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Personality Disorders (M Goodman, Section Editor)

The Use of Oxytocin in Personality Disorders: Rationale and Current Status

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Opinion statement

Impaired interpersonal functioning is a core feature of borderline, schizotypal, and avoidant personality disorders characterized by abnormal social information processing; however, pharmacologic treatments targeting social cognition are currently lacking. Oxytocin is a novel treatment for social cognitive abnormalities that has yielded promising preliminary results in the autism spectrum, social anxiety disorders, and schizophrenia. Here, we describe the main components of social cognition and review the biology of the oxytocinergic system and the hypothesized models and mechanisms through which exogenous oxytocin modulates social cognition. We then review the studies on the effect of oxytocin administration on social cognition and their application to the treatment of personality disorders. We also review the preliminary evidence supporting the use of oxytocin as an adjunct to non-pharmacologic interventions. Finally, we describe the main challenges that need to be addressed to be able to use oxytocin effectively in clinical populations.

Introduction

Different classes of drugs, including antidepressants, anxiolytics, antipsychotics, and mood stabilizers, alone or in combination, are widely used in the treatment of personality disorders. The currently available pharmacotherapies are effective in treating some of the core symptoms of personality disorders, and comorbid disorders such as major depressive episodes, but have only modest effects on the severity of the personality disorder as a whole [1–4].

Several evidence-based psychotherapies remain the first line of treatment for personality disorders. For example, dialectical behavioral therapy, mentalisation-based treatment, and transference-focused therapy are used to treat borderline personality disorder (BPD) [5]. However, their long duration, high cost, intense resource use, and staff training requirements limit the utility and availability of psychotherapeutic interventions for all patients with personality disorders.

Social cognition abnormalities have only recently been recognized as a core feature of personality disorders, and, despite clinical significance, lack pharmacologic treatment at the moment. Social cognition is not only a crucial component of interpersonal relationships [6] but it is also a predictor of success in psychotherapeutic interventions [7].

Moreover, social cognitive abnormalities are closely correlated with illness severity [8], disability [9], higher relapse rates [10], and poor prognosis, warranting early intervention.

Oxytocin is a neuropeptide hormone, available for intranasal administration, that provides promising results as a potential treatment for social cognitive deficits across diagnoses, including several of the personality disorders [11••], Class I.

Definitions and components of social cognition

Social cognition may be defined as the "psychological processes that enable individuals to take advantage of being part of a social group" [12]. It is essential to maintaining social relationships [13]. This complex multidimensional construct can be summarized into five areas [14–17] with great overlap, both conceptually and through the involvement of common interacting neural circuits subserving social information processing.

- *Theory of mind (ToM)*, also called mentalization or mentalizing, is the ability to represent others' mental states and infer other's feelings, intentions, and beliefs. It is closely related to the Research Domain Criteria (RDoC) [18] subconstruct "Understanding Mental States," within the Perception and Understanding of Others Construct in the Social Processes Domain.
- *Social perception* refers to the ability to comprehend complex or ambiguous social roles and rules, based on nonverbal and paraverbal cues [19, 20]. It also includes the ability to understand the nature of relationships (professional, friendly, romantic).
- *Social knowledge* refers to the ability to determine what rules to adhere to in social contexts [14].
- *Emotion recognition* indicates the ability to recognize emotions by facial expression or vocal prosody. Emotion recognition closely overlaps with the RDoC [18] subconstruct "Reception of Facial Communication," within the Social Communication Construct in the Social Processes Domain.
- *Attributional style* refers to the tendency to assign causality to events. Healthy individuals demonstrate a self-serving bias, tending to attribute positive events to personal internal factors while attributing negative ones to external causes [13].

Treatment

Oxytocin has prosocial, anxiolytic, and social cognitive-enhancing effects [11••], Class I, [21–23, 24••], Class I. The positive effects of exogenous intranasal oxytocin in disorders characterized by severe social cognitive deficits, such as the autism spectrum, have been consistently demonstrated in a growing number of clinical trials and a meta-analysis [11••], Class I. Preliminary data

also suggest that oxytocin may be an effective adjunct treatment, in combination with antipsychotics, in patients with schizophrenia, improving social cognitive impairments and both negative and positive symptoms of the disorder [11••] Class I, [24••] Class I.

Oxytocin is a promising treatment option for personality disorders characterized by abnormalities in social behavior, social cognition, and social information processing, such as schizotypal personality disorder (SPD), BPD, and avoidant personality disorder (AVPD) [25•] Class IV, [26] Class I. In these populations, the abnormalities in social cognition cause significant impairment, and to date, remain untreated through available medication.

