Social Synchrony and Oxytocin: From Behavior to Genes to Therapeutics

There has been an exponential increase in the emerging literature on the neuropeptide oxytocin in the development of both childhood and adult mental health problems in recent years. One line of research stems from the observation that maternal depression following childbirth may have long-term negative consequences for infant development, through dysfunctional parenting as well as genetic transmission (1). The oxytocin system in the infant brain is exquisitely influenced in early life by parenting behavior through an extragenomic feedback loop that can occur across generations. Maternal oxytocin promotes socially synchronous parenting behaviors, which in turn shape the infant's oxytocin system. Thus, maternal depression may disrupt oxytocin and social synchrony in the mother and subsequently in the infant (2). Further, genetic variations of the oxytocin receptor gene (*OXTR*) influence prosocial behaviors and risk for disorders characterized by disruptions in social synchrony and functioning; the A allele confers resilience to early mothering deprivation, whereas the G allele confers risk for depressive and autism spectrum disorders as well as an avoidant attachment style (3). This has implications for early intervention strategies for childhood disorders resulting from maternal depression.

Another line of research investigates the role of oxytocin in pair bonding and affiliation in animals, translates this to the social cognition symptom domain in humans, and applies it to disorders including autism, social anxiety disorder, schizophrenia, and personality disorders characterized by dysfunctional attachment. Patients with borderline personality disorder ascribe anger to ambiguous facial expressions and have enhanced reactions to threatening social cues along with increased amygdala reactivity. Of note, such patients with borderline personality disorder have high rates of early life trauma, abuse, and neglect, which may lead to vulnerability of the oxytocin system. Since oxytocin can increase trust, improve facial recognition, and shift attention away from negative social information, this raises the question of whether such patients might benefit from oxytocin administration.

In this issue, Apter-Levy et al. (4) examine how oxytocin is dysfunctional in depression and may underpin the effects of maternal depression on child outcomes by utilizing an extreme-case design and a community cohort of women recruited at childbirth and assessed periodically for depression across the first year of the child's life. At 6 years, mothers who were chronically depressed were compared with mothers who had had no depression since childbirth. Of the children of the chronically depressed mothers, 60% displayed axis I disorders, mainly anxiety and oppositional defiant disorders, compared with 15% among the children of the comparison mothers. Lower salivary oxytocin was found in the depressed mothers and in the fathers and children in their families, and the children had lower empathy and social engagement levels. The *OXTR* rs2254298 GG homozygous genotype was overrepresented in depressed mothers and their families and

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correlated with lower salivary oxytocin. Of note, the presence of a single rs2254298 A allele (GA or AA genotype) in depressed mothers markedly decreased the risk of child psychopathology.

This work is important because chronic maternal depression negatively affects child social outcomes and this is a large public health problem, affecting up to 15% of women in the developed world (5). These findings are the first to detail the involvement of genetic and peripheral biomarkers in the oxytocin system in families of depressed mothers. The role of oxytocin in moderating the effects of maternal depression on child psychopathology underscores the potential for oxytocin-based interventions.

In another study reported in this issue, Bertsch et al. (6) measured latency and number of initial, reflexive eye movements by using eye tracking, manual response latencies, and the blood-oxygen-level-dependent (BOLD) response of the amygdala to angry and fearful facial expressions compared with happy expressions. Patients with borderline personality disorder showed more and faster initial fixation changes than healthy women and had more saccades to the eyes of angry faces, combined with greater amygdala activation in response to angry faces, suggesting that such patients show a hypersensitivity to social threat in early, reflexive stages of information processing. Both abnormal behavioral and neural patterns were normalized after oxytocin administration, perhaps through decreases in social threat hypersensitivity and in anger and aggressive behavior. Clinical observations of the subjects are included in the supplemental material for this article. These findings also have relevance for other populations with enhanced threat-driven reactive aggression.

The [oxytocin] system does not manifest a critical developmental window in regard to intervention and can be rescued at any stage of brain development.

Both between-group diagnostic differences and within-group individual differences in response to oxytocin help to place the findings of Apter-Levy et al. (4) and Bertsch et al. (6) in context and to clarify the potential limitations of their work. For example, in patients with autism spectrum disorders (ASDs), my colleagues and I demonstrated an impact of oxytocin on social cognition symptoms (7), such as the ability to lay down social memories related to the emotion recognition in spoken language. Not only do different diagnostic groups (i.e., ASD, borderline personality disorder) manifest different clinical responses to oxytocin (7, 8), but within-group individual responses vary. For example, in typically developing healthy volunteers (9), empathic accuracy in response to oxytocin appears to relate to the baseline severity of social cognition deficits. Even within a group of patients with borderline personality, we have observed different responses based on the domains studied, the design of the study, and the outcome measures selected. Oxytocin improved stress reactivity to a socially observed mental arithmetic task in patients with borderline personality disorder (10) but actually worsened social decision making in these patients, perhaps by shifting focus away from the self toward the other participant, in subjects who already had a pathological focus on others (8).

The oxytocin system plays an important role in the labeling of salience for social information, as well as in conditioned partner preference and social reinforcement learning, all of which contribute to social synchrony. While the oxytocin system in the infant brain is exquisitely influenced by parenting behavior (4), it is of interest that the system does not manifest a critical developmental window in regard to

TABLE 1. Social Cognition Targets for Therapeutics of Child and Adult Mental Health Disorders

Potential Therapeutic Targets	
Social recognition	Social memory
Social reward	Trust
Social affiliation	Social anxiety
Social threat	Negative symptoms and paranoia
Amygdala and fusiform activation	Reactive aggression
Eye gaze	

intervention and can be rescued at any stage of brain development. In considering therapeutic targets for oxytocin within the social cognition domain, a broad range of such symptoms can be gleaned from animal and human studies and applied as potential outcome measures in therapeutic studies (see Table 1). These certainly could be applied to further studies of mental health, social engagement, and empathy in the offspring of women with maternal depression as well as in studies of threat-driven reactive aggression in borderline personality disorder.

Of course, a number of limitations might slow the development of oxytocin as a therapeutic agent in such childhood and adult psychiatric disorders. Some of these hurdles are the inability to deliver the large nine-amino-acid peptide oxytocin in an oral pill form, necessitating another method of delivery, such as an intranasal formulation; the lack of a small-molecule oxytocin receptor agonist suitable for use in humans; the lack of a PET ligand to measure oxytocin receptor binding for central nervous system targeting and for dose optimization in humans; the lack of well-validated social cognition outcome measures for different conditions and age groups; and the lack of proven early efficacy biomarkers that more closely reflect the underlying functioning of this system and are sensitive to change in treatment studies. Another challenge in drug development for these types of conditions is the substantial heterogeneity of our DSM-5 diagnostic disorders. Alternative approaches might include the use of research domain criteria (RDoC) to target the social cognition symptom domain and link such assessment to measures of social brain circuitry, as well as the use of more genetically homogeneous disorders or subgroups whose social deficits are associated with known developmental impairment of the oxytocin system, such as depressed mothers' offspring with the *OXTR* G allele (4) or subjects with Prader-Willi syndrome (who have social cognition impairment and neuropathological deficits of oxytocin neurons). However, ultimately the most promising approach may be to combine psychosocial interventions, tailored to teaching social skills and social decision making for the specific disorder, with the therapeutic use of agents that enhance oxytocin signaling. Such combination treatments might be most important for individuals with early-life vulnerability of this system and/or individuals with genetic vulnerability of this system.

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