

A New Perspective on the Pathophysiology of Borderline Personality Disorder: A Model of the Role of Oxytocin

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Borderline personality disorder is characterized by three domains of dysfunction: affect dysregulation, behavioral dyscontrol, and interpersonal hypersensitivity. Interpersonal hypersensitivity is associated with a (pre)attentive bias toward negative social information and, on the level of the brain, enhanced bottom-up emotion generation, while affect dysregulation results from abnormal top-down processes. Additionally, the problems of patients with borderline personality disorder in interpersonal functioning appear to be related to alterations in the (social) reward and empathy networks. There is increasing evidence that the oxytocinergic system may be involved in these domains of dysfunction and may thus contribute to borderline psychopathology and even open new avenues for targeted pharmacotherapeutic approaches. From studies in healthy and clinical subjects (including first studies with borderline personality disorder patients), the authors provide a conceptual

framework for future research in borderline personality disorder that is based on oxytocinergic modulation of the following biobehavioral mechanisms: 1) the brain salience network favoring adaptive social approach behavior, 2) the affect regulation circuit normalizing top-down processes, 3) the mesolimbic circuit improving social reward experiences, and 4) modulating brain regions involved in cognitive and emotional empathy. In addition, preliminary data point to interactions between the oxytocin and cannabinoid system, with implications for pain processing. These mechanisms, which the authors believe to be modulated by oxytocin, may not be specific for borderline personality disorder but rather may be common to a host of psychiatric disorders in which disturbed parent-infant attachment is a major etiological factor.

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Borderline personality disorder affects about 1%–2% of individuals in the general population, approximately 6% in primary care settings, and up to 10% of psychiatric outpatients (1, 2). Factor analyses have revealed three domains of psychopathology in this disorder: affect dysregulation, behavioral dyscontrol, and interpersonal hypersensitivity (for reviews, see references 3–5).

Affect dysregulation comprises experiences of more intense aversive emotions, higher tension, and more rapidly rising mood swings between dysphoria and euthymia in patients with borderline personality disorder compared with healthy individuals (for a review, see reference 6). Behavioral dyscontrol manifests as impulsive self-destructive and aggressive behaviors and a failure to exhibit well-balanced problem-solving behavior as well as future-oriented perspectives on life. Self-injurious behavior, the clinically most troubling manifestation of behavioral dyscontrol, is associated with diminished affective pain processing and dissociation (7). Interpersonal hypersensitivity has only recently become a major research target in the field of borderline personality disorder. According to the alternative DSM-5 model of borderline personality disorder, “interpersonal hypersensitivity” and “perceptions of others selectively biased toward negative attributes” are the most prominent characteristics

leading to interpersonal dysfunction in borderline personality disorder. These phenomena may be well depicted in the notion of “threat hypersensitivity,” which has been strongly associated with a life history of early maltreatment beyond various nosological categories (8).

There are circular mechanisms among these three domains of psychopathology. Interpersonal hypersensitivity may be regarded as a facet of enhanced emotional sensitivity or “bottom-up emotion generation” (9), which reflects the strength of the emotional response system and can be distinguished from poor affect regulation strategies (10). Interpersonal hypersensitivity may contribute to the development of a disorganized-ambivalent form of attachment typical of borderline personality disorder, which impedes early co-regulation between child and caregivers and thus may favor the development of affective instability (4). Affect dysregulation has been shown to predict maladaptive interpersonal behaviors, impulsive coping behaviors (11), and reactive aggressive behavior (12). In addition, there is a strong association between affect regulation and social cognition, with disturbances in emotion processing translating into attentional biases and distorted expectations and interpretations in the social context, and vice versa (for a review, see reference 13).

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Why should one focus on the role of oxytocin in the pathophysiology of borderline personality disorder? In 2010, Stanley and Siever (14) provided a theory on the role of neuropeptides in borderline personality disorder. Since then, a vast amount of research on oxytocin has been conducted, mostly in healthy subjects but also increasingly in patients with different psychiatric disorders, including some in patients with borderline personality disorder. There is now available evidence to advance the thesis that oxytocin exerts effects on several fundamental biobehavioral mechanisms that are closely related to the above-described domains of dysfunction in borderline personality disorder. However, we believe that the oxytocin system is one of many factors related to borderline psychopathology and that the domains of dysfunction presented here are not specific to borderline personality disorder but rather are related to disturbed parent-child attachment or early-life maltreatment (e.g., 8, 15).

THE BIOLOGICAL BASIS OF BORDERLINE PERSONALITY DISORDER

In order to develop new treatments, it is necessary to disentangle the biobehavioral mechanisms related to borderline personality disorder (16). Accordingly, in this review we begin by describing abnormalities in biobehavioral dimensions associated with borderline pathology that, according to findings in healthy and/or clinical subjects, seem to be interconnected with the oxytocin system and thus could be promising targets for oxytocin in future research on borderline personality disorder.

Interpersonal Hypersensitivity and the Salience Network

There is evidence of a profound negativity bias in facial emotion recognition in patients with borderline personality disorder (for a review, see reference 17), that is, they appear to be biased toward identifying negative emotions in others (18–20). More specifically, they concentrate their initial attention more strongly on negative facial expressions (21) and are more likely to ascribe anger to ambiguous facial expressions (18). Recently, patients with borderline personality disorder were shown to also exhibit a response bias toward perceiving other people's faces as more untrustworthy compared with healthy volunteers (22).