Biology and mechanism of intranasal oxytocin

Oxytocin is a neuropeptide hormone synthesized in the paraventricular and supraoptic nuclei of the hypothalamus by magnocellular and parvocellular neurons. Oxytocin is stored in secretory vesicles in axonal terminals in the posterior lobe of the pituitary and is released into the peripheral circulation. Oxytocin exerts effects both locally and through diffuse release into the extracellular space. Multiple aspects of social cognition are modulated by the balance between oxytocin and vasopressin [25•, 27], Class IV.

Intranasal oxytocin is thought to circumvent the blood–brain barrier [11••, 28, 29], Class I [30] and mimic the effects of the peptide naturally present in the brain, modulating regions with a known role in social cognition, such as the amygdala, medial prefrontal cortex, and anterior cingulate cortex [23]. Intranasal oxytocin generally promotes prosociality, e.g., increasing in-group trust and cooperation, and improves social cognitive abilities such as emotion recognition and perception of mental states [11••], Class I.

The mechanism by which oxytocin improves social cognition and behavior is largely unknown, and may be mediated by an increase in salience and attention towards social stimuli [31] and rewarding properties of social stimuli, through interaction with dopaminergic reward circuitry [32]. For example, oxytocin administration increased stimulus-induced pupil dilation, consistent with an increase in attention towards socially relevant stimuli [33, 34].

Additionally, the positive effects of oxytocin may be mediated by a broader reduction in the stress response in social situations. Oxytocin exerts anxiolytic and antidepressant effects through modulating stress reactivity, mediated by interactions with monoaminergic, serotonergic, and corticotrophin-releasing factor systems [27]. Clinical studies indicate that oxytocin reduces limbic and hypothalamic-pituitary-adrenal axis reactivity to social stressors [23, 35, 36], Class I, and that it mediates the anxiolytic and stress-protective effects of positive social interaction [25•], Class IV.

Reduced response to stressful stimuli after oxytocin administration has been observed through functional magnetic resonance imaging as diminished amygdale activation in the presence of stressors, as well as reduced connectivity to the brainstem, resulting in changes in both attention and reactivity to social stimuli [37].

Two theoretical models have been proposed to explain the effect of oxytocin on social cognition. According to the optimizing model, oxytocin enhances social cognitive function and prosociality regardless of baseline social cognitive skills [25•], Class IV. This model is grounded in a biological-evolutionary

model that suggests that oxytocin enhances the perception of cues that are relevant for social interaction and bonding, while decreasing the impact of socially threatening cues [26], Class I, [38•], Class IV.

The interactionist model proposes the existence of an optimal oxytocinergic tone [39•], Class IV. According to this model, the effects of oxytocin administration follow an inverted-u-shaped curve, only enhancing social cognitive function in patients with social cognitive deficits, such as autism and schizophrenia. In the absence of a true deficit, i.e., in disorders characterized by social cognitive distortions and attentional biases, such as BPD [40], Class I, its effects to increase salience and attention to emotional stimuli could be blunted [33], Class I, or result in misinterpretation of social stimuli and/or excessive reaction to social cues [39•], Class IV.

Moreover, the effects of oxytocin on social cognition and behavior appear to be modulated by other factors, such as gender, hormonal status, e.g., menstrual-cycle phase, pregnancy, lactation, menopause, early childhood experiences, and context [39•], Class IV [11••], Class I. For example, the effects of enhanced trust and cooperation of oxytocin are dependent on the perception of 'out of group'. Positive effects of oxytocin may also be diminished in individuals with a lifetime of negative interpersonal experience, having a profound effect on attachment style and epigenetic methylation of structures involved in the oxytocinergic circuitry [11••], Class I.

The effects of oxytocin administration in personality disorders

Borderline personality disorder

Severe deficits in interpersonal and social functioning are a core feature of patients with BPD, who have social cognitive abnormalities causing significant disability [41–43]. Social cognitive abnormalities in BPD include poor mentalizing accuracy due to excessive distorted mentalizing, termed hypermentalization [44, 45], excessive salience of social stimuli with excessive emotional reactions and attention towards social stimuli, and attentional biases towards negatively valenced social stimuli [39•, 46], Class IV [47], Class I [40], Class I. A dysregulation in the oxytocinergic system has been suggested to contribute to the neurobiology of BPD [48], Class IV.

