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Review

Oxytocin and Social Adaptation: Insights from Neuroimaging Studies of Healthy and Clinical Populations

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Adaptation to the social environment is critical for human survival. The neuropeptide oxytocin (OT), implicated in social cognition and emotions pivotal to sociality and well-being, is a promising pharmacological target for social and emotional dysfunction. We suggest here that the multifaceted role of OT in socio-affective processes improves the capability for social adaptation. We review OT effects on socio-affective processes, with a focus on OT-neuroimaging studies, to elucidate neuropsychological mechanisms through which OT promotes social adaptation. We also review OT-neuroimaging studies of individuals with social deficits and suggest that OT ameliorates impaired social adaptation by normalizing hyper- or hypo-brain activity. The social adaption model (SAM) provides an integrative understanding of discrepant OT effects and the modulations of OT action by personal milieu and context.

Introduction: Oxytocin Promotes Social Adaptation

Humans live in a complex social environment and rely strongly on social relations and social interactions to survive and thrive [1,2]. Impaired social functioning negatively impacts reproduction, development, mental health, and well-being. The neuropeptide **OT** (see Glossary), an evolutionarily ancient and conserved hormone, has been implicated in important reproductive and adaptive functions in animal models [2–4], including sexual behavior [5], facilitation of birth [3,6], pair bonding [7], and maternal behavior [8,9]. Intranasal administration of OT (IN-OT) in humans has been documented in the regulation of anxiety [10–14] and stress [15–19], the initiation of positive social interactions [16,20–22], and the promotion of social cognition [23–25] and prosocial behaviors [26–28]. Being trusted and socially well connected, engaging in positive social interaction, as well as experiencing reduced anxiety, stress, and interpersonal conflict, are essential for individuals to adapt to social environments. These effects provide evidence for the role of OT in promoting social adaptation (i.e., improving the processes whereby individuals fit into the complex social environment). OT is also a promising pharmacological target for treatment of psychological disorders [21,29–33], especially those characterized by heightened negative affect and social dysfunction (see [33–35] for systematic reviews of IN-OT clinical trials), including **social anxiety disorder** (SAD), **autism spectrum disorder** (ASD), schizophrenia, depression, borderline personality disorder (BPD), and post-traumatic stress disorder (PTSD). The effects of OT on social and affective processes are due to its role as a neuromodulator in the

Trends

The neuropeptide OT, implicated in social cognition and emotions pivotal to sociality and well-being, is emerging as a pharmacological target for social and emotional dysfunction.

Studies of healthy populations that integrate functional magnetic resonance imaging (fMRI) and intranasal OT indicate that OT modulates neural correlates of negative affect, positive and rewarding social experiences, and perceived salience of social signals.

OT-neuroimaging studies of individuals with social deficits suggest that OT ameliorates impaired social adaptation by normalizing hyper- or hypo-brain activity.

These findings support a SAM of OT that the multifaceted role of OT in socio-affective processes improves the capability for social adaptation.

The clinical implications of the SAM for OT therapeutic potential are discussed.

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Box 1. Pharmacological fMRI: Assessing OT Effects on Neural Activity

An increasing number of studies use fMRI to examine the effects of pharmacological manipulation on neural activity. This pharmacological-fMRI approach aims to reveal the neurochemical foundations of human emotional and cognitive functions, examine the effects of different drugs on brain responses, and/or expand knowledge on novel drug targets. Pharmacological-fMRI studies address questions such as: (i) How does a drug with established behavioral and clinical effects changes brain activity? (ii) What is the relation between the behavioral effects of the drug and changes in neuronal functioning? And (iii) What is the clinical efficacy of a drug in terms of brain–behavior relations?

A growing number of pharmacological-fMRI studies have investigated the neural effects of IN-OT. Recent OT fMRI studies have proven to be reliable in producing changes in fMRI signals and to probe multiple facets of brain function related to social and affective processes [122]. Despite the promise of using pharmacological-fMRI studies to understand the role of OT in brain function and/or for therapeutic purposes, it is important to consider some caveats of this method. Although pharmacological-fMRI studies are based on the assumption that the changes in blood oxygen level-dependent (BOLD) responses following IN-OT are neuronal in origin, OT also acts peripherally, and the relation between peripheral and central OT effects remains unclear. It is also unknown how endogenous OT levels may impact the neural influences of exogenous OT administration. Furthermore, while OT-fMRI studies implicate particular brain regions in which activity is altered by IN-OT, these do not necessarily indicate that OT is acting directly on OT receptors in those regions. Rather, the effect may represent indirect activity changes via functional connectivity with other regions on which OT is directly acting. Additionally, BOLD signals do not identify which specific neurotransmitters are producing the signal changes, and neural responses following IN-OT may involve other neurotransmitter systems with which OT interacts or modulates (Box 2). Finally, OT-elicited changes in neural activity do not necessarily result in corresponding measurable behavioral changes. Such a phenomenon may result from administration of suboptimal OT doses to modulate behavior, despite being enough to measurably altered neural activity. Alternatively, activity in the influenced neural region may not directly, or solely, produce the measured behavior; for any given complex behavior or action, multiple brain regions and factors likely have a role.