Interestingly, an attentional bias toward negative information in patients with borderline personality disorder is reflected in brain imaging data showing increased and prolonged amygdala responses (23, 24) as well as enhanced neuronal activity in the anterior insula (25, 26). The amygdala and the anterior insula, in functional coupling with the anterior cingulate cortex, mediate early bottom-up processes of stimulus evaluation for valence and salience, that is, a stimulus's capacity to be selected or prioritized by attention rather than other possible targets (27). Threat cues seem to be of particularly high salience since, in healthy individuals, threat images evoke greater and earlier blood-oxygen-level-dependent (BOLD) responses in the amygdala (and in the periaqueductal gray) than negative images in general (28).

The salience network is linked with the hypothalamus to regulate stress hormones and with the brainstem to initiate automatic behaviors such as fight-or-flight mobilization or, in the case of the experience of life threat, immobilization (29). Consistent with the notion of social stress hypersensitivity, steeper cortisol awakening responses (30) and increased hypothalamic volumes (31) have been reported in patients with borderline personality disorder. Recently, an event-related potential (ERP) study by our group (32) strengthened the assumption of an attentional bias toward threat cues in borderline personality disorder: Patients with borderline personality disorder, compared with healthy controls, not only showed a greater likelihood of classifying predominantly happy faces as angry, but these abnormalities in face perception were also accompanied by enhanced P100 amplitudes, an ERP reflecting early visual processing, while ERPs also indicated subsequent deficits in later structural face (N170) and categorical facial emotion (P300) processing. This study suggests that the processing of social threat cues is dominated by preattentive, reflex-like mechanisms of very early coarse perceptual processes in the occipital cortex at the cost of more detailed temporally and parietally located structural and categorical processes.

Affect Dysregulation and Prefrontal-Limbic Circuitry

Patients with borderline personality disorder are known to show deficits in affect regulation strategies. They 1) tend to ruminate on negative emotions, 2) are inclined to suppress their emotions, 3) are characterized by experiential avoidance, and 4) have difficulties in labeling their emotions and distinguishing different emotional qualities (for a review, see reference 10). In addition to abnormal "bottom-up emotion generation," patients with borderline personality disorder have been shown to exhibit abnormal neuronal activity in areas of the medial and lateral prefrontal cortex that control and modulate emotional activation, thereby covering "top-down processes." Functional neuroimaging studies have revealed prefrontal hypometabolism during regulatory control processes (for a review, see reference 33), and a recent meta-analysis of functional MRI (fMRI) studies across different stimulation procedures (26) revealed enhanced neuronal activity in the insula but reduced activity in the subgenual anterior cingulate cortex and dorsolateral prefrontal cortex in patients with borderline personality disorder as compared with healthy subjects. While patients had reduced activations in the rostral anterior cingulate cortex during implicit affect regulation compared with healthy subjects (34), they showed decreased orbitofrontal cortex activations in a task requiring instructed reappraisal of negative emotions (25). Interestingly, a functional disconnection between the amygdala and ventral as well as dorsal medial prefrontal cortical regions was observed in patients with borderline personality disorder in a recent fMRI study in which participants were exposed to either threat or safe stimuli (35), similar to an earlier study by New et al. (36).

Interestingly, prefrontal and limbic areas involved in affect regulation strategies have also been reported to show structural alterations in borderline personality disorder. A

whole-brain voxel-based morphometry study showed volume reduction in the cingulate gyri in addition to reduced volumes in the hippocampus and amygdala (37). One MR spectroscopy study found reduced concentration of *N*-acetylaspartate in the dorsolateral prefrontal cortex (38), while another showed significantly higher levels of glutamate in the anterior cingulate cortex (39).

Distrust, Poor Social Reward Experiences, and Mesolimbic Circuitry

Patients with borderline personality disorder are highly sensitive to social rejection and have a generalized mistrust of others, that is, they expect to be rejected, negatively judged, treated dishonestly, or otherwise emotionally hurt by others (22, 40–45). Recent studies demonstrate that patients with borderline personality disorder perceive neutral faces as less trustworthy and approachable than do healthy volunteers (22, 46). Moreover, the relationship between appraisal of untrustworthiness and borderline traits was mediated by rejection sensitivity (22, 44). In addition to deficits in the perception of trustworthiness in other people, patients with borderline personality disorder have been found to show alterations in their own facial expressions. Renneberg et al. (47) found that individuals with borderline personality disorder show more ambiguous facial expressions in social interactions, and Matzke et al. (48) reported increased mimic reactions in response to negative facial expressions but reduced mimic reactions in response to positive facial expressions.

In economic exchange games, patients with borderline personality disorder have shown reduced trust in interpersonal interactions compared with healthy volunteers and patients with major depression (45), as well as problems in maintaining cooperation, repairing broken cooperation (43), and forgiving (49). In neural terms, the latter was associated with an altered response pattern in the anterior insular cortex in patients with borderline personality disorder compared with healthy volunteers in response to offers from an interaction partner (43). These results suggest that mistrust and deficient cooperation are core deficits of borderline personality disorder, which may stem from consistent experiences of invalidation, insecurity, and maltreatment during childhood and hence may be related to an insecure attachment style (50). Consequently, patients with borderline personality disorder who perceive other people as more threatening and less trustworthy may also experience social interactions as less rewarding. Although little is yet known about social learning in borderline personality disorder, neuroimaging studies have revealed alterations in patients' activation of the brain reward system in response to social stimuli. For instance, patients have been reported to show a disturbed differentiation between reward and non-reward anticipation in the pregenual anterior cingulate cortex bilaterally as well as alterations in the ventral tegmental area and ventral striatum compared with healthy volunteers (51). In addition, electrophysiological data suggest that patients with borderline personality disorder have problems in

differentiating between positive and negative feedback and fail to adjust their behavior accordingly (52, 53).

