COMMENTARY

Oxytocin Effects on the Human Brain: Findings, Questions, and Future Directions

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Since the discovery that intranasal administration of neuropeptides can have a direct impact on the human brain, extant research has been devoted to understanding the effects of exogenous oxytocin (OT) administration on social and affiliative processes, including cognitions, behavior, physiological response, and brain activations. Although earlier studies focused on healthy, mostly male (student) samples, recent studies tested whether and how OT administration can be used as a therapeutic agent in psychopathologies involving severe disruptions to social functioning, such as autism, schizophrenia, social anxiety, and depression. On the basis of these mostly favorable outcomes, authors have proposed several underlying mechanisms for the pro-social effects of OT in humans, including: 1) stress-reduction; 2) affiliation-motivation (reward/positive valence); and 3) social salience (independent of valence). The two reports published in this issue of *Biological Psychiatry* (1,2) seem to highlight the "social salience" hypothesis as an important mechanism in facilitating OT-driven changes in human physiology and behavior (3), albeit findings are also consistent with the "social reward" hypothesis.

Each of these two studies (1,2) examined the effects of a single dose of intranasal OT administration on regional brain activations with functional magnetic resonance imaging. Specifically, with intranasal administration of 24 IU OT versus placebo, either in a within- or between-subjects design, brain patterns associated with the processing of socially relevant facial stimuli were assessed in neuro-typical female participants (1) and in male participants diagnosed with autism spectrum disorder (2).

The study by Groppe *et al.* (1) was led by the assumption that the salience effect of OT is mediated by OT influence on dopaminergic neuropathways, including the mesolimbic ventral tegmental area (VTA). The VTA—a group of neurons located in the midbrain—is widely implicated in reward circuitry and is known to play an important role in social cognition and motivation. A cross-talk between the OT system and the dopamine (DA) system has been proposed as the mechanism responsible for the effect (4), because interconnections between OT and DA are found at both the molecular and structural levels. For example, DA receptors are found on OT neurons in various brain regions but especially in hypothalamic nuclei (5) where OT is produced and distributed to other parts of the central nervous system and the periphery. The OT and DA receptors are collocated in regions of the mesolimbic DA system, and injection of OT in the VTA increases DA release in the nucleus accumbens (NAc), a core region of the mesolimbic DA system that receives projections from the VTA. Most recently, the existence of D2-OT-receptor heteromers in the rat striatum has been discovered, pointing to OT-DA interconnection at a molecular level. Yet, very little research exists with regard to the interactions of OT and DA in humans.

Recent findings from our lab point to OT–DA connection in the context of social synchrony, which might highlight the incentive value inherent in social stimuli. Mothers who displayed greater social synchrony during interactions with their infants—implying higher coordination with the nonverbal vocal, visual, and affective cues of their infants—showed higher levels of activations in the NAc in response to attachment-related cues that were functionally connected to activations in socio-cognitive cortical circuits (6). Similarly, while observing synchronous social interactions, human adults increase activations in reward-related areas, including the NAc and dorsal anterior cingulate cortex (S. Atzil, T. Hendler, R. Feldman, unpublished data). These findings, combined with those of Groppe *et al.* (1), might suggest that increasing the salience of social stimuli might also enhance their reward value. Because OT likely exerts its effect in concert with other neurotransmittors, future research is required to specify the role of OT–DA interconnections in imbuing general social cues as well as attachment-specific stimuli with reward value.

The study by Groppe *et al.* highlights an additional issue in OT administration research—that of the differential effects of the hormone according to the social traits, childrearing history, psychopathological symptoms, and culture of the participant (3). In the aforementioned study, OT was found to influence behavioral performance in the incentive delay task as a function of the level of "agreeableness" of the participants. Oxytocin improved "hit rates" in individuals scoring low on agreeableness but reduced performance among individuals high on agreeableness, thus diminishing behavioral difference between the two groups. These findings support the idea that OT effects on human performance is moderated by individual characteristics along the socio-affective continuum, such as empathy, early attachment experiences, and emotion regulation capacities (Figure 1). Similar "nuanced" results were also found in assessing the effects of OT on hormonal reactivity to social stimuli. For instance, we recently found (7) that OT administrated to the parent before interactions that elicit social stress from their infants had an impact on the hypothalamic-pituitary-adrenal reactivity of the infant, but the effect was moderated by parent–infant social synchrony. Among infants experiencing low synchrony, OT attenuated cortisol response, whereas infants experiencing high dyadic synchrony exhibited OT-driven increase in cortisol reactivity during the social stressor. These findings are consistent with current research in clinical samples, which showed that OT tends to improve functioning among less socially proficient individuals while having little effect on those with more optimal social functioning [e.g., (8)]. Perhaps these studies point to a "ceiling effect" with regard to OT-induced changes in the human social repertoire. Such hypotheses might further support the potential role of OT in improving social behavior among socially inept individuals or those suffering from conditions associated with severe social disturbances.