Despite these considerations in the interpretation of OT fMRI studies, such investigations do reveal convincing neural effects of OT, and OT fMRI has considerable translational potential for both basic and applied brain research. Drug-related modulation of relevant neuronal activity may serve as a promising biomarker for use in drug discovery as well as in basic neuroscience.

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brain [2,29,30]. OT is synthesized in magnocellular neurons in the paraventricular and supraoptic nuclei of the hypothalamus [36]. In the brain, OT travels along the axonal projections from parvocellular neurons of the hypothalamus to other brain areas, such as the amygdala, hippocampus, striatum, suprachiasmatic nucleus, bed nucleus of stria terminalis, and brainstem [31,36]. OT actions are mediated by specific OT receptors found in a variety of brain regions. For example, animal and human postmortem studies have shown the presence of OT receptors in the hypothalamus, thalamus, globus pallidus, substantia nigra, caudate, amygdala, and insula [37]. A recent study [38], using arterial spin labeling to measure *in vivo* regional cerebral blood flow (rCBF) changes in humans, showed IN-OT-induced rCBF changes in multiple brain regions expected to express OT receptors, including core regions of the brain circuitry mediating social and affective processes. Most importantly, numerous **functional magnetic resonance imaging** (fMRI) studies have examined OT influences on neural substrates of multiple socio-affective processes in humans and have shown OT effects on multiple brain regions (**pharmacological fMRI**; Box 1).

To elucidate the multiple neuropsychological mechanisms through which OT promotes social adaptation, here we first review fMRI studies that examine the effects of IN-OT on socio-affective processes and corresponding neural activity in healthy individuals. We then review OT-fMRI studies of clinical populations that show evidence that OT ameliorates impaired social adaptation in individuals with social deficits. Next, we propose a SAM of OT according to which the fundamental function of OT is to enhance the capability to adapt to the social environment (Figure 1). OT has important roles in social behaviors and emotional processes that are necessary for social adaptation. This model also helps to explain discrepant effects of OT and the modulations of OT effects by personal milieu and contexts. Finally, we discuss possible implications of IN-OT in clinical treatment strategies within the framework of social adaptation.

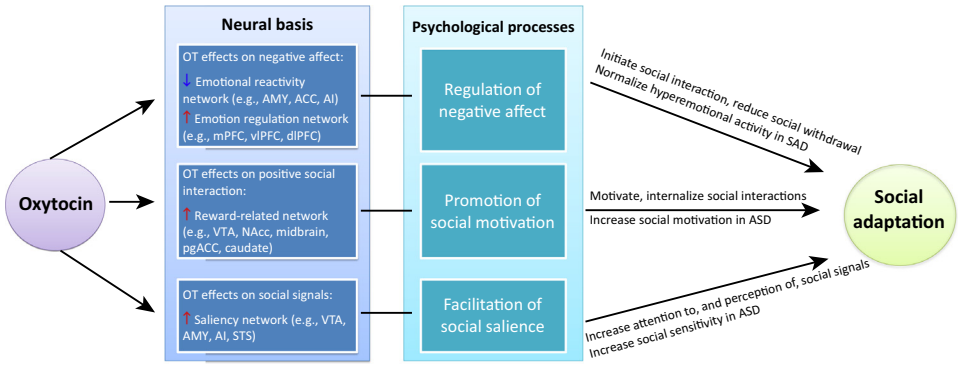

Figure 1. The Social Adaptation Model of Oxytocin (OT) Function. OT downregulates negative affect, enhances social motivation, and increases social salience of perceived stimuli by modulating activities in the emotion reaction and regulation, reward, and salience neural networks. These processes together help individuals to approach social interactions, fit into complex social contexts, and, eventually, adapt to the social environment.↑ indicates increased neural activity by OT; ↓ indicates decreased neural activity by OT. Abbreviations: ACC, anterior cingulate cortex; AI, anterior insula; AMY, amygdala; ASD, autism spectrum disorder; dlPFC, dorsal lateral prefrontal cortex; mPFC, medial prefrontal cortex; NAcc, nucleus accumbens; vlPFC, ventral lateral prefrontal cortex; SAD, social anxiety disorder; STS, superior temporal sulcus; VTA, ventral tegmental area.

OT Promotes Social Adaption through Multiple Neuropsychological Mechanisms

Early behavioral findings that IN-OT suppressed subjective and physiological responses to psychosocial stress [15] and increased prosocial behaviors during economic investment [26] inspired the first IN-OT fMRI study of the influence of OT on brain responses to threats [10]. Since then, an increasing number of IN-OT fMRI studies have examined the neural basis for the impact of OT on social and affective processes (see Table S1 in the supplementary material online for a summary of IN-OT fMRI studies). The IN-OT fMRI studies reviewed here provide neuroscience evidence for the neuropsychological mechanisms underlying OT effects on social adaptation, including regulation of negative affect, promotion of rewarding experiences from social interaction, and heightened social sensitivity.