In summary, the problems patients with borderline personality disorder have in interpersonal relationships may be related to increased sensitivity to threat and rejection (see above) and a more negative and mistrusting perception of others, possibly in association with alterations in the brain's (social) reward system.

Poor Cognitive Empathy, Enhanced Emotional Contagion, and Abnormalities in Related Brain Circuits

Theory of mind is the ability to represent one's own and other people's mental states and to infer their intentions, beliefs, and feelings; in the case of others' mental states, it may be referred to as affective theory of mind or cognitive empathy (54), which is very close to the National Institute of Mental Health's Research Domain Criteria subdomain "understanding mental states." Reduced theory of mind or cognitive empathic capacities in patients with borderline personality disorder were found in studies using self-report measures (55, 56) or ecologically valid behavioral experiments (57, 58) (for a review, see reference 59). For instance, patients showed particular deficits in the inference of other people's intentions, but also their thoughts and emotions (60). In addition, some data suggest that patients with borderline personality disorder try excessively to interpret the mental states of others and/or over-attribute others' intentions (61). In tasks requiring cognitive or affective empathic involvement, patients outperformed healthy subjects (62, 63), possibly by (compensatory) overmobilizing affective empathic strategies such as emotional imitation.

With regard to neuroimaging data (57, 63, 64), in a cognitive empathy task, patients with borderline personality disorder showed reduced activations in the superior temporal gyrus and sulcus compared with healthy volunteers, and they had enhanced amygdala and somatosensory cortex activations during affective empathy. This may suggest an overactive and poorly controlled amygdala in patients with borderline personality disorder, which may call their unfiltered attention to predominantly negative and threatening social stimuli. Together with emotional imitation processes reflected in increased activation of the somatosensory cortex, this form of "empathy" is likely to result in an affect-dominated and unmediated perception of others, known as emotional contagion (5, 65). Enhanced emotional contagion is also suggested by electromyographic data indicating higher imitation of mimic activities when negative facial emotions are presented in patients with borderline personality disorder compared with healthy volunteers, a finding that was associated with self-report of more intense negative emotions (48).

Abnormal Affective Pain Processing

Reduced affective pain processing in the context of stress has been consistently reported for individuals with borderline personality disorder (66–70). Hypoalgesia was found to be associated with a deactivation of the amygdala and lower posterior cingulate cortex connectivity with the dorsolateral

prefrontal cortex during pain induction in patients with borderline personality disorder (68, 71). Consistent with the hypothesis that self-injury is a maladaptive affect regulation strategy in the sense of strong sensory distraction, experimentally induced pain resulted in normalization of amygdala activity; the latter was found to be enhanced following the presentation of highly arousing negative affective pictures (72).

BIOBEHAVIORAL MECHANISMS SERVING AS TARGETS FOR OXYTOCIN

Oxytocinergic Modulation of Salience of Social Stimuli

Data consistently provide evidence that oxytocin facilitates the recognition of social stimuli, and particularly facial emotions (73, 74). A number of studies suggest that oxytocin specifically attenuates the processing of threatening social cues in healthy male volunteers. In a decision-making task in which participants learned whether a positive (“smiling”) or a negative (“angry” or “sad”) face was most often rewarded, oxytocin decreased the aversive aspects of angry faces, but exerted no effects on sad faces (75). In a study using video sequences showing neutral faces gradually displaying a specific emotion, oxytocin decreased eye gaze in response to angry facial expressions in a large sample of healthy male volunteers but augmented eye gaze toward neutral and happy facial expressions (76). The modulating effects of oxytocin were also shown to extend to very early automatic attentional processes. In a covert attentional task using the dot-probe paradigm in healthy males, a pronounced shift of attention was observed toward briefly presented happy but not angry facial expressions (77). Interestingly, using a similar task in healthy women, oxytocin did not enhance the attentional bias toward happy facial expressions, but diminished it toward the location of the faces presenting negative emotions. Notably, both mechanisms favor social approach rather than avoidance behavior (78). A further study in a gender-mixed sample showed increased attentional disengagement from angry and sad faces (79). Earlier studies also widely support the social salience hypothesis, although data inconsistent with this have also been published (80).

