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Authors
Bradley, Ellen R
Woolley, Joshua D

Publication Date
2017-09-01

DOI
10.1016/j.neubiorev.2017.05.007

Peer reviewed

Published in final edited form as:
Neurosci Biobehav Rev. 2017 September ; 80: 36–56. doi:10.1016/j.neubiorev.2017.05.007.

Oxytocin effects in schizophrenia: reconciling mixed findings and moving forward

Ellen R. Bradley and **Joshua D. Woolley**
Department of Psychiatry, University of California, San Francisco, 401 Parnassus Avenue, San Francisco, CA 94143

Abstract

Schizophrenia is a severe mental illness that causes major functional impairment. Current pharmacologic treatments are inadequate, particularly for addressing negative and cognitive symptoms of the disorder. Oxytocin, a neuropeptide known to moderate social behaviors, has been investigated as a potential therapeutic for schizophrenia in recent years. Results have been decidedly mixed, leading to controversy regarding oxytocin's utility. In this review, we outline several considerations for interpreting the extant literature and propose a focused agenda for future work that builds on the most compelling findings regarding oxytocin effects in schizophrenia to date. Specifically, we examine underlying causes of heterogeneity in randomized clinical trials (RCTs) conducted thus far and highlight the complexity of the human oxytocin system. We then review evidence of oxytocin's effects on specific deficits in schizophrenia, arguing for further study using objective, precise outcome measures in order to determine whether oxytocin has the potential to improve functional impairment in schizophrenia.

Keywords

Oxytocin; schizophrenia; negative symptoms; social cognition

1. Introduction

Schizophrenia is a severe neurodevelopmental disorder that affects nearly 1% of the population worldwide (McGrath et al., 2008) and results in marked functional impairment. In recent years, the neuropeptide oxytocin, known to play a key role in bonding and social behavior, has been heralded as an important player in the etiology, symptom severity, and possible treatment of schizophrenia. Interest in this area of research stems from numerous studies suggesting pro-social effects of intranasal oxytocin in both non-clinical and clinical human populations. However, initial enthusiasm about oxytocin has now given way to doubt

Correspondence: Name: Ellen R. Bradley, ellen.bradley@ucsf.edu, Phone: (415) 476-7334, Mail: 4150 Clement St, San Francisco CA 94121.

Conflict of interest statement: The authors declare that they have no conflicts of interest.

and controversy. Mounting evidence suggests that the oxytocin system is highly complex and has multifaceted influences on behavior. The human oxytocin literature is limited by small sample sizes, failures to replicate (Nave et al., 2015), disputed statistical approaches (Conlisk, 2011; Walum et al., 2015), incomplete understanding of pharmacodynamics (Leng and Ludwig, 2015), possible publication bias (Lane et al., 2016), and variable study design. The subset of this literature focused on schizophrenia is limited by the same challenges (Oya et al., 2015). As a result, understanding of oxytocin's role in schizophrenia remains insufficient and we continue to lack consensus regarding its place, if any, in future treatment protocols.

Others have already published thorough and excellent reviews regarding oxytocin and schizophrenia (Bartholomeusz et al., 2015; Feifel et al., 2015; K. Macdonald and Feifel, 2012; Meyer-Lindenberg et al., 2011). In this review, we aim to contribute to the existing body of work in a few specific ways. First, we summarize the literature on oxytocin effects on positive and negative symptoms of schizophrenia and explore potential causes of heterogeneity in these studies, including study design factors as well as individual-level factors such as antipsychotic dosage. Second, we review evidence of oxytocin effects on social cognition and other deficits in schizophrenia, arguing that these areas warrant further study. Specifically, we highlight promising early findings regarding oxytocin's effects on mentalizing, as well as on non-social cognition, facial expressivity, and olfaction. Finally, we propose an agenda for future research, emphasizing the importance of more objective, precise outcome measures in order to rigorously characterize oxytocin's role in schizophrenia and explore its utility as a treatment.

2. Functional impairment in schizophrenia

Schizophrenia is characterized by three symptom domains: positive, negative, and cognitive (American Psychiatric Association, 2013). Positive symptoms include disorganized behavior, delusions, and perceptual aberrations such as auditory hallucinations. Negative symptoms are a multi-dimensional construct, referring to a cluster of deficits that affect motivation (asociality, avolition, anhedonia) and emotional expressivity (alogia, blunted affect) (Blanchard and Cohen, 2006). Cognitive deficits span multiple areas, affecting both social (Green et al., 2015) and non-social (Green and Harvey, 2014) domains. Together, these symptoms make schizophrenia a particularly devastating illness that ranks among the top 25 leading causes of disability worldwide (Chong et al., 2016) and costs over $60 billion annually in the U.S. alone (Marcus and Olfson, 2008). Affected individuals suffer from high levels of unemployment, limited ability to function independently, and social isolation (World Health Organization, 2008). These impairments lead to productivity losses that are the greatest contributor to the overall societal cost of schizophrenia (Wu et al., 2005).

Unfortunately, the functional impairment associated with schizophrenia has changed little over the past several decades (Hegarty et al., 1994; Jääskeläinen et al., 2013). Although there is widespread use of antipsychotic medications to treat the illness, these medications typically only ameliorate positive symptoms and fail to improve negative or cognitive symptoms (Carpenter and Koenig, 2008; Fusar-Poli et al., 2015; Kirkpatrick, 2000). Developing treatments to improve negative and cognitive symptoms in schizophrenia is

essential, as severity of impairment in these domains is consistently associated with quality of life and functional outcomes (Mancuso et al., 2011; McGlashan and Fenton, 1992; Rabinowitz et al., 2012). Given that the costs associated with psychiatric illness continue to escalate (Bloom et al., 2012) while development of new therapeutics in the field has slowed (Hyman, 2012; Miller, 2010), investigating novel potentially effective treatments is a critical task to reduce morbidity.

3. The promise of oxytocin and current challenges

Oxytocin, a highly conserved neuropeptide produced in the hypothalamus, is widely recognized as a moderator of affiliation, stress, memory, and learning in animals and humans (Caldwell, 2012; Churchland and Winkielman, 2012; Sarnyai and Kovács, 2014). Research involving administration of oxytocin has increased dramatically over the last decade, and studies in non-human primates demonstrating that intranasal oxytocin can elevate oxytocin concentrations in the cerebrospinal fluid (CSF) (Chang et al., 2012; Dal Monte et al., 2014; Modi et al., 2014a) have supported the widespread adoption of intranasal administration in human populations. Administration of a single dose of oxytocin to healthy individuals has been shown to improve retention of social information (Guastella et al., 2012), reduce anxiety associated with social threat (Meyer-Lindenberg et al., 2011), facilitate interpretation of faces expressing complex mental states and social emotions (Domes et al., 2007; Leknes et al., 2013), and promote trust during interpersonal economic transactions with human (versus computer) partners (Kosfeld et al., 2005). Neuroimaging studies have implicated oxytocin in a variety of social brain processes and shown that the amygdala, medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), insula, and temporal regions are modulated by exogenous oxytocin (Adolphs, 2009; Bethlehem et al., 2013; Wigton et al., 2015a). Oxytocin has also been linked with non-social cognitive processes, such as spatial and episodic memory and cognitive flexibility (Chini et al., 2014). These promising findings have generated enthusiasm for oxytocin's potential as a therapeutic in multiple psychiatric disorders.