Downregulation of Negative Affect

The regulatory capacity of OT on negative affect was first established from animal studies showing OT as an important modulator of anxiety and stress responses [39–41]. Stemming from these early animal studies, the first IN-OT fMRI study of humans [10] monitored amygdala activity in response to social and nonsocial threats in a double-blind crossover comparison of OT and placebo. Fifteen healthy men were intranasally administered with OT (27 IU) or placebo 50 min before scanning, where subjects performed emotion-matching tasks separately on social (threatening and angry faces) and nonsocial (threatening and fearful scenes) threats. Compared with placebo, IN-OT significantly suppressed amygdala activation and amygdala-brainstem **functional connectivity** to both social and nonsocial threatening stimuli, although the OT effects were more pronounced for social than nonsocial threats. This finding provided the first neural evidence for reduction of negative affect by OT in humans and has been replicated in subsequent studies using different stimuli and paradigms. Specifically, IN-OT has been shown to reduce amygdala activity to negative emotional expression (fearful [10,11,14,42,43], angry [10,11,44], or sad [45] faces), aversive pictures [10,14,46,47], conditioned fear [48,49], and physical pain [50,51]. IN-OT also reduced amygdala activity during negative social interactions, such as experiencing social trust betrayal [27], having attempted cooperation be unreciprocated [52], imagining partner infidelity [53], listening to an infant crying [13], experiencing social evaluative threats [19], and seeing others in pain [54]. Findings from these studies also showed

Glossary

Autism spectrum disorder (ASD): a range of conditions classified as neurodevelopmental disorders in the DSM-V. The DSM-V redefined the ASD to encompass the previous (DSM-IV-TR) diagnoses of autism, Asperger syndrome, pervasive developmental disorder not otherwise specified (PDD-NOS), and childhood disintegrative disorder. These disorders are characterized by social deficits and communication difficulties, stereotyped or repetitive behaviors and interests, sensory issues, and, in some cases, cognitive delays.

False belief: the recognition that others can have beliefs about the world that are diverging. Gaining the ability to attribute false belief is critical in the theory of mind development. To gain false belief ability, one has to understand that people's beliefs are based on their own knowledge, that mental states can differ from reality, and that people's behavior can be predicted by their mental states.

Functional connectivity: the connectivity between brain regions that share functional properties. More specifically, it can be defined as the temporal correlation between spatially remote neurophysiological events, expressed as deviation from statistical independence across these events in distributed neuronal groups and areas. This applies to both resting state and task-state studies.

Functional magnetic resonance imaging (fMRI): a noninvasive method for recording blood oxygenation level-dependent signals that have high spatial resolution and are used to examine brain activations associated with specific stimuli or tasks, or the intrinsic activity of the brain during a resting state.

Oxytocin (OT): an evolutionarily conserved neuropeptide hormone that is known for its regulation of anxiety, initiation of positive social interactions, and promotion of social cognition. In the brain, OT travels along the axonal projections from parvocellular neurons of the hypothalamus to different areas, including the amygdala, hippocampus, striatum, suprachiasmatic nucleus, bed nucleus of stria terminalis, and brainstem.

Pharmacological-fMRI: a technique combining fMRI with a

the complexity of the attenuating effect of OT on amygdala activity by revealing that the OT effect can be modulated by eye gaze [42,48,55] and eye whites of the fearful faces [43], and perhaps mediated by different subregions of the amygdala [42]. In addition, IN-OT affected functional connectivity between amygdala and other brain regions, during both socio-affective tasks [10,42,47,49,52,56–59] and rest [60–63]. Interestingly, recent work has indicated homologies between macaque monkeys and humans in the neural circuits mediating the OT effects on negative emotion. Specifically, in response to negative emotional facial expression, OT-induced modulation of the amygdala, as well as other face-responsive regions, was recently reported for macaque monkeys treated with IN-OT. IN-OT also selectively reduced functional connectivity between the amygdala and areas in the occipital and inferior temporal cortex.

As well as modulating amygdala responses, OT also influences other regions of the neural circuitry underlying emotional reactivity and emotion regulation. In response to negative affect, IN-OT reduced activity in brain regions shown to mediate negative affective experiences [64–69], including the anterior cingulate cortex (ACC [43,48,52,53]), anterior insula (AI [27,44,54]), midbrain [27,44,50], orbitofrontal cortex (OFC [50,51,53]), and thalamus [11,19,44]. By contrast, IN-OT may increase the capacity to regulate negative affect by increasing activity in the medial prefrontal cortex (mPFC [19,48,49]), ventral lateral prefrontal cortex (vlPFC [13,48,50,52,70]), and dorsal lPFC [49,70], which comprise the neural circuits for automatic and effortful regulation of emotion [66,71,72].

Taken together, these findings highlight two OT effects on negative affect; that is, decreasing brain reactivity to negative emotion and increasing neural activity involved in emotion regulation. These effects may in turn influence social behavior and benefit individuals socially by reducing social withdrawal, encouraging social involvement, evoking initiation of social interaction, and even helping with recovery from previously experienced negative social interactions. Thus, OT promotes social adaptation by downregulating social anxiety and/or stress and facilitating social interaction.