On the neuronal level, oxytocin seems to reliably modulate the brain salience network. Early studies applying an oxytocin challenge procedure reported amygdala deactivation compared with the placebo condition in healthy men viewing threatening faces or scenes (81). Domes et al. (82) replicated this finding but also extended it to facial stimuli independent of valence. Gamer et al. (83) suggest that oxytocin exerts different effects on subregions of the amygdala. In their study, oxytocin attenuated activation in response to fearful faces but increased activation in response to happy faces in the lateral and dorsal region of the amygdala. In addition, the posterior amygdala mediated oxytocin effects on reflexive gaze shifts toward the eye region irrespective of the depicted emotional expression. A recent study by Kanat et al. (84) projects an even more complex picture of oxytocin effects, reporting that oxytocin decreased amygdala reactivity to masked emotions

when attending to salient facial regions, such as the eye region of angry faces and the mouth region of happy faces (84). A threat-attenuating effect of oxytocin was indicated by the authors’ observation that oxytocin decreased neural activities within the fusiform gyrus and brainstem areas of healthy males, as well as functional connectivity between the amygdala and the fusiform gyrus specifically for threat cues from the eyes. Oxytocin effects were also found during emotion processing tasks in the anterior insula. Domes et al. (85) found enhanced activation in the insula in response to fearful and happy facial cues in females. Intensified activation of the insula was also found when women listened to highly salient acoustic stimuli of a crying infant (86).

Importantly, oxytocin effects appear to vary with gender and interindividual factors (for reviews, see references 87, 88). In healthy women, amygdala activity was found to be enhanced rather than diminished (as in healthy men) in response to fearful faces and threatening scenes, independent of basal plasma levels of oxytocin, estradiol, and progesterone following intranasal oxytocin administration (85, 89). With regard to interindividual factors that significantly modulate oxytocin effects, psychopathology might be of particular importance. While, for instance, oxytocin dampens amygdala response in individuals with social anxiety (90), it enhances amygdala activity in individuals with autism spectrum disorder (91) who experience low interest in their conspecifics.

In conclusion, oxytocin effects on attentional processing of facial stimuli point to specific effects favoring social approach behavior, by modulating the salience of social stimuli. The valence of social stimuli, however, does not appear to be affected in the same way (for a review, see reference 92). The role of oxytocin apparently extends beyond a simple decrease in emotional arousal, but studies from clinical samples—e.g., borderline personality disorder (see below)—suggest that oxytocin rather modulates the salience of social cues to optimize social adaptation, probably also in accordance with different gender-related generative tasks.

Oxytocinergic Modulation of Affect Regulation

As affect regulation is mediated in a prefrontal-limbic network, it is of interest whether oxytocin also affects prefrontal regulating areas. Indeed, oxytocin has been found to significantly reduce the typically increased neuronal activity in the medial prefrontal cortex and the anterior cingulate cortex in individuals with social anxiety disorder (93). In addition, oxytocin has been reported to attenuate activity in ventrolateral and dorsolateral prefrontal areas, which also play a major role in emotion regulation (for a review, see reference 94). Of particular interest are neuroimaging studies of cerebral networks of functionally linked areas. These studies have elucidated preliminary information on how oxytocin may modulate brain circuits mediating affect regulation, selecting the amygdala as the seed region in their analysis of neuronal networks (for a review, see reference 95).

A study investigating oxytocin’s effects on functional connectivity in a resting-state paradigm in healthy individuals

showed increased connectivity between both amygdalae and the rostral medial prefrontal cortex (96). A study in healthy men reported reduced coupling of the amygdala to brainstem regions involved in autonomic and behavioral manifestations of fear while processing threatening faces (81). Most of the studies that have focused on oxytocin's effects on functional connectivity have been performed in individuals with social anxiety, targeting the regulation of social fear. In this population, enhanced functional connectivity was found between the amygdala and the left and right insula as well as the dorsal anterior cingulate gyrus during the processing of fearful faces in the oxytocin compared with the placebo condition (97). Using a resting-state paradigm, the same research group reported enhanced functional coupling between the amygdala and the rostral anterior cingulate cortex in individuals with social phobia, with oxytocin normalizing the reduced amygdala-prefrontal connectivity compared with healthy controls (98).

On the whole, preliminary data suggest that oxytocin does not exert its effects solely on single areas, such as the amygdala, the insula, and the prefrontal cortex, but it affects the functioning of a broader affect regulation circuit. Since this network is highly significant for our understanding of the pathophysiology of borderline personality disorder, studies are warranted that focus on this network (see below) with the aim of clarifying whether modulating brain activity is in fact accompanied by improvement of affect regulation and thus borderline psychopathology.

Oxytocinergic Modulation of Social Reward Experiences

A high oxytocin receptor density has been found in brain regions involved in motivation and reward, such as the amygdala (99), the ventral striatum, and the nucleus accumbens (100). In addition, results of rodent studies suggest that an interaction of oxytocin and dopamine, particularly within the mesolimbic reward system, is involved in the formation of pair bonds, affiliation, and social interaction (101, 102; for reviews, see references 103, 104). In humans, there is only limited direct evidence of an involvement of oxytocin in social reward learning beyond the above-discussed findings indicating an increased salience of positive, socially rewarding stimuli.

Hurlemann et al. (105) showed that intranasal administration of oxytocin potentiates socially reinforced learning in healthy men. Importantly, oxytocin did not have an effect on learning in general, as shown in a nonsocial control condition. In addition, there is some evidence that oxytocin affects financial reward learning in social situations. For instance, Evans et al. (75) found that oxytocin may reduce aversion to angry faces, given that healthy male participants in the oxytocin condition chose an angry face more often when this face was associated with a high financial reward, whereas participants in the placebo condition tended to avoid angry but highly rewarding faces. However, in a second study, Clark-Elford et al. (106) revealed that oxytocin may selectively reduce reward learning from happy faces in healthy

volunteers, possibly because of an increased salience of happy faces after oxytocin administration.