A dramatic rise in the number of oxytocin studies in clinical populations over the past decade reflects this enthusiasm (Quintana et al., 2015b). In addition to targeting deficits in schizophrenia, oxytocin has been investigated as a treatment for deficits in autism (Alvares et al., 2016; Ooi et al., 2016; Guastella and Hickie, 2016), alexithymia (Luminet et al., 2011), Prader-Willi Syndrome (Einfeld et al., 2014; Tauber et al., 2011) and social anxiety (Guastella et al., 2009; Labuschagne et al., 2010; Tabak et al., 2016). Results of these clinical studies have been notably inconsistent, however. A growing body of evidence now suggests that oxytocin's effects are more complex than previously thought: rather than being simply “pro-social,” it appears to modulate social interaction in a context-specific manner (Bartz et al., 2011) that is impacted by individual differences (K. Macdonald and Feifel, 2012; Tabak, 2013). In addition, there is debate about intranasal oxytocin's ability to consistently reach neural targets, lack of clarity about its pharmacodynamics (Bakermans-Kranenburg and van I Jzendoorn, 2013; Leng and Ludwig, 2015; Quintana and Woolley, 2015), and incomplete understanding of oxytocin receptor distribution in the human brain (Freeman and L. J. Young, 2016). Perhaps not surprisingly, there have been recent failures to replicate some of the early oxytocin findings in healthy humans (Nave et al., 2015). These

issues present major challenges to investigating oxytocin's effects in schizophrenia, and have tempered the excitement that followed early work. Still, given oxytocin's critical role in socialization and the marked impairment that results from schizophrenia-associated deficits, tackling such challenges may prove to be a worthwhile effort.

4. Oxytocin and the pathophysiology of schizophrenia

Evidence from animal and human models suggests that oxytocin system dysregulation may play a role in the pathophysiology of schizophrenia. Results from rodent studies suggest that oxytocin could influence both positive (Caldwell et al., 2009; Feifel and Reza, 1999) and negative symptomatology (Meziane et al., 2015; Peñagarikano et al., 2015) (for a review see Feifel at al. (2015)). One neurofunctional model posits that abnormal oxytocinergic and dopaminergic signaling in the amygdala influences emotional salience processing, potentially leading to some of the social cognitive deficits observed in schizophrenia (Rosenfeld et al., 2010). Neuroimaging studies have shown that the amygdala and other social brain regions such as the PFC as well as the temporal gyri and sulci are modulated by exogenous oxytocin in healthy individuals (for a review see Bartholomeusz et al. (2015)). Taken together, these findings suggest a relationship between the oxytocin system and social brain function that may have important implications for treatment of schizophrenia.

Understanding of the link between impairments in schizophrenia and endogenous oxytocin system functioning, however, remains limited. Multiple studies have examined central and peripheral oxytocin levels in individuals with schizophrenia, with mixed results. CSF oxytocin levels correlated with negative symptoms in one study (Sasayama et al., 2012), but another found no difference in levels between individuals with and without schizophrenia (Glovinsky et al., 1994). Others have observed correlations between plasma oxytocin levels and facial affect identification (Goldman et al., 2008; Rubin et al., 2011), perception of emotion in dynamic body expressions (Strauss et al., 2015b), and less severe negative symptoms (Kéri et al., 2009) in schizophrenia. However, elevated plasma oxytocin levels in individuals with schizophrenia have also been associated with more severe positive symptoms (Rubin et al., 2014; Walss-Bass et al., 2013) and social cognitive impairment (Walss-Bass et al., 2013). Moreover, the utility of peripheral oxytocin measurement has been called into question: it is unclear whether plasma levels consistently reflect levels in the brain (Carson et al., 2014; Kagerbauer et al., 2013; Takagi et al., 1985). Thus, though the oxytocin system may play an important role in terms of etiology and symptom severity, its relationship with the deficits associated with schizophrenia is far from clear.

5. Oxytocin effects on positive and negative symptoms of schizophrenia

Despite this lack of clarity, a number of studies have investigated oxytocin's ability to treat symptoms of schizophrenia (see Table 1). The majority of RCTs conducted thus far have assessed the effects of intranasal oxytocin on positive and negative symptoms, with mixed results. In a within-subject cross-over study of 15 outpatients, Feifel et al. (2010) found improvement in both positive and negative symptoms after three weeks of twice daily 40 IU doses of oxytocin. Pedersen et al. (2011) found significant within-subject improvement in positive symptoms, paranoia, and general psychopathology in the oxytocin group after two

weeks of 24 IU twice daily in a between-subject study of a mixed sample of 20 inpatients and outpatients. Similarly, Lee et al. (2013) administered 20 IU twice daily to a sample of 28 inpatients and outpatients in a between-subject study. They found that oxytocin improved negative symptoms only in the subset of inpatient participants. Modabbernia et al. (2013) administered 40 IU twice a day in a between-subject study to a sample of 40 inpatients for eight weeks, and found that oxytocin improved both positive and negative symptoms. Gibson et al. (2014) evaluated the effects of six weeks of twice daily 24 IU of oxytocin in fourteen outpatients, finding a significant reduction in negative symptoms in the oxytocin group relative to placebo. Davis et al. (2014) and Cacciotti-Saija et al. (2015) both investigated the impact of oxytocin combined with social cognition training. Davis et al. (2014) administered 40 IU of oxytocin twice per week and conducted social cognitive training sessions in 27 individuals with schizophrenia in a between-subject study. The authors found no significant oxytocin effects on symptoms post-treatment or at one month follow-up, though all testing occurred off of oxytocin. Cacciotti-Saija et al. (2015) investigated the effect of twice-daily administration of 24 IU in a cohort of 52 patients diagnosed with an early psychotic illness in a between-subject study, and saw no oxytocin-induced improvements in symptoms after six weeks of treatment.

A meta-analysis of these RCTs (Oya et al., 2015) with a combined sample size of N=206 found that oxytocin was superior to placebo only on a subset of general symptom measures, and not on positive or negative symptoms specifically. Significant heterogeneity among studies was noted, however, and the authors emphasized the need for further work. Dagani et al. (2016) subsequently conducted the longest trial to date, an 8-month within-subject study in 32 outpatients with a relatively short duration of illness (<11 years). They found no treatment effects on negative or positive symptoms. Recently, a second meta-analysis (Williams and Burkner, 2016) used a Bayesian approach to analyze all eight longitudinal RCTs conducted thus far. With a combined sample size of N=238, the authors found no effects on either negative or positive symptoms (again noting significant heterogeneity). Finally, in addition to these longitudinal RCTs, one single-dose, between-subject study has evaluated clinical symptoms: Davis et al. (2013) found no effect of 40 IU of oxytocin on symptom severity in a sample of 23 outpatients. In summary, while early work was promising, recent findings regarding oxytocin's effects on clinical symptoms of schizophrenia have generally been discouraging with multiple studies failing to find meaningful impact.