Promotion of Social Motivation

Another mechanism through which OT may promote social adaptation is by facilitating intrinsic reward and motivating individuals to initiate and maintain social interactions. Several IN-OT fMRI studies provide neural evidence for this mechanism [42,52,70,73–78]. For example, Scheele and colleagues [73] examined OT effects on interpersonal touch, a behavior conveying highly salient socio-emotional signals in primates [79,80]. After IN-OT or placebo, heterosexual male adults were scanned while they believed they were being touched by either a man or a woman, although in reality were always touched by the same experimenter. When participants believed they were being touched by a woman (not a man), IN-OT increased the perceived pleasantness and neural responses in the insula, precuneus, pregenual ACC (pgACC), and OFC, which are regions shown to mediate reward [64,65]. This suggested that OT increased the perceived hedonic value of heterosexual interpersonal touch [73]. IN-OT also increased neural responses in other reward-related brain regions [including ventral tegmental area (VTA), putamen, caudate, insula, nucleus accumbens (NAcc), and midbrain] while viewing positive social stimuli (e.g., happy face [42,70] or partner's or own child's images [75,76]), anticipating social reward [74], and engaging in positive social interactions (e.g., cooperation with others [52,77,78]). The OT-induced hyperactivity in the reward system provides a neural basis for a possible role of OT in attributing reward value to social contexts, thereby facilitating motivation to initiate social interactions, stay connected with others, and solidify social relations. Although OT-induced hyperactivity in the reward-related system has been repeatedly reported in men [42,52,73–76], there is a potential gender difference [77,78], with a less consistent, potentially more complicated picture for women [57,70,81,82].

pharmacological challenge, which shows promising results in assessing the integrity of various neurotransmitter systems. This technique is sensitive to changes in blood oxygenation as a result of neuronal activity in response to pharmacological challenges and, therefore, provides an index of neurotransmitter function.

Salience neural network: adaptive behavior depends on appropriately selecting stimuli to which we assign salience. The salience neural network responds to behaviorally salient events and comprises three main cortical areas: the dorsal anterior cingulate cortex, the anterior insula, and the inferior frontal gyrus [119]. The activity within the salience network signals the need for behavioral change [120] and often relates to the regulation of activity in other networks [121].

Social anxiety disorder (SAD): also known as social phobia; an anxiety disorder characterized by an intense fear in social situations causing considerable distress and impaired ability to function in at least some parts of daily life. These fears can be triggered by perceived or actual scrutiny from others.

Social salience: given the limited perceptual resources of the human brain, the detection of salience of stimuli is considered a key attentional mechanism that enables focusing on important information. Social salience refers to increasing the contrasts between social and nonsocial stimuli. By framing OT effects in terms of their modulatory role on assignment of salience, the social salience hypothesis of OT proposes that the behavioral effects of OT are highly dependent on the degree to which social cues are made relevant in comparison to nonsocial cues.

Facilitation of Social Salience

Humans are social creatures, and a high level of social sensitivity is important for the adaptation of individuals to the social environment. While early OT behavioral studies have suggested that IN-OT promotes prosociality [26,27], recent research revealed that the social influences of OT vary across social contexts rather than being always positive. For example, IN-OT can increase antisocial behaviors, including violence [83] and envy [84]. The incongruent findings have been proposed to reflect a general role of OT in increasing the salience of social cues that is sensitive to social contexts and individual differences [85,86].

Several IN-OT fMRI studies have uncovered the neural basis of OT effects on **social salience**. Groppe *et al.* [74] investigated OT effects on the neural processing of socially salient cues and showed that IN-OT enhanced VTA activity to cues signaling social punishment (angry face) in addition to social reward (friendly face). Furthermore, IN-OT increased activity in brain regions related to reward (e.g., NAcc, striatum, and OFC) and social processing (posterior superior temporal sulcus and premotor cortex) during social judgments and decrease activity in these regions during nonsocial judgments [87]. It has also been demonstrated that IN-OT also increases functional connectivity between amygdala and the **saliency network**, such as insula and caudate [52,58]. Moreover, an OT-driven increase in functional connectivity between amygdala and insula/caudate has been associated with improved social learning [58]. It has been suggested that the increased salience of social cues following OT is related to enhanced attentional orienting to social stimuli [88]. In support of this proposition, it was found that IN-OT enhances attentional orientation to the eye regions [89], possibly by modulating amygdala activity [42]. By increasing social salience through modulating attention to, and perception of, social cues, OT improves sensitivity to social signals, which assists the processing of social information and helps individuals to prepare for social engagement and social consequences, so as to adapt to social environments. Given that directing attention and assigning saliency to relevant information is regulated by the dopaminergic system [90], it is possible that OT exerts these effects by altering attentional neural mechanisms through its interaction with the dopaminergic system (Box 2).