Oxytocin administration was also found to increase the proportion of positive communication behaviors and to reduce cortisol levels during couple conflict discussions (107) and to increase the attractiveness of the intimate partners (108). The latter was associated with increased activations in the brain reward system, including the ventral tegmental area and nucleus accumbens, and it appeared to be specific to intimate partners, which is in line with the suggested interaction of oxytocin and dopamine in the rewarding component of intimate pair bonding and social attachment. Recently, Kis et al. (109) reported that social treatment, including eye contact and social touch, and oxytocin administration had similar effects on a subsequent facial recognition task. Healthy male volunteers in both conditions rated negative facial expressions as more positive and trustworthy than did volunteers in the nonsocial or placebo conditions.

Taken together, although evidence on oxytocin modulation of unfamiliar faces and the reward learning from unfamiliar (emotional) faces remains controversial, oxytocin does seem to increase the perceived attractiveness of and positive communication with intimate partners, which may be associated with increased activations in brain reward regions. Oxytocin might thus have the potential to improve social interactions with and attachment to familiar people such as friends or psychotherapists in patients with borderline personality disorder.

Oxytocinergic Modulation of Cognitive and Emotional Empathic Capacity

So far, little is known about the oxytocinergic modulation of empathic capacities beyond the above-discussed enhancement of emotion recognition in healthy volunteers. There is some evidence of increased performance in tasks that involve cognitive empathy capacities (110, 111) and of enhanced verbal emotional sharing (112) after oxytocin administration. For instance, oxytocin improved performance in the Reading the Mind in the Eyes test in a large sample of healthy male volunteers (111) and enhanced empathetic accuracy in less socially proficient healthy individuals, while it had no effect in highly socially proficient individuals when judging other people's feelings (110). Oxytocin effects have also been reported in regions involved in the processing of emotional states of others, such as the superior temporal gyrus, with increased activations during emotional face processing after oxytocin administration in healthy women (85). In a study by Hurlemann et al. (105), however, oxytocin only facilitated emotional empathy (measured by self-report) and did not have an effect on cognitive empathy in the Multifaceted Empathy Test.

In summary, studies have mainly focused on oxytocinergic modulation of emotion recognition, and little is yet known about the effects of oxytocin on the inference of other people's intentions and beliefs and thus their theory-of-mind

capacities. Much more research is needed to disentangle the effects of oxytocin on the interwoven components of emotion recognition, emotional and cognitive empathy, theory of mind, self-other differentiation, and emotion regulation, as they play a major role in the psychopathology of borderline personality disorder.

Oxytocinergic Modulation of Affective Pain Processing

Oxytocin synthesis and release from the hypothalamic magnocellular neurons and neurohypophysis are modulated by endocannabinoids (113). Interestingly, patients with borderline personality disorder have recently been shown to exhibit lower serum levels of the endocannabinoids anandamide and 2-arachidonoylglycerol than do healthy subjects (114). An interesting question for future research will be whether oxytocin, in linkage with the endocannabinoid system, mediates abnormalities in affective pain perception in borderline personality disorder—all the more so because 2-arachidonoylglycerol induces analgesia (115) and the endocannabinoid receptor CB₁ plays a key role in the anti-hyperalgesic effect of oxytocin in a mouse model (116). The endocannabinoid system is also involved in brain circuits that modulate emotion regulation and reward processes and thus might have additional effects on abnormal biobehavioral mechanisms in borderline personality disorder.

Oxytocin and Borderline Personality Disorder

The first two pilot studies reporting an oxytocin effect in borderline personality disorder were published in 2011. Simeon et al. (117) found that oxytocin may attenuate dysphoric emotional and salivary cortisol responses to social stress in a small, mixed-gender sample of 14 patients with borderline personality disorder and 13 healthy volunteers who received either oxytocin or placebo. Contrary to previous studies, no effects were observed in the healthy sample. The results of a second study by the same group (118), again consisting of 14 patients with borderline personality disorder and 13 healthy volunteers, indicate that in patients, oxytocin may decrease trust and the likelihood of cooperative responses in a financial trust game. The finding of reduced financial trust in patients after oxytocin administration was supported by a study by Ebert et al. (119) in a cross-over design with 13 patients with borderline personality disorder and 13 healthy volunteers. Despite the small sample sizes, which limit the interpretation of these studies, the results suggest that oxytocin may have different effects on patients with borderline personality disorder, depending on chronic interpersonal insecurities, and possible differences in the oxytocin system regulation. This is in line with an “interactionist model” proposed by Bartz et al. (87), who emphasized the moderating role of contextual factors and interindividual differences in oxytocinergic modulations of social cognition and behavior. For the study of borderline personality disorder, interindividual differences in rearing conditions, including early-life maltreatment and attachment style (120), appear to be of particular significance, as more than 90% of patients with