Unlike the results in the autism spectrum or schizophrenia, the effects of intranasal oxytocin in several preliminary studies in patients with BPD have been mixed (see Table 1). On the one hand, oxytocin decreased emotional responses to stress [60], Class I, decreased avoidant reactions and attentional biases to angry facial stimuli [47], Class I, and improved the hypersensitivity to social threat found in BPD patients, resulting in decreased anger and threat-driven aggression [40], Class I.

In contrast, other clinical trials of oxytocin administration in BPD show negative or mixed results, with worsened interpersonal anxiety and decreased cooperative behavior in BPD, in comparison to healthy controls [25•], Class IV [59], Class I [11••], Class I [46], Class I, particularly among those anxiously attached [46] or reporting a history of emotional neglect in childhood [59].

The interactionist model could account for the mixed results observed in BPD, given the social cognitive distortions, e.g., hypermentalization and attentional biases, present at baseline in this disorder [39•], Class IV.

Table 1. Clinical trials of the effect of oxytocin on schizophrenia, as an adjunct to antipsychotics; borderline personality disorder and the social anxiety spectrum

Study	Diagnosis	N	Dosing	Results: Oxytocin vs. Placebo	Design
Averbeck [49]	SCZ	21M	sd 24 IU	+ Improve emotion recognition	rdbpc, co
Davis [50]	SCZ	23M	sd 40 IU	+ Improve understanding of mental states and empathy	rdbpc
Feifel [51, 52]	SCZ	19	3 weeks up to 40 IU bid	+ Decrease symptoms (PANSS, CGI), increase verbal memory (CVLT)	rdbpc, co
Fischer [53]	SCZ	31	sd 24 IU	+ Improve emotion recognition of fearful facial stimuli	rdbpc, co
(Fischer-Shofty et al. [54]	SCZ	35	sd 24 IU	+ Improve social perception of kinship and intimacy	rdbpc, co
Goldman [55]	SCZ	13	sd 10 IU, 20 IU	± Improve emotion recognition only in a subset (20 IU dose in SCZ+PD)	rdbpc, co
Lee [56]	SCZ	28	3 weeks 20 IU bid	± Improve odor identification, decrease negative symptoms in inpatients	rdbpc
Modabbernia [57]	SCZ	40	3 weeks up to 40 IU bid	+ Decrease symptoms (PANSS)	rdbpc
Pedersen [58]	SCZ	20	2 weeks 24 IU/day	+ Improve understanding of mental states; decrease symptoms (PANSS)	rdbpc
Bartz [46]	BPD	14	sd 40 IU	– Decreases trust and cooperation in those anxiously attached	rdbpc
Bertsch [40]	BPD	40F	sd 26 IU	+ Decreases attentional bias (gaze) and amygdala reactivity to angry faces	rdbpc
Brune [47]	BPD	13	sd 24 IU	+ Decreases avoidant reactions and attentional bias to angry faces	rdbpc, co
Ebert [59]	BPD	13	sd 24 IU	– Decreases trust (inversely correlated with childhood emotional neglect)	rdbpc, co
Simeon [60]	BPD	14	sd 40 IU	+ Decreases emotional response, trend level decrease in cortisol response to stress	rdbpc
Dodhia [61]	GSAD	18M	sd 24 IU	+ Normalizes the reduced amygdala-frontal resting-state functional connectivity observed in GSAD	rdbpc, co
Gorka [62]	GSAD	17M	sd 24 IU	+ Enhances integration and modulation of social responses through increased connectivity between amygdala and the bilateral insula and middle cingulate/dorsal anterior cingulate gyrus during processing of fearful faces	rdbpc, co
Guastella [26]	SAD	25M	Four-weekly doses of 24 IU before sessions two to five of weekly group exposure therapy	+ Improved self-perceptions of speech performance and appearance after a speech exposure task	rdbpc
Labuschagne [63]	GSAD	18M	sd 24 IU	+ Attenuates the excessive amygdala response to fearful faces found in GSAD	rdbpc, co

Table 1. (Continued)

Study	Diagnosis	N	Dosing	Results: Oxytocin vs. Placebo	Design
Hall [64]	FXS	8M	sd 24 IU and 48 IU	+ Increased eye gaze frequency and decreased cortisol levels during a social challenge	rdbpc, co
Labuschagne [65]	GSAD	18M	sd 24 IU	+ Attenuates exaggerated cortical response to non-threatening negative social cues	rdbpc, co

BPD borderline personality disorder, *bid* twice daily, *CGI* Clinical Global Impression scale, *CVLT* California Verbal Learning Test, *F* female, *FXS* Fragile X syndrome, *GSAD* generalized social anxiety disorder, *M* male, *N* sample size (cases), *PANSS* Positive and Negative Symptom Scale, *PD* polydipsia, *rdbpc* randomized, double-blind, placebo-controlled, *co* crossover, *SAD* social anxiety disorder, *SCZ* schizophrenia, *sd* single dose, + positive results, – negative results, ± mixed

Adverse childhood experiences and abnormalities in attachment, which likely moderate the effect of oxytocin on social cognition, are often reported among BPD patients. There is a complex interaction between developmental history and parental attachment, genetic variables, and interpersonal context, resulting in differential effects of oxytocin and warranting further research before implementation in this patient population [66], Class IV.

