypothalamus, bed nucleus of the stria terminalis, hippocampus, amygdala, and brainstem [54–57]. Of those, the amygdala is considered the key structure involved in processing of a wide range of emotions, especially fear reactions [58]. Sensory information from external stimuli that are predictors of the fear reaction was shown to reach the amygdala through thalamic and cortical pathways. They are projected into the basolateral nuclei of the amygdala, i. e. areas of neural networks where fear memory develops due to long-term modification of synapses [59]. Available evidence shows that the basolateral region of the amygdala controls autonomic responses to fear via close connections with the periaqueductal gray matter of the midbrain, reticular formation and hypothalamus, thus triggering reactions inherent to a perceived threat such as defensive behavior, activation of the sympathetic nervous system, hypoalgesia, and release of stress hormones [60, 61].

D. Huber et al. recorded spontaneous spiking activity in acute brain slices of the central amygdala and found two distinct neurone populations: the first one was excited by OXT receptor activation, while the second was inhibited by OXT receptor activation but excited by VP receptor stimulation [62]. Neural cells excited by VP were located both in and beyond the central nucleus of the amygdala.

K. Motoki et al. showed that higher VP plasma levels positively correlated with activation of the amygdala in men but not in women [6]. Such an evident polarity can be explained by the fact that VP-positive neurons are located in the amygdala, where higher levels of VP receptors were found in males but not in females [63]. Reports on intense VP release in the amygdala and prefrontal cortex of male rats in response to low-intensity stress were also quite unexpected [64]. A lower degree of anxiety response was recorded in rats after high-intensity stress with no visible changes after low-intensity stress. O.J. Bosch et al. found intensive VP release in the central amygdala of lactating female rats with high anxiety, which positively correlated with aggressive behavior [8].

These gender differences in VP levels and their relationship with emotionally charged events remain unclear due to available inconsistent data and their unknown molecular cellular mechanism.

VP was shown to directly influence activation of the stress state, which is the key factor contributing to the consolidation of fear memory and associative learning [65, 66]. VP levels were shown to be increased in the central amygdala [67].

Not only did VP modulate associative learning and fear expression during stress but also fear-conditioned learning [22].

The amygdala is also involved in the reconsolidation and extinction of fear memory [68], i.e. two opposing functions

for contextual fear memory: reconsolidation maintains or strengthens fear memory, while extinction represents learning that generates inhibitory biochemical pathways that suppress fear response [69]. The pathway from the medial prefrontal cortex to the amygdala is the most likely neural pathway that mediates fear extinction response [59]. According to C.F. Zink et al., VP modulates the medial prefrontal cortex-amygdala circuit and connectivity patterns, which is reflected in social behavior related to fear and anxiety (Figure 2) [70]. Available data indicate that OXT promotes social fear extinction, while VP prevents this [71]. Prolonged fear can become a predictor for the development of anxiety disorders.

Considering a well-studied causal relationship between chronic stress and mood disorders, significant efforts have been made to find medication treatment options for anxiety and depression. R.A. Hodgson et al. proposed V1B-30N as a highly selective antagonist of V1b receptors with good oral bioavailability, which decreased plasma levels of the stress hormone and had an anxiolytic effect by reducing V1b-receptor activity [72]. This further confirms the significant role of VP in the formation of emotionally charged behavioral reactions in the context of stress-induced events, which are encoded by the hippocampus-amygdala-medial prefrontal cortex neural network with subsequent transformation of emotionally charged events into long-term memory.

Oxytocin as a neuropeptide modulator of non-verbal interpersonal communication

Visual perception of faces in the context of interpersonal relationships is usually unconscious and allows the extraction of socially relevant information such as gender, age, and emotions, thus regulating social interactions (i. e. approach and avoidance) [73]. Substantial evidence supports the hypothesis of OXT influence on the perception of social information, which is reflected in the regulation of social behavior, inducing processing of positive stimuli and attenuating negative ones, as well as increasing the salience of both social and emotional stimuli [74–76] (Figure 3).

In primates, exogenous OXT enhanced the perceptual salience of the eyes and the propensity to interact with a social partner in response to naturalistic social stimuli [77]. These OXT effects can be seen after its single administration. L.A. Parr et al. showed that OXT after repeated administration significantly increased the time monkeys spent viewing the lipsmack and threat videos (i. e. dynamic facial expressions) but selectively reduced attention to the eyes in neutral faces in a dose dependent manner [78]. The authors suggested that this unexpected non-prosocial effect of OXT may be explained by the suppression of OXT receptor expression in the brain regions responsible for regulation of social attention as a result of repeated administration of the neuropeptide. This calls into question the efficacy of exogenous OXT used in the long-term as a medication therapy for social behavior disorders.