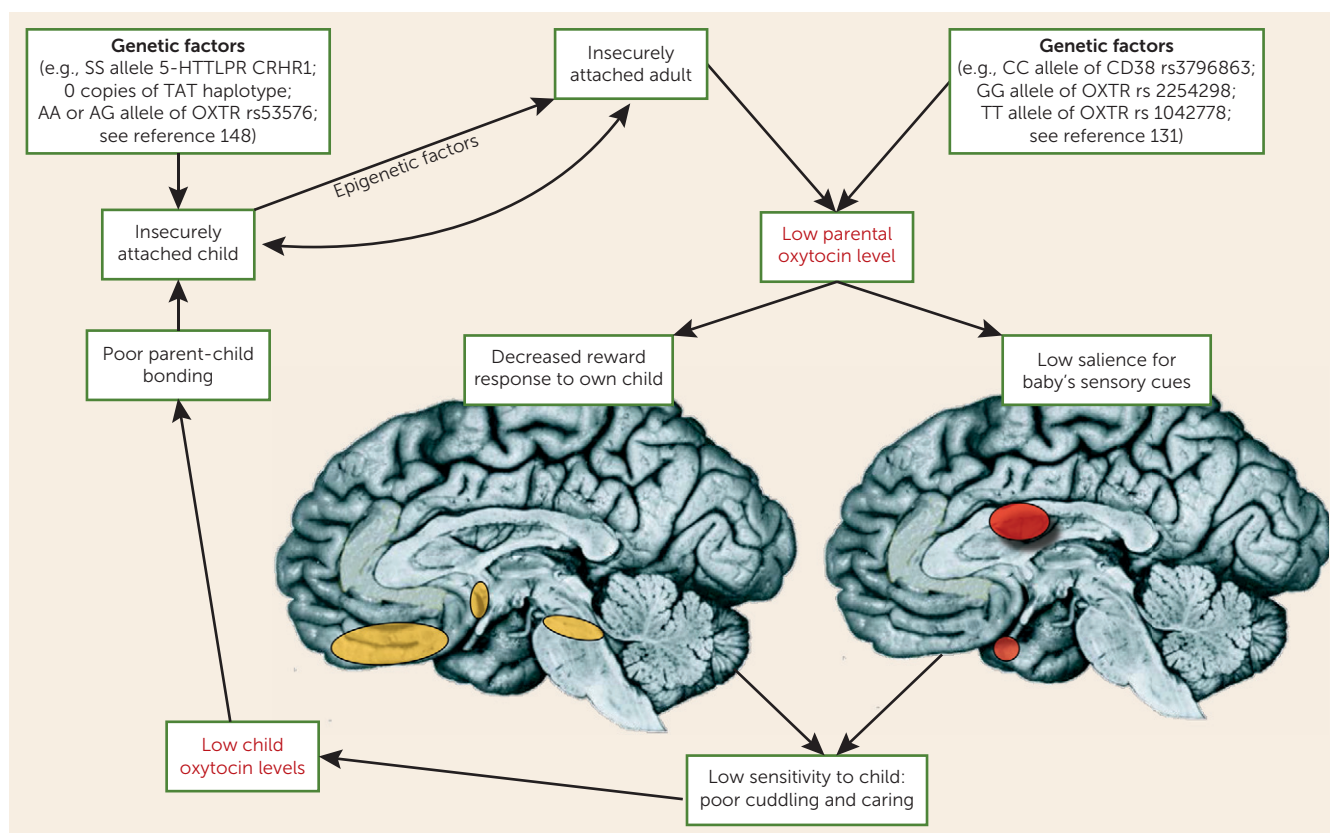
borderline personality disorder show insecure attachment classifications, with a high frequency of unresolved attachment representations. Interestingly, an additional data analysis in one of the above-reported studies (118) revealed that across patients with borderline personality disorder and healthy volunteers, oxytocin increased cooperative behavior for high-anxious, low-avoidant participants but decreased cooperation for high-anxious, high-avoidant participants. Differences in acute stressors (121); comorbid disorders, such as posttraumatic stress disorder (122); treatment experiences; levels of endogenous oxytocin (see below), vasopressin, cortisol, and/or testosterone (30); and variations in the activity or function of the oxytocin and vasopressin receptor genes may be particularly relevant modulators of oxytocin effects.

To date, two studies have investigated the effects of intranasal administration of oxytocin on the emotional stimulus processing. Brüne et al. (123) compared 13 patients with borderline personality disorder and 13 healthy volunteers, using a dot-probe task to examine attentional biases to happy and angry faces. Oxytocin was found to attenuate avoidant reactions to angry faces in patients with borderline personality disorder. Recently, our group provided first evidence that oxytocin has the potential to diminish threat hypersensitivity in borderline personality disorder (124). In a placebo-controlled double-blind group design, 40 female patients with borderline personality disorder and 41 healthy women took part in a combined eye-tracking and fMRI emotion classification experiment. In this task, patients showed more and faster initial fixation changes to the eyes of very briefly presented (150 ms) angry faces, which was associated with increased activation of the posterior amygdala. Oxytocin reduced posterior amygdala hyperactivity as well as the attentional bias toward socially threatening cues (i.e., the eyes of angry, but not fearful or happy faces) in patients.

Hence, there is limited evidence for beneficial effects from exogenous oxytocin administration in borderline personality disorder, with reports of reduced amygdala-driven threat hypersensitivity and decreased avoidant behavior. Nevertheless, much more research is needed to address moderating influences of gender and interindividual differences in trait variables, attachment style, and social functioning. It also remains unclear whether borderline personality disorder is related to dysfunction in the oxytocin receptors that may yield greater binding of oxytocin to vasopressin receptors and hence could also lead to adverse effects if administered in larger doses or on a regular basis. These questions need to be addressed in animal models and large genetic studies.