OT Facilitates Social Adaptation in Individuals with Social Dysfunction

The findings of OT neural effects in regulating negative affect and facilitating social cognition have inspired an increasing number of clinical trials using IN-OT to treat social deficits in several psychological disorders. IN-OT fMRI studies in clinical groups with specific deficits in emotion-regulation and social cognition have helped researchers further understand specific neural mechanisms through which OT may act on the symptoms. Here, we mainly review OT effects on brain activity in SAD and ASD (two types of psychological disorder typically characterized by social dysfunction), given that IN-OT fMRI studies of clinical populations have mainly examined OT effects in patients with these conditions (see [33–35] for systematic reviews of IN-OT behavioral effects on other psychological disorders, such as depression, schizophrenia, etc.). Although through different neural networks, OT has been shown to affect patients with SAD and ASD toward the same end, making them resemble healthy individuals in the capacity of social adaption [12,45,56]. These IN-OT fMRI studies provide neural evidence that OT promotes social adaptation in individuals with social dysfunction.

Patients with SAD experience intense fear in social situations [91,92] and show amygdala hyperactivity to threatening social cues (such as fearful, angry faces [93–95]). Thus, one line of research has investigated how OT modulates affective neural responses in such patients [12,45,56,60]. In a double-blind placebo-controlled within-subjects design, Labuschagne *et al.* [12] measured amygdala activity to fearful, angry, and happy faces in an emotion-match task in which 18 patients with SAD and 18 healthy controls were asked to select one of two faces to match the emotion of a target face following IN-OT (24 IU) and placebo. Patients with SAD

Box 2. The Relation between the OT, Dopamine, and Vasopressin Systems

It is well documented that OT interacts with other neuromodulators to modulate behaviors and brain responses [123,124]. For example, it has been suggested that the interaction between the oxytocinergic and serotoninergic systems has a major role in mediating the rewarding properties of social interactions in both rodents [125] and humans [126]. Yet, the interaction between the oxytocinergic and dopaminergic (DA) systems is particularly relevant to the SAM.

Social adaptation requires efficient learning from social feedback as well as appropriate detection of, and attunement to, social signals. It has been repeatedly reported that the DA system mediates the attribution of incentive salience to otherwise neutral events [127,128]. Thus, it is possible that, while the DA system has a general role in regulating the salience of stimuli, the interaction between the OT and DA systems has a unique role in modulating the salience of social cues to promote adaptive behavior. In line with the role of OT–DA interactions in increasing social adaptation, numerous studies have found that IN-OT regulates the activity of DA mechanisms, including the ventral striatum and VTA. For example, it has been reported that OT increases ratings of attractiveness of female partners in pair-bonded men and that these ratings predicted activity in the ventral striatum [76]. Furthermore, it has been recently found that IN-OT increases VTA activation to both crying infant and sexual images [82]. Moreover, the perceived hedonic value of interpersonal touch is facilitated by IN-OT and regulated by activity in the AI, OFC, and pgACC [73]. Furthermore, a recent positron emission tomography (PET) study showed that, although OT did not change [11C]raclopride binding in the striatum, it increased binding and reduced the perfusion rate in subregions of the right dorsomedial prefrontal gyrus and superior parietal gyrus [129], suggesting that OT also regulates cortical DA. It has also been reported that amygdala activation in response to social stimuli was interactively modulated by the *CD38* gene (which is involved in OT secretion) and the catechol-*O*-methyltransferase (COMT) genotype (which is involved in the degradation of DA) [14]. Collectively, it may be argued that the OT system interacts with the DA system to modulate the salience of social cues to promote adaptive behavior.

It should be noted that, because OT is closely related to arginine vasopressin (AVP) both pharmacologically and functionally, there may also be an application for AVP in the SAM. OT and AVP are small neuropeptides, differing by only two amino acids. They are thought to have evolved by gene duplication from a single peptide [130]; the human *OT* and *AVP* genes are adjacent to each other on the same chromosome, separated by only 12 kilobases of DNA [131]. OT and AVP are produced in separate populations of neurons in the paraventricular and supraoptic nuclei of the hypothalamus [130]. Furthermore, due to their structurally similarity, OT and AVP have the capability to act on each other's receptors in discrete, mainly nonoverlapping brain regions [132,133]. Behaviorally, in both animals and humans, OT and AVP seem to similarly promote social recognition and memory. However, these neuropeptides can substantially differ in their function, even acting in opposite ways. For example, generally OT increases social interaction and acts in an anxiolytic fashion, whereas AVP can increase social stress and promote anxiety, especially in men [21,31,134]. Overall, the relation between OT and AVP effects on social behavior and corresponding neural activity suggest that the SAM of OT function also involves interplay with the AVP system.