Any face image has at the same time signs of identity and expression, i.e. who the person is and what feelings they experience. This clearly distinguishes visual stimuli from others, where at any given time a face will convey multiple independent signals that are thought to be processed by a neural network distributed in interconnected face-selective brain regions [79, 80].

In a clinical study, intranasal OXT improved recognition memory for neutral and angry faces with no effect for happy faces,

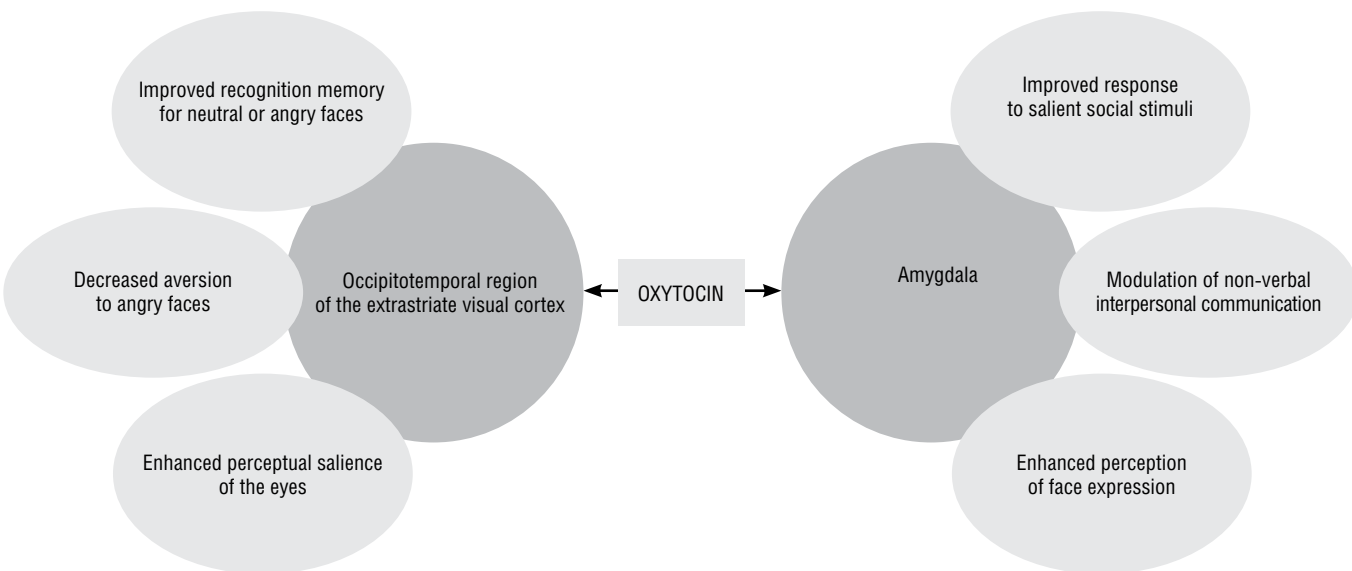

Fig. 3. Oxytocinergic regulation of social interaction.

regardless of participants' gender. However, OXT had no effect on the formation of facial expression memory. This selective influence of OXT on identity and facial expression memory may contribute to the modulation of social behavior [81].

It is noteworthy that OXT was able to modulate the awareness of socially salient emotional information in the environment even with short-term stimulus presentation (i.e. 18, 35 or 53 ms), which was manifested in an improvement in performance for facial stimuli with a more pronounced effect on happy faces [82].

Moreover, OXT specifically decreased the aversive aspects of angry faces, while having no effect on sad faces, which also have negative emotional valence. Financial feedback (reward), either positive (win) or negative (lose), did not have any significant effect on social preferences [83].

These effects of OXT are likely to be mediated by an activated neural network in the occipitotemporal regions of the extrastriate visual cortex, which are involved in visual analysis of faces, as well as the fusiform gyrus and superior temporal sulcus, which are involved in the representation of invariable and variable aspects of facial expressions, respectively [84–86].