6. Potential sources of heterogeneity in extant studies

The mixed results described above have made it challenging to draw conclusions about oxytocin's potential to improve positive and negative symptoms of schizophrenia. Multiple authors have made the important observation that small, underpowered studies may make it difficult to detect any effects of oxytocin (Oya et al., 2015; Shilling and Feifel, 2016; Williams and Burkner, 2016). In addition to these limitations, several moderating factors arising from study design and from differences at the individual level appear to modulate oxytocin's influence. These factors are critical to consider as potential sources of the heterogeneity between and within extant studies. Below, we summarize study and individual-difference factors that may significantly influence results.

6.1 Study factors

Use of symptom rating scales—An identified challenge in the meta-analyses described above (Oya et al., 2015; Williams and Burkner, 2016) is synthesizing outcomes generated by the variety of metrics used across studies. The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) is the most established scale to track changes in symptom severity schizophrenia (Obermeier et al., 2010) and has been used most frequently in the literature. The PANSS is conducted by a clinician using a semi-structured interview and consists of a total of 30 items divided into negative, positive, and general psychopathology subscales (the general psychopathology subscale is a collection of non-specific symptoms distinct from the positive and negative categories) (Kay et al., 1987). To date, four oxytocin studies have assessed schizophrenia symptoms using the PANSS (Feifel et al., 2010; Gibson et al., 2014; Modabbernia et al., 2013b; Pedersen et al., 2011a). Two others (M. C. Davis et al., 2014a; Lee et al., 2013) have used the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), an 18-item instrument used to assess general psychopathology. The Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984), 25-item tools that evaluate symptom factors using a Likert scale, have also been used (Lee et al., 2013) (Cacciotti-Saija et al., 2015). Finally, one study (M. C. Davis et al., 2014a) used the Clinical Assessment Interview for Negative Symptoms (CAINS), a 13-item, interview-based tool (Kring et al., 2013) to assess symptoms. Despite significant overlap in terms of content, these instruments are distinct—there are no agreed-upon methods to compare or convert scores between any of them. Even the PANSS and BPRS, which contain several identically-named items, are not interchangeable (BELL et al., 1992). Use of these different instruments therefore presents a challenge to effectively comparing outcomes across studies.

Furthermore, clinical assessment tools themselves may limit our ability to adequately capture the effects of oxytocin in schizophrenia. The widely-used PANSS, for instance, has several drawbacks including a 7-point rating scale that may not reflect clinically meaningful change (e.g., examiners may not actually be able to distinguish between auditory hallucinations that are a “4 - moderate” versus a “5 – moderate severe” in severity) (Levine et al., 2011), item redundancy (Lehoux et al., 2009), incomplete measurement of positive symptoms (Aboraya and Nasrallah, 2016), and reliance on a structured clinical interview (a requirement that many studies do not meet) (Nicotra et al., 2015). In addition, the PANSS may not capture the most salient elements of psychotic illness. For instance, core symptoms of schizophrenia per the DSM-V are represented by only eight of the thirty total PANSS items (P1-delusions, P2-conceptual disorganization, P3-hallucinatory behavior, P5-grandiose delusions, P6-persecutory delusions, G1-somatic delusions, P6-persecutory delusions, G1-somatic delusions, G3-delusions of guilt, and G9-unusual thought content). A lower PANSS score, then, does not necessarily reflect reduced severity of psychosis (Aboraya and Nasrallah, 2016).

The PANSS and other symptom rating scales may be particularly problematic when it comes to assessing negative symptoms. As discussed above, negative symptoms are multidimensional and challenging to evaluate. Existing rating scales can be divided into older, first-generation and newer, second-generation tools (Marder and Kirkpatrick, 2014).

First-generation tools, such as the PANSS negative subscale, BPRS, and SANS are limited in that they do not capture all negative symptoms (such as asociality, avolition, and anhedonia), and rely more heavily on behavior for assessment rather than internal experiences (Paz Garcia-Portilla et al., 2015). The PANSS, a comprehensive scale to asses psychopathology (Kay et al., 1987), was not designed to measure negative symptoms independently (Marder and Kirkpatrick, 2014). Furthermore, the PANSS and the SANS include constructs outside of the five negative symptom domains (blunted affect, alogia, asociality, anhedonia and avolition) recognized by the National Institute of Mental Health (NIMH) consensus statement (Kirkpatrick et al., 2006). Though frequently used, these first-generation tools reflect an incomplete and outdated approach to negative symptom assessment.

Second-generation assessment scales, such as the Brief Negative Symptom Scale (BNSS) (Kirkpatrick et al., 2011) and the CAINS, were developed to address limitations of earlier tools. They are organized to reflect an updated understanding of negative symptoms, including the five negative symptom domains and distinguishing between internal experience versus expressive behavior (Kane, 2013; Marder and Kirkpatrick, 2014). The BNSS and CAINS have consistently shown a similar factor structure (Marder and Kirkpatrick, 2014), and evidence supports their inter-rater reliability, test-retest reliability, and external validity (Kring et al., 2013). Comparison of the BNSS with the SANS and BPRS (Strauss and J. M. Gold, 2016; Strauss et al., 2012) indicates that although BNSS total scores correlate with the scores from both of these first-generation tools, the BNSS is distinct and not redundant with either. In particular, items relating to motivation and pleasure demonstrate lower levels of convergence between the BNSS and the BPRS (Strauss and J. M. Gold, 2016). A comparison of the CAINS with the BPRS showed that the CAINS Expression subscale does correlate strongly with BPRS negative symptom ratings; however, the Experience subscale correlates to a much lesser degree (Horan et al., 2011). Although the BNSS and CAINS share a similar framework and overlap significantly, they are still not considered equivalent (Marder and Kirkpatrick, 2014) and there is no conversion between them. As both are in relatively early stages of development, they will also likely be adapted in the future. Thus far, the CAINS has only been used in one trial of oxytocin in schizophrenia (M. C. Davis et al., 2014a) and the BNSS has not yet been used in any such studies. Importantly, even implementation of these newer, improved tools may not mean better capture of oxytocin effects. All of the symptom-rating scales discussed here rely on a clinical interview, which requires subjective judgment of symptom severity rather than objective measurement. This approach may introduce significant variability even within each assessment tool, and limits our ability to rigorously examine oxytocin's effects on specific symptoms in schizophrenia.

Dosing and duration of treatment—Studies in both animals and humans have shown divergent responses to oxytocin at different doses. In rodents, low doses of exogenous oxytocin have pro-social effects but high doses can be socially impairing (Benelli et al., 1995; Popik et al., 1992). The vast majority of oxytocin studies in humans have administered 20 to 40 IU intranasally (K. Macdonald and Feifel, 2012), following precedent rather than empirical evidence (Quintana et al., 2015b)—no study has systematically evaluated dose-

response and clearance of oxytocin from the CSF and blood (Striepens et al., 2011). A handful of small studies, however, have directly compared multiple dosages of oxytocin. Administration of a single dose of 24 IU to 17 healthy men attenuated cortisol levels relative to placebo, while 48 IU did not (Cardoso et al., 2013). In contrast, administration of a single dose of oxytocin in a sample of 46 healthy women resulted in significantly elevated salivary oxytocin levels, but the dose received (16 IU versus 24 IU) did not appear to matter (van IJzendoorn et al., 2012). Hall et al. (2012) administered a single dose of oxytocin to a sample of eight men with Fragile X syndrome, and found that eye gaze frequency improved significantly in response to 24 IU, but not 48 IU. Using four treatment conditions (two different single doses of intranasal oxytocin, intravenous oxytocin, and placebo), Quintana et al. (2016) compared amygdala response to emotional faces by fMRI in a within-subject study of 16 healthy men. The lower dosage (8 IU) of intranasal oxytocin, but not the higher dosage (24 IU), dampened amygdala activation. The cause of these divergent responses is unclear, though the authors highlight cross-reactivity between oxytocin and arginine vasopressin (AVP) receptors at higher doses as a potential explanation (Quintana et al., 2015b).