(relative to healthy controls) exhibited amygdala hyperactivity specifically to fearful faces, which was significantly attenuated by IN-OT to a level comparable to that in healthy controls. Subsequent studies showed that, in patients with SAD, IN-OT normalized hyperactivity in the mPFC and ACC to sad faces [45] and influenced functional connectivity between subregions of the emotional network [56,60]. While patients with SAD showed weaker amygdala-frontal connectivity [96,97], IN-OT normalized the amygdala-frontal hypoconnectivity in these patients during rest and when perceiving fearful faces [56,60]. By normalizing the abnormal neural responses (amygdala hyperactivity and amygdala-frontal hypoconnectivity) to social threats in patients with SAD, OT may help such patients approach social interaction and adapt to the social environment with resemblance to typically developed individuals.

Another line of research examines OT neural effects in patients with ASD, who exhibit impaired social function. To-date (as of July 2015), five published OT fMRI studies have examined OT effects in ASD. These studies showed that IN-OT facilitates neural responses during social perception of faces, eyes, and mouths [87,98,99], and social inference (i.e., mind reading and social judgment [87,100,101]) in brain regions typically shown to mediate social cognitive and affective processing [102,103], such as amygdala [98,99], mPFC/ACC [87,99,100], inferior and middle frontal gyrus (IFG, MFG [87,99–101]), superior and middle temporal cortices [87,99–101], and AI [99,101]. The OT neural effect in ASD is selectively observed during social processes, such as passively viewing faces (but not houses [98]), or inferring mental state from eyes (but not categorizing vehicles [87]). Moreover, in ASD, OT increased prefrontal activity (dmPFC, ACC, and superior frontal cortex) specifically during nonverbal-based social judgment

[100]. Relative to typically developed individuals, when patients with ASD were asked to make friend or foe judgments based on verbal (i.e., emotionally positive or negative word) or nonverbal (i.e., emotionally positive or negative facial and vocal expressions) social information, they made nonverbal-based judgments less frequently and more slowly, and showed reduced activity in the prefrontal (ACC, mPFC, and IFG) and AI during nonverbal-based social judgment [100]. IN-OT significantly increased the frequency and speed of nonverbal-based judgments and increased the originally diminished brain activity in the PFC in patients with ASD. The same research group further examined OT behavioral and neural effects in inferring other's social emotion or beliefs separately in ASD. In the case-control study, 17 men with ASD were asked to infer the social emotions or beliefs of the character in a typical false belief story (a modified **false belief task**) after NI-OT or placebo [101]. The authors reported that, when patients with ASD inferred the social emotions of characters in a typical **false belief story**, they showed diminished behavioral performance and weakened neural responses in AI [101]. IN-OT significantly improved the originally diminished performance of patients with ASD and increased their brain activity in the right AI, anterior middle temporal gyrus, and IFG when inferring others' social emotions. These findings suggested that OT improved social communication by facilitating nonverbal social judgment and social emotion inference in ASD.

OT produces differential behavioral effects in SAD and ASD (i.e., anxiolytic effects for SAD and pro-social effects for ASD), as well as differential neural activity associated with social information processing (i.e., decreasing amygdala and mPFC/ACC responses to negative social signals in SAD, but increasing amygdala, AI, superior temporal, and prefrontal activity to social information in ASD). However, the seemingly opposite OT effects in SAD and ASD can be reconciled by considering that OT promotes social adaptation in both cases. The pattern of OT modulations of neural activity depends on how the modulation can facilitate social interaction by either reducing negative affect or enhancing social affective processing. OT takes different neural pathways to the same end of normalizing the abnormal behavioral and neural responses to a similar level as that in healthy individuals, facilitating engagement in social interaction with others and adaptation to the social environment.

In addition, several studies have revealed that OT effects are more evident in patients than in healthy individuals [12,45,56,98,99]. This is consistent with the findings in healthy individuals that the effect of OT is stronger in less socially proficient individuals [17,18,25,104]. For example, IN-OT improves empathic accuracy selectively in less socially capable individuals [25], enhances mentalizing accuracy specifically in individuals with lower empathy scores [104], and facilitates stress regulation only in individuals with low emotion regulation abilities [17]. Thus, OT may improve social adaptation to a greater degree in those with lower social capabilities, but produce less pronounced effects in those who already adapt well to the social environment.

A Social Adaptation Model of OT Effects

Here, we propose a SAM to understand the OT effects revealed in the literature. According to SAM, the fundamental function of OT is to promote social adaptation by modulating emotional responses and adjusting behaviors during social interactions. At the neural level, OT promotes social adaption by modulating brain activity in the emotion reaction and regulation networks, the reward network, and the saliency network. OT can rectify either hyper- or hypoactivity in individuals experiencing social dysfunction so as to adjust their social and affective processes, and help them fit into social environments. At the psychological level, OT can reduce negative affect associated with social stimuli, increase positive emotions and rewarding experiences during social interactions, and make social signals salient by facilitating attentional and perceptual processing of social information. These effects together help individuals to initiate and maintain social communication, social interaction, and social relations, thus improving their adaptation to the social environment (Figure 1).