Avoidant personality disorder

Severe deficits in interpersonal relationships characterize AvPD, causing significant disability. Indeed, in a nationally representative sample of US adults, AvPD was significantly associated with disability [67] and with receiving public assistance. This may be related to their avoidance of occupational activities requiring social contact [68].

AvPD and social phobia/social anxiety are highly comorbid and share many overlapping features, including risk factors, neurobiology, and genetic underpinnings. In fact, some hypothesize that AvPD and social phobia may be a single condition or reflect a spectrum of social anxiety. There is a lack of evidence for treatment outcomes in AvPD, and treatment strategies developed for social anxiety/social phobia are extrapolated to treat AvPD. These include medications such as antidepressants or anxiolytics [4, 69], none of which specifically target the core social cognitive dysfunctions, and cognitive behavioral therapy including exposure and social skills training [70].

The social anxiety spectrum is characterized by exaggerated amygdala reactivity to social-emotional stimuli, particularly fear-related stimuli, and abnormal connectivity patterns within a neural circuit, including the amygdala, the medial prefrontal cortex, the insula, and the cingulate cortex, among other areas, subserving social threat processing and emotion regulation [62, 71].

The prosocial and anxiolytic effects of oxytocin make it a promising treatment in the social anxiety spectrum. There is evidence that oxytocin enhances several stages of the conceptual processing of positive social stimuli over social-threat stimuli [38•], Class IV. Oxytocin is known to decrease amygdala activation and decreased coupling to brainstem regions critical to autonomic and behavioral reactions to fear [37, 72]. In healthy volunteers, oxytocin facilitated approach in the presence of social threat stimuli, angry faces [73], Class I.

Oxytocin infusion in rodents predisposes them to overcome the social anxiety induced by defeat (bullying) and demonstrate a preference for prosocial stimuli as opposed to non-social stimuli [74], Class I.

Several studies of oxytocin administration in patients (see Table 1) also suggest that it improves many of the social threat processing abnormalities in social anxiety, suggesting a potential role for intranasal oxytocin in the treatment of disorders within the social anxiety spectrum, including AvPD.

For example, intranasal oxytocin attenuated the excessive amygdala response to fearful faces [63], Class I, and normalized the reduced amygdala-frontal resting-state functional connectivity observed in patients with generalized social anxiety disorder [61], Class I. Oxytocin administration also increased functional connectivity, measured with functional magnetic resonance imaging, between amygdala and the bilateral insula and middle cingulate/dorsal anterior cingulate gyrus during processing of fearful faces in patients with generalized social anxiety disorder. This was interpreted by the authors as an enhancement of integration and modulation of social responses by oxytocin, which may have important prosocial implications in patients with social anxiety spectrum disorders [62].

In patients with generalized social anxiety disorder, oxytocin administration also attenuated the exaggerated cortical hyperactivity to non-threatening negative, but not positive social cues [65], Class I. Moreover, intranasal oxytocin as an adjunct to therapy improved self-perceptions of performance and appearance following a speech exposure task in patients with social anxiety disorder [26], Class I. In male individuals with Fragile X syndrome, who display hyperarousal and extreme eye gaze avoidance in social situations, oxytocin significantly increased eye gaze frequency and decreased cortisol levels during a social challenge [64], Class I.

Given the lack of data in AvPD, studies are needed that examine the effect of intranasal oxytocin as a promising treatment for the social cognitive abnormalities that characterize AvPD. Surprisingly, women have not been included in any of the published studies analyzing the effect of intranasal oxytocin in the social anxiety spectrum. Because the effects of exogenous oxytocin may differ across sexes and are likely moderated by other factors including hormonal status [75], Class I, it is critical to perform studies including both men and women.

Schizotypal personality disorder

SPD is a personality disorder that is part of the schizophrenia spectrum. Data support a continuum from severe chronic schizophrenia to the attenuated schizophrenia-like traits of SPD, sharing genetic, psychophysiologic, and neural underpinnings [76].