Oxytocin acts primarily through the oxytocin receptor (OXTR), but also has affinity for arginine vasopressin (AVP) receptors (Manning et al., 2012). The balance between oxytocin and AVP, which tends to enhance anxiogenic and depressive effects in the brain, is thought to be key for the regulation of social behavior and psychopathology (Neumann and Landgraf, 2012). Different doses of exogenous oxytocin may exert different effects on the equilibrium between AVP and oxytocin, which could lead to divergent behavioral outcomes. In the only intranasal oxytocin study to compare multiple dosages in individuals with schizophrenia, divergent responses were observed, but in the opposite direction seen in Quintana et al. (2015b). Goldman et al. (2011) administered 10 IU, 20 IU, and placebo in a between-subject study in 13 individuals with schizophrenia and 11 healthy controls. Emotion recognition worsened in individuals with schizophrenia following the 10 IU dose, and only improved in a subgroup—those with polydipsic schizophrenia—following the higher 20 IU dose. Dysregulation of the antidiuretic hormone AVP in polydipsic schizophrenia has been linked to deficits in CNS oxytocin activity (Goldman, 2009), highlighting the possibility that activity of the endogenous oxytocin and AVP systems may have implications for exogenous oxytocin dosage in schizophrenia. Additional work is needed to clarify neuroendocrine dynamics in schizophrenia in order to implement evidence-based, optimal dosing of oxytocin in clinical trials.

Furthermore, preclinical studies in healthy animals suggest that oxytocin has markedly different effects when administered acutely versus chronically. In prairie voles, a single dose of oxytocin enhances social behavior, whereas long-term treatment with oxytocin during adolescence causes a deficit in partner preference behavior in adulthood (Bales et al., 2013). A single dose of oxytocin in rats significantly increased pre-pulse inhibition (PPI) (Feifel et al., 2012b), a measure of sensorimotor gating deficient in individuals with schizophrenia that may underlie positive symptoms (Greenwood et al., 2013). Chronic dosing in mice, however, had no effect on PPI and even reduced OXTR throughout the brain (Huang et al., 2014). In another mouse study, administration of chronic oxytocin at high doses induced an anxiogenic phenotype that correlated with reduced OXTR binding. Administering low doses

chronically, however, was protective against the effects of stress (Peters et al., 2014). Finally, a study in infant macaques showed that chronic administration of intranasal oxytocin resulted in decreased attention to the eye region of faces (Parr et al., 2016). Taken together, these studies suggest that prolonged oxytocin administration may disrupt social behavior in healthy animals, possibly via down-regulation of OXTR expression in social brain regions.

In the setting of neuropsychiatric illness, chronic oxytocin treatment may produce notably different effects. In a rat model of post-traumatic stress disorder (PTSD), for example, chronic low doses of oxytocin were shown to have cumulative and persistent anxiolytic effects (Janezic et al., 2016). The implications of such animal studies for humans are unclear, as oxytocin's role varies significantly between species (Insel, 2016), but they suggest the need to thoroughly investigating chronic oxytocin treatment at clinically effective doses in individuals with schizophrenia. Almost all pharmacologic treatments for neuropsychiatric disorders involve chronic daily administration, and many require weeks of use before significant changes are observed (K. Macdonald and Feifel, 2013). Some agents, such as selective serotonin reuptake inhibitors (SSRIs) can have notably different acute versus chronic effects (Burghardt and Bauer, 2013). Studies of oxytocin have shown positive effects following treatment of a variety of regimens ranging from a single dose to several weeks, but it is a challenge to interpret these findings as long as optimal administration protocols and clinically effective dosages remain unknown. Developing clear dose-response curves and conducting longitudinal studies in larger samples are essential steps in ultimately understanding oxytocin's effects in schizophrenia.

Administration protocols—Poor bioavailability by oral administration and rapid metabolism in peripheral circulation present challenges for using neuropeptides as therapeutics (Insel, 2016). Almost all human studies have therefore relied on intranasal administration using a nasal spray to deliver oxytocin in order to maximize delivery to the CNS. In non-human primates, intranasal oxytocin has been shown to elevate CSF oxytocin levels (Chang et al., 2012; Dal Monte et al., 2014; Freeman et al., 2016; Modi et al., 2014b), offering promising evidence that oxytocin is able to reach the CNS via the intranasal route. However, the consistency of this method has not been fully examined (Quintana et al., 2015a) and may represent another source of heterogeneity both between and within studies. First, the pharmacokinetics of intranasally administered oxytocin are not yet well understood. In non-human primate studies, elevated CSF oxytocin levels have been observed at different time points following intranasal administration, ranging from 15 (Freeman et al., 2016) to 120 minutes (Modi et al., 2014b). In the only study in humans examining CSF oxytocin levels following intranasal administration (Striepens et al., 2013), a dose of 24 IU of oxytocin administered to eleven individuals led to elevation of CSF levels after 75 minutes. Protocols in human oxytocin studies have generally included a 30-minute delay after administration of oxytocin before beginning assessments. This convention arose from studies showing robust oxytocin-induced behavioral and physiological responses using this delay in healthy individuals (K. Macdonald and T. M. Macdonald, 2010). The peak and duration of oxytocin's CNS effects, however, are unknown. Studies examining oxytocin in schizophrenia have used a variety of assessment protocols with a range of lengths.

Differences in the timing of oxytocin administration relative to assessments may impact whether oxytocin effects are captured, or not, in a given study.

Second, intranasal administration poses several challenges. Guastella et al. (2013) and Quintana et al. (2015) have published excellent reviews detailing many of the considerations regarding intranasal oxytocin administration. Briefly, although multiple pathways from the nose to the central nervous system (CNS) have been described, the nasal cavity has complex anatomy that makes drug administration by this route less than ideal (Guastella et al., 2013). Specifically, dimensions of the nasal valve vary over time and across individuals, and additional variability in terms of drug delivery can be introduced by body position, breathing patterns during delivery, and operator coordination (Djupesland, 2013). Furthermore, standard nasal spray devices generally deposit drug anterior to the nasal valve, though oxytocin must access the upper portion of the cavity beyond the valve to ultimately reach the brain (Djupesland, 2013). A study in macaques found different effects of oxytocin on CSF levels when the drug was delivered via intranasal spray versus nebulizer (Modi et al., 2014b), and Quintana et al. (2015) demonstrated in humans that nasal valve dimensions were associated with oxytocin treatment response on a measure of social cognition. These findings suggest that nasal cavity anatomy and delivery method may significantly influence the effects of oxytocin, and that improving intranasal delivery of oxytocin to target sites in the nasal cavity could lead to better and more reliable CNS penetration. Recently, there have been promising developments in intranasal delivery device technology (e.g. OptiNose (Djupesland, 2013) and Impel (Lochhead and Thorne, 2012)), offering potential alternatives to the traditional nasal spray used in studies thus far and an opportunity to improve standardization of oxytocin administration.