The SAM of OT function can reconcile the seemingly incongruent OT effects. We take the effects of OT on amygdala activity as an example. Opposite OT effects on amygdala activity (i.e., OT-induced increases versus decreases) have been documented in the literature, but can be understood within the social adaptation framework. For instance, IN-OT has been shown to decrease amygdala activity to negative social information, such as negative facial expression [10,11,14,42–45] and aversive pictures [10,14], but increase amygdala activity during positive social-affective processes (e.g., cooperation [52,77], social feedback [58], infant and sexual pictures [81], and happy faces [42]). Both reducing negative and/or threatening experiences and enhancing pleasant and/or positive experiences during social interaction are adaptive and facilitative of individual well-being and, thus, produce the same end of promotion of social adaptation. Furthermore, the OT effect of reduced amygdala activity to negative affect is mainly observed in men, and several OT fMRI studies of women (using similar paradigms) have reported opposite OT effects; for example, IN-OT enhanced amygdala activity in response to fearful faces and threatening pictures in women [70,75] (but see [46]). Such gender-dependent opposing OT effects can be understood by considering the adaptive value. During evolution, men face higher level of intrasexual competition and favor risk-taking and status fights, whereas women evolve adaptively to be cautious and protective of their offspring [105,106]. Attenuated fear of social threat (possibly mediated by amygdala reactivity decreases) can be beneficial for men in successful competition with other men [105,106]. However, increased sensitivity and a high level of fearfulness to social threats (associated with increased amygdala activity) in women can help them to avoid possible dangers and succeed in securing offspring survival [106,107]. Therefore, the gender-driven opposite OT effects of attenuated or heightened amygdala reactivity to social threats have an adaptive function in both sexes.

In addition to OT influences in the amygdala, discrepant OT effects in other brain regions can also be reconciled under the social adaptation framework. For example, in a recent OT fMRI study [108], after IN-OT or placebo, women were scanned while listening to the same infant crying in the context of 'This infant is sick' or 'This infant is bored'. IN-OT increased empathy-related activity in the AI and IFG during exposure to sick infant crying, but decreased activation in these regions when listening to bored infant crying. The authors suggested that OT enhances empathic responses to sick crying, but reduces the perceived urgency of bored crying. The opposing OT effects on the same infant crying labeled as 'sick' or as 'bored' fit well with the SAM in that OT flexibly adapts parental responses to infant crying by promoting responsiveness to necessary needs (sickness) as well as preventing parents from being overwhelmed when there is no urgency (boredom). This study also provides potential neural mechanisms through which OT enhances parents' social adaptation during parent–infant interactions.

Moreover, in apparent contradiction to the anxiolytic effects of OT and associated dampening of relevant neural responses, IN-OT has been shown to potentiate acoustic startle responses to negative stimuli, as well as increase subsequent memory toward negative social stimuli compared with neutral items and corresponding insula activity [47]. In accordance with the SAM, Streipens *et al.* [47] suggested that such an OT effect is protective by increasing preparedness for defense. Similarly, a recent fMRI investigation showed that IN-OT facilitates Pavlovian fear conditioning on both the behavioral and neural levels [109]. Pavlovian fear conditioning, as a pivotal mechanism for transforming threat into adaptive behaviors, has evolved as an adaptive mechanism promoting survival and reproductive success [110]. As such, the OT-related facilitation of Pavlovian fear conditioning may help individuals predict aversive events, suggesting that OT enables rapid and flexible adaptation to fear signals in social contexts. These findings lend direct evidence for OT in facilitating social adaptation [47,109].

It is widely observed that the OT effects are modulated by the features of individuals (e.g., psychopathology, gender, or personality traits) and contexts (e.g., in- or out-group relations,

valence socio-affective processes, or interpersonal relationship; reviewed in [86]). To adapt to the social environment requires sensitivity to interpersonal situations and social contexts. Thus, the SAM provides an integrative framework for understanding the modulation of personal milieu and contexts on OT effects. For example, IN-OT promotes in-group favoritism [111,112] and cooperation [28,111], but increases out-group derogation [112] and defensive aggression [111]. Humans have evolved to facilitate benefits of their own group and to defend against competing out-groups [113,114]. Thus, both OT effects of promoting in-group cooperation and out-group aggression can be beneficial for individuals' social lives. The discrepant OT effects on interpersonal relations facilitate adaptation to social environments.

Taken together, these behavioral and neural effects of OT support the SAM, which provides an integrated framework for understanding the complexity of OT effect on social cognition and behaviors. However, OT effects of facilitating social adaptation are not limited to the social domain. Behavioral and fMRI studies have also documented OT effects on nonsocial processes. For example, IN-OT inhibited subjective rating and neural responses to physical painful experience [50,51]. The reduced sensitivity and reactivity to physical pain may make individuals less focused on their own negative feelings and pay more attention to social information, which may benefit social interactions.