Another perspective regarding the impact of OXT on social behavior is associated with social salience. It was hypothesized that OXT improves response to salient social stimuli [87, 88]. In other words, this is interpreted as the "social salience hypothesis", which is consistent with reports of several authors who suggested OXT-induced improvements in "face reading" with the eyes and an increase in eye contact [75, 89, 90], thereby contributing to the modulation of non-verbal interpersonal communication.

Although detailed understanding of the neural mechanisms underlying OXT effects on attention to the eyes is not yet fully developed, neuroimaging data suggest the involvement of the amygdala in attention to facial features in general [91–94] and the role of the superior colliculus in modulation of attention to facial features mediated via OXT [95].

According to J. Taubert et al. intranasal administration of OXT in rhesus monkeys improved perception of face expressions to a greater extent than face identity [96]. A subsequent detailed analysis showed that this was mainly related to the presence of a stimulus expressing fear or aggression (i. e. negative emotions). Accuracy in perceiving lip-smacking facial expressions as a sign of appeasement and submission, which has a positive social value, was noticeably lower in rhesus monkeys. This selective influence of exogenous OT on behavioral responses to facial expressions with negative valence supports the theory that OT effects are tuned to the socioemotional value of a visual stimulus that signals about fear or aggression as a sign of potential danger or hostility. These effects are mediated by activation of the OXT signaling pathway, which contributes to the manifestation of social cognition [96].

Current evidence regarding OXT effects on visual scanning of emotional faces is inconsistent. According to A. Lischke et al., OXT promoted emotion recognition from dynamic facial expressions regardless of modulation of visual attention to specific face areas [28]. OXT-induced improvement in emotion recognition was related to its direct involvement in the formation of memory for faces and expressions [97], which allows identifying whether the facial expression corresponds to those previously remembered. No OXT involvement in visual attention to the eye is likely to be related to its participation in prioritization, i. e. initial allocation of attention to social stimuli. This was confirmed by a more recent study where OXT reduced face processing time but had no effect on eye-gaze patterns when viewing static emotional faces [98].

However, Sosnowski M.J. et al., who investigated effects of endogenous and exogenous OXT on visual attention to facial features, did not found any significant differences in the visual attention of capuchin monkeys to the eye or mouth area in the categorization test (i.e. classifying males depicted in photographs as "dominant" or "subordinate"), regardless of OXT administration method [99]. The latter influenced the frequency and duration of the gaze at the entire face: endogenous OXT, in contrast to exogenous one, increased the test gaze parameters, which suggests their different influence on the gaze.

The effects of OXT were highly dependent on individual personality traits and context [100, 101]. OXT does not always promote positive social behavior in everyone and in all situations [18], so it may increase visual attention to the eye under certain conditions only. In this context, deep mechanisms underlying OXT effects depending on the person's characteristics and the situation remain unknown. The "social significance hypothesis" cannot fully explain the inconsistence of OXT-induced effects.

Modulatory effects of vasopressin on perception and social behavior

Instant, efficient, and accurate recognition of facial expressions represents a fundamental and unique ability of humans to participate in interpersonal communication. A growing body of experimental brain neuroimaging evidence demonstrates that the neural circuits responsible for empathy and emotion recognition are located primarily in the limbic system, prefrontal cortex, and frontoparietal regions [101–103]. Therefore, VP is an important neuromodulator that activates brain areas that are directly involved in the regulation of emotions, in particular, the limbic system (cingulate gyrus, amygdala) [70]. According to R.R. Thompson et al., VP exhibited dual effects on social communication in men and

women [104]. In men, exogenous VP stimulated agonistic facial motor patterns in response to the faces of unfamiliar men and decreased perceptions of the friendliness of those faces. In women, in contrast, AVP stimulated affiliative facial motor patterns in response to the faces of unfamiliar women and increased perceptions of the friendliness of those faces. It is also possible that VP effects on autonomic, motor, and psychological responses each resulted from its independent actions in different brain regions. If so, the orthogonal effects of VP on social communication patterns in men and women may be the result of sex differences in receptor distributions in the brain, such that VP directly activates specific fight or flight circuits in men and tend and befriend circuits in women.

In a study by F. Uzefovsky et al., exogenous VP significantly reduced the ability of male participants to recognize emotions of other men (this effect was restricted to recognition of negative emotions only), which may further promote aggression due to lack of empathy [29]. R. Polk et al. evaluated the VP-social cognition link in aging and showed that higher plasma VP levels did not correlate with the accuracy of dynamic emotion identification [105].