EARLY MALTREATMENT, PARENTING, OXYTOCIN, AND IMPACTS ON SOCIAL DEVELOPMENT

From the few studies that have shown beneficial effects of oxytocin on functional domains in borderline personality disorder, we do not conclude that these are disorder-specific effects, but rather regard these effects to be common to a host

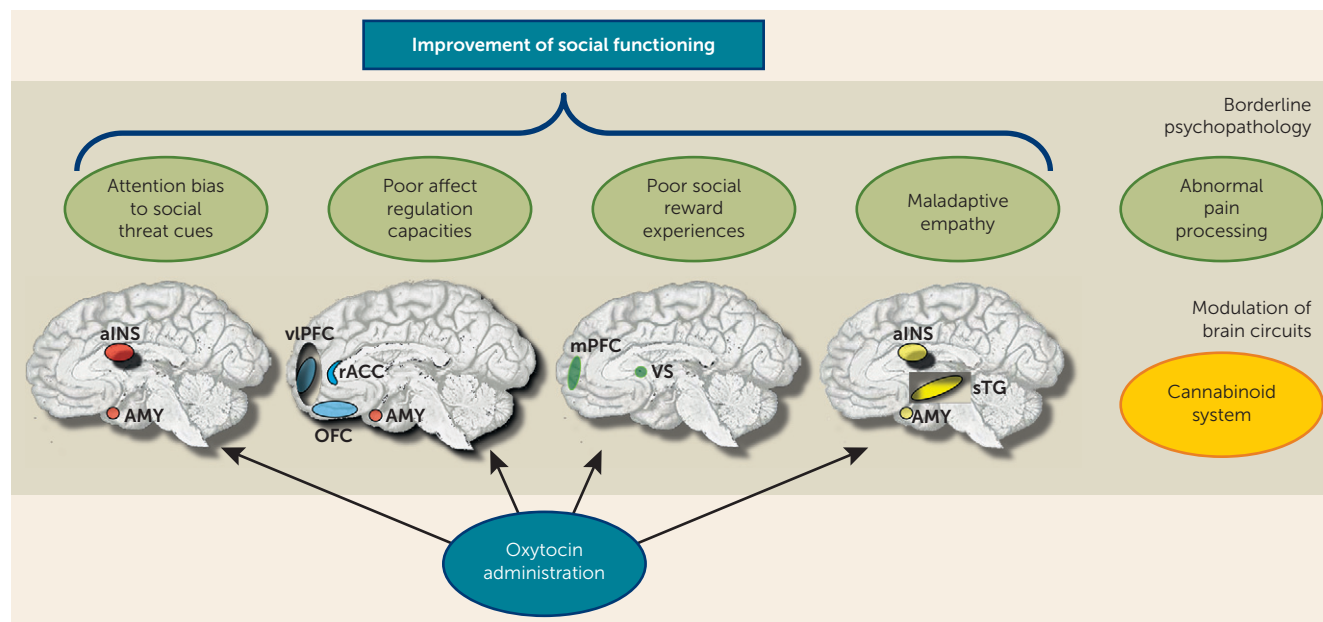
FIGURE 1. Model of the Implications of a Dysfunctional Oxytocin System on Parent-Child Bonding


of psychiatric disorders in which early-life stress and disturbed parent-infant attachment trigger abnormal biobehavioral mechanisms as described above. Borderline personality disorder appears to be an exemplary disorder for studying the effects of unsuccessful parent-child bonding on the oxytocinergic system, with an impact on the development of brain circuits underlying adaptive affect regulation and social cognition.

During pregnancy, estrogen and progesterone levels rise, with estrogens priming the brain for synthesis of oxytocin and oxytocin receptors. At the end of pregnancy, a sudden drop in progesterone level signals the upcoming parturition and further enhances brain sensitivity to oxytocin and increases induction of oxytocin receptors (for a review, see reference 103), contributing to preparing mothers for the establishment of the early mother-infant bond (for a review, see reference 125). In correspondence with the major role played by oxytocin in parenthood (also see reference 126), peripheral concentrations of oxytocin in the serum or saliva have been shown to be positively correlated with sensitive and affectionate dyadic interactions of mothers and fathers with their child (127); this means that the higher the parents' oxytocin level, the more they will touch and cuddle their baby. Notably, neuronal activities in gender-specific brain circuits that mediate parental behavior have been shown to correlate with oxytocin concentrations in mothers and fathers (128). Interestingly, oxytocin not only exerts effects on early

caregivers but plays a major role in establishing the early attachment relationship on both sides of the dyad. In line with this, oxytocin administration to fathers has been found to augment peripheral concentrations not only in the fathers themselves but also in their 5-month-old infants with whom they had entered into social play (129). More specifically, a cross-generation gene-by-environment effect was recently detected by the same research group (130), with low child oxytocin levels being predicted by poor maternal care in infancy in interaction with a maternal high-risk CD38 allele that is associated with reduced release of oxytocin from hypothalamic neurons (130). In addition, infants' social reciprocity with a friend at age 3 was predicted by the child's peripheral oxytocin concentration, by the mother's oxytocin levels and oxytocin-related genes, and by mother-child bonding. These findings suggest that maternal care in interaction with oxytocin shapes the infant's affiliative biology and actual social interaction capacity.