Along the same lines, the study by Domes *et al.* (2) in this issue of *Biological Psychiatry* showed that, after OT treatment,

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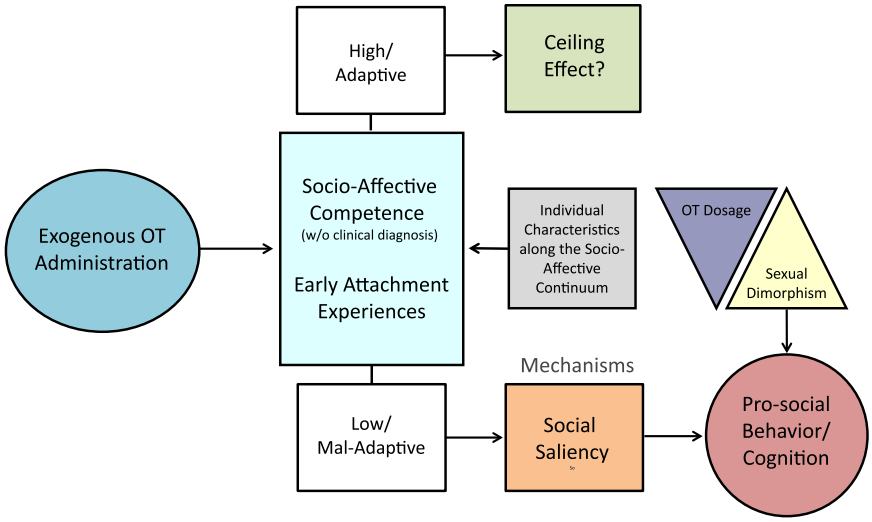

Figure 1. Flow chart illustrating the effects of exogenous oxytocin (OT) on human social repertoire—behaviors, cognitions, brain activations—as a function of trait characteristics along the socio-affective continuum. Prosocial effect of OT is suggested to be mediated through a mechanism of social saliency.

individuals with Asperger syndrome showed an enhanced right posterior amygdala activation toward facial stimuli compared with houses. These findings are consistent with most human neuroimaging studies, which demonstrated that OT modulates amygdala responsiveness to social stimuli (9). Importantly, however, the amygdala is not only a mediator of OT effects but is also a central target of the DA system, and research has pointed to the modulatory effects of DA on amygdala activity during the processing of negative emotional stimuli. In animals, dopaminergic neurons in the central amygdala are activated during fear learning, and similar to the findings for the VTA, enhanced mesolimbic DA release has been reported after OT injection into the amygdala, suggesting a role for the amygdala as one mediator of OT–DA interactions.

Similar to the findings reported by Groppe *et al.* (1), Domes *et al.* (2) reported that OT modulated the processing of socially relevant stimuli among autism spectrum disorder individuals, further supporting the social salience hypothesis as an important mechanism underpinning OT effects on human social learning and social behavior. Moreover, the authors reported that OT enhanced regional brain activity toward faces only among the less socially proficient participants, those with Asperger syndrome, but decreased brain activity in neuro-typical subjects, findings consistent with the notion that the less socially competent individuals might be more sensitive to the beneficial effects of OT.

The effects of OT on social salience and social reward and the role of both the DA reward system and the amygdala network in modulating these effects require much further research in healthy and high-risk populations. The two studies published here add to a growing literature that aims to apply elegant models, imaging techniques, and hypotheses-driven research to begin unraveling these important issues.

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