On the other hand, some authors suggested that VP was directly involved in pair-bonding behavior. In particular, intranasal administration of VP increased the willingness for mutually beneficial cooperation between strangers [106, 107] and selectively enhanced human cognition for sexual stimuli, regardless of valence [53]. VP-induced inhibition of activity in the left dorsolateral prefrontal cortex (i. e. an area responsible for decision-making under risk conditions) and increased functional connectivity of the left dorsolateral prefrontal cortex with the ventral medial striatum can be possible neural mechanism underlying the increased tendency to collaborate [108]. In the latter, as a structural component of the basal ganglia, where both V1a VP receptors and dopamine receptors are concentrated with a sufficiently high density, a reward system forms as a result of social interaction. Therefore, the interaction of the dopaminergic and vasopressinergic systems in the ventral medial striatum was shown to encode a beneficial component of social interactions by facilitating social recognition and pair bonding [109, 110].

X. Wu et al. showed gender-specific effects of VP in response to same-gender and other-gender facial expressions among males and females; males rated lower approachability scores to neutral and positive male faces, while females rated higher approachability scores to negative female faces [111]. VP is likely to modulate the perception of emotional stimuli to a greater extent than neutral ones. Such distinctive effects of VP on socio-emotional stimuli directly depend on gender and context.

This also demonstrates that VP has gender-specific effects on social behavior and associated emotional response.

Effects of oxytocin on "face reading" in patients with mental disorders

Considering the critical role of OT in social cognition (perception of social signals, identification of emotional body gestures, recognition of facial emotions, handling of emotionally charged situations, approach-avoidance behavior) and interpersonal interaction, the oxytocinergic system is a promising target for the treatment of mental disorders.

It should be considered that "face reading" requires the rapid and accurate perception of primary social stimuli as the primary communication tools for conveying necessary social and contextual information, emotional feedback, understanding of social norms, and the ability to recall and attribute different emotions to others. These aspects of social cognition are fundamentally impaired in patients with mental disorders.

A. Vehlen et al. reported that despite largely preserved basic facial emotions recognition, attention in social perception may be altered in patients with chronic depression disorders, and the latter was sensitive to intranasal treatment with oxytocin [112].

Evaluating an association between endogenous oxytocin levels and facial emotion recognition accuracy in individuals with schizophrenia, MJ. Spilka et al. showed that lower plasma OXT levels were associated with a significant reduction in accuracy of identifying high-intensity fearful facial expressions and low-intensity sad expressions [113]. This did not affect visual attention to salient facial features.

According to B.B. Averbeck et al., single low doses of OXT (24 IU) administered intranasally to patients with schizophrenia improved their ability to identify most emotions, whether the images presented to the patients depicted neutral or emotional faces (i.e. with happiness, surprise, fear, sadness, aversion, or anger) [114]. However, this contradicts to a recent randomized double-blind study [115] where such low acute doses of OXT had a limited and modest effect on social emotional face processing and did not affect eye gaze duration or gaze dwell time on faces. This is consistent with the data of J.K. Wynn et al., who, using electroencephalography and pupillometry, demonstrated that moderate OXT doses (36–48 IU) were optimal and effective for enhancing emotion recognition in patients with schizophrenia [116].

In this context, long-term (4-month) therapy with OXT in patients with schizophrenia improved the patients' ability to recognize and understand the emotional state of others, which is crucial in interpersonal communication and social behavior [117].

According to R. Wigton et al., OXT-induced improvement in social cognition in patients with schizophrenia is based on

attenuated neural activity in the brain regions that support mentalizing, processing of facial emotions, salience, aversion, uncertainty and ambiguity in social stimuli, including amygdala, temporo-parietal junction, posterior cingulate cortex, precuneus, and insula [118].

As shown by L.R. Horta de Macedo et al., exogenous OXT did not improve performance of patients with schizophrenia in a facial emotion matching task [119]. According to the authors, such unexpected results could have been caused by high doses of OXT (i.e. 48 IU) and the use of the facial emotion matching task contrasting with previous studies using emotion labeling tasks.

A. Schmidt et al. showed that OXT administration did not have any significant effects on inferring others' beliefs and social emotions in people at clinical high risk for psychosis [120]; this result was quite unexpected. Moreover, there was a decrease in neural activity in the bilateral inferior frontal gyrus while inferring others' beliefs and social emotions. Inhibition of activity in this brain region was seen in individuals at clinical high risk for psychosis with high social-emotional abilities. This demonstrates selective effects of OXT on emotions in pathophysiological conditions and directly depends on the ability to have emotional empathy.