Although neurocognitive impairment was identified as a core feature of schizophrenia since the first descriptions of the disorder, social cognition has only become an area of interest in schizophrenia research during the last decade [77]. Patients in the schizophrenia spectrum, including SPD [78] and psychometric schizotypy [79–81], have severe social cognitive abnormalities that have significant effects on functioning [82–84], may cause more disability than psychosis [85–88], are independent from broader cognitive deficits [89–91], and are not adequately treated by currently available medications [89, 92–94].

Social cognitive impairments in the schizophrenia spectrum include decreased emotion recognition [95, 96], low salience/attention towards social-emotional stimuli, e.g., as measured with eye gaze and pupil dilation [97], low amygdala reactivity to emotional stimuli (likely reflecting low salience) [98], and decreased emotional modulation of amygdala reactivity [99].

While current medications are ineffective in treating social cognitive impairment [92, 93], preliminary data suggest that adjunct intranasal oxytocin in patients with schizophrenia treated with antipsychotics improves these social cognitive impairments (see Table 1) [24••], Class I, increasing emotion recognition [49, 54, 55], Class I, understanding of mental states [50, 54, 58], Class I, and empathy [50], Class I, and improving both positive and negative symptoms [51, 56–58], Class I.

Surprisingly, no studies have yet examined the effect of intranasal oxytocin in SPD patients, who are a unique population to test the effect of oxytocin on social cognition in the schizophrenia spectrum without the confounds of psychosis and antipsychotic medications.

Oxytocin as an adjunct for non-pharmacologic interventions

Social cognitive remediation has not been well studied in patients with personality disorders, with some exceptions [100]. Non-pharmacologic interventions for social cognitive deficits have been tested more extensively in patients with schizophrenia, targeting social cognitive components including emotion perception, ToM, and attributional style. Meta-analytic findings examining 19 studies found moderate to large effects on facial affect recognition, with small to moderate effects on ToM and non-significant effects on social cue perception and attributional bias [101], Class I.

Social cognition and interaction training [102] is a relatively recent treatment targeting social cognition with promising results. More recently, oxytocin has been incorporated as an adjunct for social cognitive training in schizophrenia [103], Class I. Participants who received oxytocin demonstrated improved empathic accuracy at the end of the treatment, and 1 month after, compared with the placebo group. These results suggest that combining oxytocin with social cognitive remediation is more effective than social cognitive remediation alone [103], Class I.

Another potential application for oxytocin is in combination with psychotherapy, administered immediately before a session to enhance its effect [26, 104]. Oxytocin may result in enhanced effects of psychotherapy as it leads to improved social cognition, self-perception, and reduced social anxiety. Although the limited preliminary evidence holds promise, systematic studies combining oxytocin and psychotherapy are needed to identify the individual and combined effects, and to explore the neural mechanisms explaining the effects [105•], Class IV.

Conclusion

Oxytocin is a promising treatment for social cognitive impairments across disorders, although further research is warranted to fully understand its effects on social cognition in humans [11••], Class I. Prior to implementing the use of intranasal oxytocin in clinical populations, it is crucial to answer several questions that remain unknown.

First, the models and mechanisms of action of action of intranasal oxytocin, optimal dosing, and effects across disorders and in both men and women need to be tested through dose-finding clinical trials and challenge studies in different populations using multimodal measures of social cognition. Ideally, studies should include different units of analysis to uncover markers of the effect of oxytocin, e.g., brain circuits, psychophysiology, eye tracking, behavioral performance in social cognitive tasks, and measures of social functioning in real-life situations. The bioavailability and distribution in the central nervous system of intranasal oxytocin need to be elucidated, requiring the development of in vivo assays to characterize the distribution of oxytocin receptors in the human brain.

Given that the effect of oxytocin on social cognition is moderated by multiple factors, such as the individual's characteristics, context, and childhood experiences, a particular challenge is to identify those populations that would benefit most from treatment with oxytocin.

Compliance with Ethics Guidelines

Conflict of Interest

Mercedes M. Perez-Rodriguez declares that she has no conflict of interest.
Nicole E. Derish declares that she has no conflict of interest.
Antonia S. New declares that she has no conflict of interest.
This work was performed at the Department of Psychiatry, Icahn School of Medicine at Mount Sinai, and MIRECC at James J. Peters VA Medical Center, Bronx, NY, USA

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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An overview of social cognitive deficits in the schizophrenia spectrum, bipolar and major depressive disorders, and a review of the clinical trials of intranasal oxytocin administration in these disorders.