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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 neuro-
peptide 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

social functioning negatively impacts reproduc-
tion, development, mental health,

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

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 i o* 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 c

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

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 e 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 e 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

(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

[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 e 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, Watanabe 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,

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

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