The inferior frontal gyrus is an important part of the mirror neuron system, which is involved in significant aspects of social interaction, from imitation to emotional empathy [121]. Being a key target for the neurophysiological effects of OXT, the inferior frontal gyrus is directly involved in emotion recognition tasks, such as sentence processing guided by intonation [122] and discriminating facial expressions [123].

OXT modulates impairments in emotion perception and the ability to draw conclusions about others' thoughts and beliefs; these impairments can be considered predictors of mental disorders. This is done through selective OXT effects on certain brain regions, which can be considered in the development of new strategies for targeted therapy of social emotional disorders.

Role of vasopressin in the selective activation of brain activity during the recognition of emotions in patients with mental disorders

B. Bloch et al. demonstrated that the effects of exogenous VP on emotion recognition in individuals with schizophrenia were multidirectional and directly dependent on gender [124]. VP resulted in a significant decrease in the ability to recognize angry faces in men and sad faces in women. A VP-induced improvement in the perception of fearful facial expressions was found in women.

Levels of endogenous VP in patients with schizophrenia were significantly reduced, which correlated with the severity of symptoms and impaired recognition of others' emotions [125].

Considering neuroimaging data, L.H. Rubin et al. showed that basal VP levels in men and women with schizophrenia were associated with activity in the middle, medial and superior frontal gyri, as well as the cingulate cortex [126]. VP differentially modulated brain networks in the brain regions important for social cognition and emotion processing in women and men with schizophrenia. VP-mediated reductions in functional network connectivity of the frontal cortex (superior frontal gyrus) were found in women, while men had increased functional network connectivity in the middle frontal gyrus/cingulate gyrus. L.H. Rubin et al. showed a relationship between selective modulatory activity of VP, brain region and gender, which determines the different role of this neuropeptide in the recognition of emotions in male and female patients with schizophrenia.

An unexpected conclusion was made by D.S. Carson et al., who showed that VP blood levels in people with autism spectrum disorder aged 4–64 years significantly and positively correlated with VP levels in the cerebrospinal fluid. In addition, VP levels in the blood predicted severity of symptoms in the context of the theory of mind performance as the ability of adequate perception and understanding of others' emotions, thoughts, beliefs, and desires [127]. These results clearly demonstrated that VP levels in blood samples can be used not only as a reliable tool for a routine assessment of its activity in the brain but also as a biomarker for impaired social cognition in children with autism spectrum disorder.

In their neuroimaging study, X.J. Shou et al. found evidence that the development and progression of autism spectrum disorder is associated with pathological changes in the morphology and functionality of the brain regions where VP neurons are mostly localized [128]. Children with autism spectrum disorder had a decrease in the volume of the gray matter in the hypothalamus and an increase in the volume of the left amygdala and left hippocampus. The reduction in the volume of the hypothalamus might suggest dysplasia of neurons and/or neuropil in the hypothalamus that leads to decreased VP levels and the manifestation of autistic symptoms. Moreover, the degree of abnormal expansion of the amygdala was positively correlated with the severity of social and communication impairment.

Therefore, VP can be considered a promising neuropeptide that influences the social and emotional functions of the brain in the context of interpersonal relationships, which may be useful for understanding the etiology and neurobiological basis of mental disorders.

Conclusion

Research to investigate the multifaceted effects of OXT and VP remains an exciting direction for deeper understanding of the structure and functioning of the so-called "emotional

and social brain". Data accumulated over the past few decades have significantly enriched our understanding of OXT-ergic and VP-ergic regulation for processes that are vital for socialization, effective and flexible interpersonal communication, such as social cognition, social behavior, emotion recognition, and attention and memory to emotionally salient stimuli. However, data on OXT and VP effects on emotions and memory are sometimes inconsistent, so further studies are needed to investigate how context-dependent intracellular signaling cascades produce specific behavioral responses. Solving this scientific problem will allow obtaining unique knowledge about OXT-induced and VP-induced cellular response and signaling mechanisms in the neural networks of the brain structures that are responsible for the implementation of behavior. This will undoubtedly be decisive in the development of more effective therapeutic strategies using OXT, VP and their analogs for the treatment of mental disorders.

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