Review

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,

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

Facilitationof 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 in uences 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 ndings have been proposed to re ect 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) duu(signaling)Tj /F3 1 Tf .5669 0 0 06635.3984 58.93F4 669 122.1947 52530 Tm ( )50 0 3 138.3307

[100]. Relative to typically developed individuals, when patients with ASD were asked to make

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

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.

C ca l ca SAM OT E c

We have reviewed evidence of OT effects on modulating behavior and neural responses

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

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