Long-lasting effects on children's development occur because during this early co-regulation, neural links are rapidly developing in brain circuits underlying emotional processing, cognitive empathy, and social reward, thus involving limbic structures, that is, the amygdala, the striatum, the ventral tegmental area, and the hippocampus, and their connections with the prefrontal cortex (e.g., the medial orbitofrontal cortex), all of which have a high density of

FIGURE 2. Model of the Significance of the Oxytocin System on Biobehavioral Mechanisms Underlying Borderline Psychopathology^a

^a aINS=anterior insula; AMY=amygdala; vIPFC=ventrolateral prefrontal cortex; rACC=rostral anterior cingulate cortex; OFC=orbitofrontal cortex; mPFC=medial prefrontal cortex; sTG= superior temporal gyrus; VS=ventral striatum.

oxytocin receptors (131). It has been hypothesized that epigenetic processes play a major role in the long-lasting effects of early attachment relationships on brain functioning and that differential methylation of the oxytocin receptor gene might provide a particularly significant mechanism for explaining individual differences in social behavior (for a review, see reference 132).

On the basis of these data on the biology of parenting, one might speculate that decreased serum concentrations of oxytocin in patients with borderline personality disorder compared with healthy subjects (133)—probably in interaction with adverse genetic disposition—result from early maltreatment, which has been frequently reported in borderline personality disorder (134), and correlated with oxytocin levels in this study (133). This assumption is supported by data showing lower cerebrospinal concentrations of oxytocin in individuals with a history of early traumatization (135). Low oxytocin concentrations may increase the risk of poor social reciprocity in the adult life of individuals with borderline personality disorder, may contribute to threat hypersensitivity, and may impede affect regulation capacities and experiences of social reward and support. Thus, oxytocin may be an important mediator of the intergenerational transmission of early adversities in borderline personality disorder (for a review, see reference 136). This conclusion is supported by data showing that mothers with secure attachment exhibited a higher oxytocin response while interacting with their 7-month-old child compared with mothers with insecure/dismissing attachment, and oxytocin response was associated with greater neuronal activity in the reward circuit while the mothers were viewing their own child smiling and crying (137). Figure 1 provides

a model of the implications of a dysfunctional oxytocin system on parent-child bonding, although its significance for borderline personality disorder remains speculative.

IMPLICATIONS FOR TREATMENT WITH OXYTOCIN OR OXYTOCIN AGONISTS

Although standard psychiatric medications (antidepressants, antipsychotics, mood stabilizers) are known to exert effects on brain circuits significant for the understanding of borderline personality disorder—e.g., selective serotonin reuptake inhibitors (SSRIs) may increase the functional connectivity in the prefrontal-limbic circuit and decrease limbic activity in response to negative stimuli (138), and antipsychotics may modulate the prefrontal output to basal ganglia circuits (for a review, see reference 139)—they are of limited benefit in treating borderline personality disorder (140, 141). Psychotherapy is recommended as the primary treatment for the disorder (142), with evidence-based psychotherapy programs having common and differential treatment targets. Dialectical behavior therapy has a major focus on improving affect dysregulation via modulation of amygdala activity and prefrontal-limbic connectivity (143; R. Schmitt et al., unpublished 2015 data), mentalization-based therapy primarily targets attachment and empathy processes (144), and schema-focused therapy deals with rejection hypersensitivity and affect dysregulation (145).

The development of more effective pharmacotherapy that may boost or enhance the effects of psychotherapy is urgently needed for this highly disabling psychiatric disorder. Although research on the therapeutic potential of oxytocin is in

its infancy, this review suggests that oxytocin may exert effects on at least five biobehavioral mechanisms that are central to borderline psychopathology (Figure 2). Indeed, there is currently at least one ongoing study that addresses oxytocin's potential to enhance dialectical behavior therapy effects in patients with borderline personality disorder (ClinicalTrials.gov identifier: NCT01243658). Thus, we recommend that in future research, the therapeutic potential of oxytocin be explored in terms of the following aspects: 1) effects on social hypersensitivity and threat hypersensitivity, in particular through modulation of the salience circuit, 2) effects on affect dysregulation by modulating the prefrontal-limbic circuitry, 3) effects on social reward experiences mediated in the mesolimbic circuit, 4) probable effects on empathy and related brain circuits, and 5) effects on abnormal pain processing by effects on the cannabinoid system. Administration of oxytocin immediately before a psychotherapeutic session might enhance the session's effects by improving the therapeutic bond through decreased social threat hypersensitivity, improved social cognition, and facilitated experiences of social support and reward. In addition, oxytocin might play a role in the prevention of borderline personality disorder and other disorders related to early maltreatment, as it may enhance the efficacy of psychosocial interventions in young parents in need, with the aim of improving the quality of the early infant-caregiver relationship. However, before we can think of applying oxytocin in treatment, several challenges must be addressed, including the development of in vivo assays to characterize the distribution and binding of oxytocin receptors and drug delivery and dosage issues.

Our aim in this review was to illustrate that borderline personality disorder, because of its three major domains of dysfunction (affect dysregulation, behavioral dyscontrol, and interpersonal hypersensitivity) and its etiological roots in maladaptive parent-infant attachment, can serve as an exemplary disorder for understanding disease mechanisms involving the oxytocinergic system and inspiring the development of innovative treatments that target these functional domains. It is an interesting question for the future whether disease mechanisms related to the oxytocinergic system are specific to borderline personality disorder or are common to a variety of psychiatric disorders that occur as sequelae of early-life maltreatment.

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