A related issue is the variation in intranasal administration protocols between, and even within, studies that may result in significant differences in oxytocin bioavailability. In several studies, a trained technician administered oxytocin in the laboratory or inpatient setting (Feifel et al., 2010; Fischer-Shofty et al., 2013b; Guastella et al., 2015; Lee et al., 2013; Modabbernia et al., 2013b). In other studies, participants self-administered the drug, with ((Averbeck et al., 2012; Pedersen et al., 2011b; Woolley et al., 2014); inpatient subgroup in Pedersen et al. (2011)) or without (Cacciotti-Saija et al., 2015; Lee et al., 2013; Pedersen et al., 2011a) supervision. These different protocols may have led to variability in adherence that, in turn, impacted oxytocin effects. For instance, in the study conducted by Lee et al. (2013), only the inpatient subgroup, which received drug administered by a technician, showed significant improvement in negative symptoms with oxytocin. There was no improvement in the outpatient subgroup, which self-administered the drug without supervision. In addition, Cacciotti-Saija et al. (2015) found that the amount of nasal spray used by participants significantly correlated with a reduction in negative symptoms. The range of administration techniques used in oxytocin trials thus far, incomplete understanding of the pharmacokinetics of intranasal oxytocin, and the variability of nasal drug delivery are likely important to consider when interpreting study results. All represent potential sources of heterogeneity that cloud our understanding of oxytocin effects in schizophrenia.

Context—Oxytocin acts as a modulator of complex social interactions and may promote pro-social, group-differentiating, or even aggressive behaviors depending on the situation

(Bakermans-Kranenburg and van IJzendoorn, 2014; Shamay-Tsoory and Abu-Akel, 2016). Thus, the context in which oxytocin is administered may have an important influence on study results (for a review see Bartz et al., (2011)). In healthy individuals, intranasal administration has been shown to increase feelings of envy and schadenfreude when other players won more money (Shamay-Tsoory et al., 2009). De Dreu et al. conducted a series of studies in which oxytocin increased in-group, but not out-group, trust during various games (De Dreu and Kret, 2016). Similarly, during a prisoner's dilemma task, effects of oxytocin depended on whether or not participants interacted with one another prior to the experiment (Declerck et al., 2014). A critical implication of these findings is the fact that oxytocin's pro-social effects within groups may ultimately contribute to intergroup tension and conflict (De Dreu and Kret, 2016). Oxytocin has even been shown to increase inclinations towards intimate partner violence in individuals with high trait aggression (DeWall et al., 2014). Reconciling these findings with oxytocin's pro-social effects, one model proposes that oxytocin impacts the salience of various social stimuli, regardless of valence (Shamay-Tsoory and Abu-Akel, 2016). Oxytocin's role as a modulator of social salience may be important to consider when designing clinical studies and interpreting results that are likely to be influenced by context. Furthermore, there may be particularly complex implications for schizophrenia research, as individuals with schizophrenia tend to demonstrate impaired salience processing (Hahn et al., 2010; Holt et al., 2006b). Improved understanding of the ways in which context impacts oxytocin's effects is needed in order to thoroughly test its ability to improve deficits in schizophrenia. In the extant literature, influence of different contexts between and within studies may be another significant contributor to heterogeneous findings.

6.2 Individual factors

Gene-environment interactions and early life experiences—Differences in genetic expression and early life events may account for some of the observed variability in individuals' responses to oxytocin. In healthy individuals, certain *OXTR* variants have been associated with social phenotypes such as empathy, prosocial behavior, stress reactivity, and mentalizing (see Meyer-Lindenberg et al., (2011) for a review). Lower DNA methylation of the structural gene for oxytocin (*OXT*) has been associated with more secure attachment style, improved ability to detect facial expressions, and greater superior temporal sulcus activity during social tasks (Haas et al., 2016). Early life events may influence the oxytocin system through such epigenetic mechanisms: abuse or neglect in childhood, for example, has been associated with lower central oxytocin levels in rhesus monkeys (Winslow et al., 2003) and in women (Heim et al., 2009). In individuals with schizophrenia, there is early evidence to suggest that certain *OXTR* and *OXT* variants may correlate with symptom severity (Montag et al., 2013; Souza et al., 2010; Watanabe et al., 2012) as well as social cognitive impairments (M. C. Davis et al., 2014b; for a review see Bartholomeusz et al., (2015)). Furthermore, *OXTR* methylation has been associated with cognitive performance in individuals with psychosis (Grove et al., 2016). Taken together, these findings suggest that genotype, early life experiences, and epigenetic signatures likely impact development of the human oxytocin system.

Endogenous oxytocin system functioning may, in turn, have important implications for responsiveness to oxytocin administration. For example, intranasal oxytocin administration has been shown to attenuate stress responses in individuals with poor emotion regulation abilities, but not in those with normal emotion regulation (Cardoso et al., 2012; Quirin et al., 2011). However, there is also evidence to suggest that, in individuals who faced childhood adversity, oxytocin administration fails to produce pro-social effects (Bakermans-Kranenburg et al., 2012; van IJzendoorn et al., 2011; for a review see Bakermans-Kranenburg and van IJzendoorn, (2013)). Clearly, further work is needed to characterize the complex interactions between genetic variation in oxytocin pathway genes, environmental conditions during development, and oxytocin system function. Improved understanding of the ways that genotype, epigenetic signatures, and developmental events ultimately affect sensitivity to oxytocin in schizophrenia is critical to the interpretation of clinical trial results.

Sex—Sex differences in oxytocin modulatory effects, which have been observed in both animal and human studies (Dumais and Veenema, 2016), represent another source of heterogeneity in the extant literature. Neuroimaging studies have demonstrated divergent activation in the temporal lobes of men and women in response to oxytocin administration (for a review see Wigton et al., (2015)), sex hormones influence expression of *OXTR* in the brain as well as central oxytocin release (Gabor et al., 2012), and intranasal oxytocin administration may have differing effects on amygdala reactivity (Domes et al., 2010; Lischke et al., 2012) and salience of social cues (Gao et al., 2016) in men and women. Women's higher circulating levels of oxytocin and the hormonal shifts involved in the menstrual cycle may complicate their responsiveness to exogenous oxytocin (Bakermans-Kranenburg and van I Jzendoorn, 2013). Unfortunately, the impact of sex differences on oxytocin responsiveness is poorly understood, as the vast majority of clinical studies have enrolled only male participants.

The sex differences seen in schizophrenia—men are more likely to have the illness (Hafner, 2003), develop symptoms at an earlier age (Aleman et al., 2003), and tend to have a more severe course (Desai et al., 2013; Halbreich and Kahn, 2003)—complicate the picture further. It is unclear how sex differences in schizophrenia and in oxytocin responsiveness relate to one another, but there is early evidence to suggest that sex may be an important modulating factor. For example, greater *OXTR* methylation has been associated with social cognitive impairment in women with schizophrenia, but not in men (Rubin et al., 2016). Furthermore, *OXTR* methylation and peripheral levels of oxytocin were positively correlated in women, but negatively correlated in men. Thus far, several studies of oxytocin in schizophrenia have used samples with varying percentages of both men and women (Feifel et al., 2010; Fischer-Shofty et al., 2013b; Gibson et al., 2014; Goldman et al., 2011; Lee et al., 2013; Modabbernia et al., 2013b; Pedersen et al., 2011b; Woolley et al., 2015), while others have included only male participants (Averbeck et al., 2012; M. C. Davis et al., 2014a; 2013; Horta de Macedo et al., 2014; Michalopoulou et al., 2015; Woolley et al., 2014). Differences between these study samples, and between individual men and women in terms of their responsiveness to oxytocin, add another challenge to interpreting findings. Better characterization and accounting for sex differences may be a critical step in predicting

individuals' responsiveness to oxytocin and ultimately reducing heterogeneity in the literature.