Clinical Implications for SAM of OT Effects

We have reviewed evidence of OT effects on modulating behavior and neural responses to promote social adaptation in healthy and clinical populations. Most published OT fMRI studies and clinical OT trials examined the effect of a single IN-OT dose and showed its effects on promoting social adaptation. To date, only a few clinical trials have examined the chronic use of OT for treating psychological disorders [34,115]. Thus, the therapeutic potential of chronic IN-OT on social adaptation, which is critical for individuals with social dysfunction, remains elusive and needs to be addressed by future clinical trials and OT fMRI studies. In a recent randomized, double-blind, placebo-controlled, crossover trial, Watanable *et al.* [115] examined the behavioral and neural effects of 6-week IN-OT on patients with ASD. The treatment reduced autism core symptoms and enhanced resting-state functional connectivity between ACC and dmPFC. Moreover, IN-OT significantly mitigated behavioral and neural responses during a social judgment task, both of which were originally impaired in the patients. However, these effect sizes were no larger than those seen in previous single-dose IN-OT, highlighting the necessity to seek optimal regimens for chronic IN-OT treatment in future studies.

IN-OT is not the only way to promote social adaptation. Social learning and cognitive training provide pivotal experiences that make individuals competent for social communication and interaction. Future research can take advantage of the well-documented effects of single-dose OT on social adaptation and combine such treatment with cognitive training. For example, patients with ASD often avoid eye contact and lack motivation to socially interact, and patients with SAD show intense fear or negative emotional reactivity to social threats and social interactions [91–95]. Conventional cognitive training would be less efficient when patients avoid basic social involvement. Therefore, a combination of an early single-dose IN-OT (to direct attention to social signal, motivate social involvement, and regulate acute negative reactivity to social interactions) and follow-up cognitive training (to develop and consolidate adaptive behavioral and neural patterns) may result in better therapeutic effects, a possibility worth addressing in future research. Moreover, OT may enhance the buffering effect of social support on stress responsiveness [15], further indicating that IN-OT may boost the efficacy of cognitive therapy.

While potential therapeutic applications of OT are promising, particularly through OT modulation of neural activity, its effectiveness may require a personalized medicine approach considering several idiosyncratic factors that influence the effects of IN-OT in humans. Interestingly, the SAM

of OT function provides a reasonable explanation of why these particular characteristics modulate the influence of OT. It has been demonstrated in several studies that the influence of OT on neural activity and behavior is dampened or even reversed in individuals who report early life stress or childhood adverse events [19,24,62]. The interaction between OT and early life stress may reflect the maladaptive social behavioral patterns [19,25,116] and interference with the endogenous oxytocinergic system [117] that childhood adverse events can produce. As reviewed above, sex can greatly influence OT neural and behavioral effects, with men and women reacting often oppositely to IN-OT. Differences in the oxytocinergic system may underlie sex differences in social adaptation patterns (as detailed in the 'A Social Adaptation Model of OT Effects' section), and the clinical use of OT will likely have to consider sex in determining drug efficacy. Finally, recent research has demonstrated that one's genetic makeup, particularly in oxytocinergic system genes, can determine the influence that IN-OT has on neural activity [14,55,118]. Identifying and characterizing the various factors that underlie idiosyncratic responses of IN-OT in humans continues to be an active area of research and will be vital for the effective use of OT for therapeutic purposes, likely related to social adaptation processes.

Concluding Remarks

Our systematic review of OT fMRI studies in healthy and clinical populations supports a SAM of OT function. OT has multifaceted roles in socio-affective processes that enhance individuals' capability to adapt to the social environment. By modulating the activity of neural circuits implicated in the processing of negative affect, positive and rewarding experience during social interactions, and social sensitivity, OT increases individuals' sensitivity to social signals, enhances motivation for social involvement, and reduces anxiety about social interactions. This is particularly true for socially less competent individuals who may be less adaptive to the social environment and for patients with social dysfunctions. While the SAM provides an integrative framework to reconcile discrepant OT effects in different populations and contexts, the efficacy of OT treatment requires a personalized medicine approach considering these idiosyncratic factors that affect OT effects. This model also raises outstanding questions (see Outstanding Questions). Direct application of the SAM in empirical studies and its implication in facilitating OT therapeutic potential in clinical trials need to be addressed in future research.

Outstanding Questions

How do the neural effects of IN-OT vary across individuals with different social adaptive capability? How does IN-OT influence behavioral and neural responses during socio-affective processes in individuals who have acquired maladaptive behavioral patterns?

How do individuals' social and biological features (e.g., gender, early childhood experience, endogenous OT level, genetic makeup, personality, etc.) influence the effects of IN-OT on social adaptation?

How do other clinical populations (beyond SAD and ASD) with social adaptation deficits benefit from IN-OT?

How does chronic IN-OT influence social adaptation processes in clinical populations?

How can we integrate different measures (e.g., behavioral performance, subjective reports, brain activity, functional connectivity, etc.) to estimate OT effects on social adaptation in different clinical groups?

How does the endogenous OT level influence the effect of IN-OT? To what extent do sex differences in the endogenous OT level account for the distinct IN-OT effects in men and women?

What is the relation between individuals' social adaptive capability and endogenous OT levels?

How has the function of OT in evolutionarily older mammals changed with its later-evolving functions to maximize social adaptation?

How does OT neurochemically support various functions in socio-affective processes that mediate social adaptation?

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