Age—Age may also be an important moderator of oxytocin effects that has the potential to introduce heterogeneity. Oxytocin's role in social cognition and behavior may be regulated by age-related factors such as shifts in gonadal hormone levels and neuroendocrine function (Bos et al., 2012). In healthy humans, complex age-related changes in social abilities are observed: some abilities, such as emotion regulation, tend to improve with age, while others, such as emotion recognition, decline (see Isaacowitz et al., (2007) and Ruffman et al., (2008) for reviews). These changes are not fully explained by the changes in visual processing or neurocognition that occur with aging (Samanez-Larkin and Carstensen, 2011). Whether alterations in the oxytocin system could underlie changes in social abilities is unclear, as research on oxytocin and aging is extremely limited (Ebner et al., 2013). The few studies involving exogenous oxytocin administration in humans, however, suggest that age may be an important moderator to consider: in healthy individuals, intranasal oxytocin has been shown to improve emotion recognition in older men, but not in older women or young adults (Campbell et al., 2014), and to increase attention to one's own feelings only in older men and young women (Ebner et al., 2015a). Furthermore, intranasal oxytocin's ability to modulate resting-state connectivity between the amygdala and mPFC, regions involved in social cognitive processing, is impacted by both age and sex in healthy individuals (Ebner et al., 2016). In line with these intriguing findings, there has been growning interest in examining the impact of aging on oxytocin's role in social behavior (Ebner et al., 2013; 2015b; Huffmeijer et al., 2013). In fact, Ebner et al. (2013) articulated an Age-Related Genetic, Neurobiological, Sociobehavioral Model of Oxytocin (AGeNeS-OT), proposing that oxytocin research be considered from a developmental perspective and thoroughly explore age-related variation.

In the extant literature on oxytocin in schizophrenia, no studies have examined age-related changes in the endogenous oxytocin system or compared oxytocin effects in younger versus older individuals. Furthermore, no studies have taken into account the age of symptom onset in individuals with schizophrenia. Schizophrenia is not a monolithic disorder, and there is some evidence that early age of onset (during adolescence) is associated with a more severe form of the illness (Hollis, 2000). A recent meta-analysis of the longitudinal trials evaluating oxytocin effects on clinical symptoms (Williams and Burkner, 2016) found that variability in participant age did not explain a significant amount of heterogeneity between studies; however, it is unclear whether age contributes to heterogeneity within studies in the extant literature. Given the relevance of age to symptom development and severity in schizophrenia, it may be particularly important to determine whether age is a moderator of oxytocin effects at the level of the individual.

Antipsychotic medication—Anti-dopaminergic agents present another challenge to understanding the role of oxytocin in schizophrenia, as their interaction with the oxytocin system is not yet well understood (Liu and Wang, 2003). There is evidence to suggest that dopamine may play a role in social behavior known to be modulated by oxytocin, such as mother-infant bonding. For example, Atzil et al. (2017) used a combined fMRI-PET scanner

to explore mothers' dopamine reponses to their infants as well as connectivity between the nucleus accumbens (NAcc), the amygdala, and the medial prefrontal cortex (mPFC), an intrinsic network that supports social functioning. The authors found that synchronous behavior between mothers and infants as well as greater network connectivity were associated with increased dopamine reponses. There is also evidence that oxytocin may impact reward-related dopaminergic activity (Mickey et al., 2016), potentially influencing social salience and valence assignment as well as inhibiting defensive behaviors (Skuse and Gallagher, 2011; 2009). Studies showing oxytocin effects on attraction to faces (Theodoridou et al., 2009) and enhanced activation of the striatum with increasing facial attractiveness (Aharon et al., 2001; Cloutier et al., 2008; Liang et al., 2010; Winston et al., 2007), for instance, suggest that oxytocin may modulate striatal dopaminergic reward mechanisms. However, the relationship between the oxytocin and dopamine systems is far from clear. In a study measuring dopamine release by positron emission tomography (PET), Striepens et al. (2014) found no evidence that oxytocin-induced increased attractiveness ratings for faces were associated with increased dopaminergic activity in reward-related brain areas. Further work in this area is essential to understand the interface between oxytocin and dopaminergic circuits.

Interactions between oxytocin and dopamine are are also unclear in the setting of schizophrenia. In animal models of psychosis, oxytocin administration has been shown to reduce dopaminergic hyperactivity in the nucleus accumbens and striatum (Qi et al., 2008), and animal work has also suggested that atypical antipsychotic agents such as clozapine and amperozide, but not the typical agent haloperidol (Uvnäs-Moberg et al., 1992), are associated with an increase in plasma oxytocin concentration. In humans, there is evidence that higher doses of antipsychotic medication are associated with lower levels of plasma (Goldman et al., 2008) and CSF oxytocin levels (Sasayama et al., 2012) in individuals with schizophrenia. It is unclear whether antipsychotic medication leads to lower endogenous oxytocin levels, possibly via antipsychotic-induced disinhibition of prolactin secretion leading to suppressed oxytocin secretion (Sirzen-Zelenskaya et al., 2011), or whether patients with lower oxytocin levels respond less well to antipsychotics and therefore tend to take higher doses of medication (Sasayama et al., 2012). Furthermore, little is understood about how endogenous oxytocin may moderate responses to exogenous oxytocin administration.

To explore the relationship between antipsychotic dosages and oxytocin sensitivity, Woolley et al. examined whether antipsychotic dosage moderated oxytocin effects in three recent studies. Chlorpromazine (CPZ) equivalents were calculated for patients using a standardized conversion table (Andreasen et al., 2010), and oxytocin-induced changes were calculated by subtracting the placebo day performance from the oxytocin day performance for each study task. Using nonparametric rank correlations, the authors found that lower antipsychotic dosage was associated with greater oxytocin-induced improvements in mentalizing (Figure 1A; CPZ equivalents $\rho = -0.34$; $p=0.042$; (Woolley et al., 2014) see supplemental materials), and facial expressivity (Figure 1B; $\rho = -0.48$; $p=0.004$; (Woolley et al., 2017) see supplemental materials). The authors did not find a significant association between antipsychotic dosage and olfactory detection thresholds (Figure 1C; $\rho = -0.118$, $p=0.535$; (Woolley et al., 2015) see supplemental materials). These findings offer further support for

the idea that antipsychotic medications may interact with oxytocin effects, and highlight the need for additional study to clarify predictors of oxytocin sensitivity in schizophrenia.

Differences in antipsychotic medication dosages and the other individual factors described in this section likely combine with study factors to explain a significant amount of the observed heterogeneity in the literature on oxytocin in schizophrenia (see Figure 2). Without improved understanding of how such factors impact clinical oxytocin studies, our ability to draw conclusions from their results remains limited.

7. Oxytocin effects on social cognitive deficits in schizophrenia

In addition to the RCTs that have primarily assessed oxytocin's effects on symptom ratings in schizophrenia, several studies have examined its effects on social cognition. In this section, we summarize a model of social cognition in schizophrenia, and discuss study findings that point to a potential role for oxytocin in ameliorating deficits in a specific social cognitive domain.

7.1 Social cognition in schizophrenia

Increasingly, social cognitive deficits are recognized as a core feature of schizophrenia. Individuals with schizophrenia commonly demonstrate impairments in the ability to interpret the intentions and behavior of others (Pinkham et al., 2003), and social cognitive impairment has a greater impact on an individual's level of functioning than non-social cognitive impairment (Fett et al., 2011). Neuroimaging studies have found that individuals with first-episode psychosis and schizophrenia tend to have structural abnormalities in social brain regions (Jung et al., 2010; Mechelli et al., 2011; Pantelis et al., 2003; 2009; Takahashi et al., 2009) and display hypoactivations in these regions during social cognitive tasks (Das et al., 2007; Reske et al., 2009; Sugranyes et al., 2011). Specific social cognitive deficits tend to develop prior to the onset of positive symptoms, remain stable across the course of illness (Fett et al., 2011; Green et al., 2015), and are seen in individuals at ultra-high risk for developing psychosis as well as unaffected family members (Bora and Pantelis, 2013). Taken together, these findings suggest that social cognitive deficits may be an endophenotype for schizophrenia. Furthermore, individuals' ability to cope with the threatening experiences that arise from positive symptoms (such as paranoia and hallucinations) may be limited by poor social cognitive skills (Gumley et al., 2014). Despite their clinical importance, there are no currently available pharmacological treatments for social cognitive deficits.

There is growing consensus that social cognition is made up of distinct domains, and that some but not all social processes are impaired in schizophrenia. The model articulated by Green et al. (2015) (see Figure 3) defined four main subcomponents of social cognition: 1) social cue perception, 2) mentalizing, 3) experience and regulation of emotion, and 4) experience sharing. 1) Social cue perception involves the ability to recognize information embedded in others' faces, voices, and body movements, and is known to be impaired in schizophrenia. Deficits in the perception of facial expressions, for example, are correlated with aberrant neural activity (Delvecchio et al., 2013; Li et al., 2010; Taylor et al., 2012), and neuroimaging studies have suggested that individuals with schizophrenia tend to

perceive neutral faces as threatening (Holt et al., 2006a; Morris et al., 2009). Studies using behavioral paradigms (R. Gold et al., 2012; Leitman et al., 2005) have also found deficits in the perception of voices, particularly pitch and rhythm. 2) Mentalizing (also known as theory of mind, or mental state attribution) is the ability to infer the mental states of others (Baron-Cohen et al., 2001) and is also known to be impaired in schizophrenia (Brüne et al., 2009; Harrington et al., 2005; Savla et al., 2013). Mentalizing deficits result in misinterpretation of hints, intentions, deception, metaphor, and irony (Penn et al., 2008). Impairments may also lead to the over-attribution of intention, or "hypermentalizing," which has been linked to paranoid ideation in schizophrenia (Ciaramidaro et al., 2015; Frith, 2004). Neuroimaging studies have implicated a dispersed network of brain regions that play a role in mentalizing. In schizophrenia, dysfunction appears to be related to hypoactivation in the medial prefrontal cortex (mPFC), thalamus, middle and superior temporal regions, temporoparietal junction (TPJ), as well as hyperactivation in the posterior cingulate cortex (PCC), precuneus, and somatosensory cortices (Sugranyes et al., 2011; Walter et al., 2009). 3) Experience and regulation of emotion refers to individuals' adaptive responses to social complexities, and 4) experience sharing to the vicarious neural activation triggered when an individual observes someone else's actions (Iacoboni, 2009). As these have been well-reviewed (Green et al. 2015) and are less relevant to this discussion, they will not be detailed here. The four subcomponents articulated in this model reflect important neural and functional separations within the broad area of social cognition, providing a framework for more precise examination of oxytocin effects.

7.2 Oxytocin effects on social cue perception

Studies that have investigated the effects of oxytocin on social cue perception in schizophrenia have generally found no effects or the effects have failed to replicate (see Table 2). Two within-subject studies using single doses of 20 IU (Goldman et al., 2011) and 24 IU (Averbeck et al., 2012) found some small improvements in facial affect identification, but the effect seen by Goldman et al. was only in a small subgroup of patients with polydipsia, and lower doses (10 IU) actually worsened social cue perception. Another within-subject study administered a single dose of 48 IU of oxytocin and found no improvement on facial emotion matching (Horta de Macedo et al., 2014).

Brambilla et al. (2016), notably, did observe decreased reaction times for facial affect recognition using an Emotional Priming Paradigm (EPP) in their longitudinal study (see Dagani et al., (2016)), though there were no changes in implicit emotional priming effects or for the differences between emotional categories. Gibson et al. (2014) included additional social cue perception tasks in their study: the Emotion Recognition 40 (ER-40) (Kohler et al., 2004), and a trustworthiness task (Adolphs et al., 1998). They found a significant oxytocin effect only in fear recognition within the ER-40 (there was no improvement in recognition of anger, sadness, happiness, or neutrality) in the oxytocin group. There was no oxytocin effect on the trustworthiness task. Woolley et al. (2017) also failed to find an effect of oxytocin on the same trustworthiness task in a recent study of 33 participants with schizophrenia spectrum disorders and 35 age-matched healthy controls.

Multiple studies (Cacciotti-Saija et al., 2015; Gibson et al., 2014; Brambilla et al., 2016) have used the Reading the Mind in the Eyes Test (RMET) to assess social cognition (see Table 3). In RMET, participants identify mental states depicted in photographs of the eye region of faces (Baron-Cohen et al., 2001). Though the mental states are semantically complex (e.g., “jealous”), the task does not require the participant to integrate a state with other contextual information or social cues (e.g., who is the target of jealousy and why) and thus is best categorized as a measure of social cue perception. None of these studies found an effect of oxytocin on RMET performance. Taken together, these results suggest that oxytocin may not have a meaningful impact on social cue perception in schizophrenia.

7.3 Oxytocin effects on mentalizing

In contrast, studies measuring oxytocin effects on mentalizing in schizophrenia have been more consistently promising. Several have used The Awareness of Social Inference Test (TASIT), an audiovisual tool that allows for assessment of multiple domains of social cognitive processing (McDonald et al., 2003). In TASIT, participants make social inferences after viewing video clips of actors engaging in various scenarios. Divided into three parts, the task tests progressively more complex aspects of social cognition. Part I, the Emotion Evaluation Test (EET), and part II, Social Inference-Minimal (SI-M), require basic emotion recognition and immediate social cue detection. Part III, Social Inference-Enriched (SI-E), involves additional contextual information to help the viewer comprehend the speakers' intentions, perspective, and emotional state. SI-E is further divided into two categories: White Lies and Complex Sarcasm, allowing for more specific evaluation of participants' comprehension. TASIT has strong test-retest reliability and discriminant validity in patients with neuropsychiatric illness (McDonald et al., 2006), making it a strong candidate for use in social cognition studies, and its design allows for objective examination of oxytocin's effects on different levels of social cognition.

In their study, (M. C. Davis et al., 2013) derived two social cognition scores, one measuring “lower-level” social cognition (facial affect perception, social perception, detection of lies) and one measuring “higher-level” social cognition (detection of sarcasm and deception, empathy). The lower-level score was calculated from performance on multiple social cue perception tasks (the Half-Profile of Non-Verbal Sensitivity (Half-PONS) (Rosenthal et al., 1979), the Ekman facial affect recognition task (Ekman, 2007; Ekman and Friesen, 1976), and the Lie detection subsection of TASIT III). The higher-level social cognition score was calculated from tasks requiring mentalizing ability: the Emotional Perspective Taking Task (EPTT) (Derntl et al., 2009) and the Complex Sarcasm detection subsection of TASIT III. The authors found that a single dose of 40 IU of oxytocin selectively improved higher-level but not lower-level social cognition scores in a sample of 23 male outpatients. In another study administering 40 IU of oxytocin in a sample of 29 male participants with schizophrenia and 31 age-matched, healthy controls, Woolley et al. (2014) saw similar complexity in terms of oxytocin effects: while oxytocin significantly improved performance on mentalizing ability as assessed by TASIT III, it had no effect on tasks measuring social cue detection (RMET, TASIT I and TASIT II performance).

In addition to TASIT, several other tools have been used to examine oxytocin's effect on multiple levels of social cognition. The study by Pedersen et al. (2011) found significant improvement on the Brune second order false belief test (Brüne, 2003), a measure of mentalizing ability, but no effect on a facial trustworthiness task. Guastella et al. (2015) administered a single dose of oxytocin in a within-subject study of 21 men with schizophrenia and assessed multiple domains of social cognition as well. They tested emotion recognition using the Diagnostic Analysis of Non-Verbal Accuracy (DANVA) (Nowicki and Duke, 1994) as well as the Facial Expressions of Emotions Task (FEEST) (A. W. Young et al., 2002), another emotion recognition measure using still photographs, and the RMET. Oxytocin improved accuracy for detecting vocal intonations of affect, a subcomponent of the DANVA, but otherwise had no effect on these measures of social cue perception. Three additional tasks were used to assess mentalizing: the False Belief Picture Sequencing Task (FBPST) (Langdon et al., 1997), a verbal hinting task (Corcoran et al., 1995; Marjoram et al., 2005), and the Faux Pas Recognition Task (Baron-Cohen et al., 1999). Oxytocin improved performance on both the hinting task and the non-faux condition of the Faux Pas Recognition task, again suggesting that oxytocin may selectively improve complex social processing that involves integration of social nuances.

Gibson et al. (2014) included multiple tasks related to mentalizing in their study, described above. One of these is performance-based task, the Brune False Belief Test, and two others are self-report tools: the Ambiguous Intentions Hostility Questionnaire (AIHQ) (Combs et al., 2007), and the Interpersonal Reactivity Index (IRI) (M. H. Davis, 1980). The authors saw no drug effect on mentalizing as assessed by the Brune task. They also failed to find a drug effect on the AIHQ, which quantifies hostile social cognitive biases. The oxytocin group did, however, show a significant increase in perspective taking, one of the four subscales of the IRI and the one that relates most closely to mentalizing ability. Fischer-Schofty et al. (2013) administered a single dose of 24 IU of oxytocin to 35 patients with schizophrenia and 46 healthy controls in a within-subject study that evaluated complex social judgments as assessed by the Interpersonal Perception Task (IPT) (Costanzo and Archer, 1989). The authors found that oxytocin significantly improved accuracy on measures of complex perception that involve processing of subtle, ambiguous social interactions. Brambilla et al. (2016) reported that four months of oxytocin administration improved performance on the Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT), which requires participants to solve problems related to emotion (Mayer et al., 2003). Specifically, they observed improvement in patients' scores on the Understanding Emotion component of the MSCEIT, which assesses ability to understand the causes of emotions and how they may change and develop depending on context.

Not all studies have found a positive effect of oxytocin on the mentalizing domain. For example, Cacciotti-Saija et al. (2015) saw no improvement on the FBPST or the Faux Pas Task. In this study, however, both oxytocin and placebo groups received social cognition training, and significant improvements were seen in both groups over the study period. It is possible, then, that the effects of social cognitive training masked an oxytocin effect. Taken together, the findings summarized here suggest that oxytocin may have important effects specifically on mentalizing. Given the associations between mentalizing and functional outcomes in schizophrenia (Sergi et al., 2007), this is a particularly compelling area for

future research. Further study with larger samples is needed to better characterize oxytocin effects on mentalizing deficits in schizophrenia.

8. Oxytocin effects on other deficits in schizophrenia

In addition to playing a role in social cognition, oxytocin may have important effects on other clinically important, but less often studied, deficits in schizophrenia. Here, we highlight findings in three of these areas: non-social cognition, facial expressivity, and olfaction.

8.1 Facial expressivity

Of the trials assessing oxytocin effects on symptoms, some reported significant oxytocin-induced improvements on negative symptom scales (Feifel et al., 2010; Gibson et al., 2014; Modabbernia et al., 2013b) while others found an ambiguous effect or none at all (Cacciotti-Saija et al., 2015; Dagani et al., 2016; M. C. Davis et al., 2014a; Lee et al., 2013; Pedersen et al., 2011b). These conflicting results are not surprising given that negative symptoms represent a heterogeneous group of deficits affecting a variety of functions: emotion, social ability, goal-directed behavior, and communication. Oxytocin may impact some of these deficits but not others, in which case investigating specific symptoms could prove useful. This is consistent with growing support in recent years for dividing negative symptoms into two distinct elements: 1) an experiential dimension comprised of avolition, anhedonia, and asociality; and, 2) an expressivity dimension comprised of restricted affect and poverty of speech (Reddy et al., 2015).

Decreased or blunted facial expressivity is a core component of the latter element (Blanchard and Cohen, 2006) that disrupts the ability to communicate emotions. It is commonly present many years before the development of frank psychotic symptoms, and typically continues into the chronic phase of the illness after treatment with antipsychotic medications (Gur et al., 2006). It is associated with difficulties navigating social situations, more severe anxiety, depression, and functional outcomes, and is predictive of poor prognosis (Kring and Moran, 2008). Blunted affect is included as an item on the symptom rating scales commonly used in studies of oxytocin in schizophrenia: the PANSS negative subscale, the BPRS, the SANS, and the CAINS (note that we contacted authors of the studies using each of these scales, hoping to analyze oxytocin effects on blunted affect specifically; unfortunately none were able to provide that data). As is the case for other negative symptoms, currently available pharmacological agents are ineffective at remediating impaired facial expressivity (Gur et al., 2006). Evidence that oxytocin may specifically normalize the neural circuitry dysfunction that is believed to underlie blunted facial affect (Kirsch et al., 2005; Shin et al., 2015; Sripada et al., 2013) has raised the question of whether oxytocin could improve this deficit in schizophrenia. In a within-subject study described above, (Woolley et al., 2017), individuals with schizophrenia and healthy controls were video recorded while they viewed emotionally evocative photos. Using an objective coding system (Kring and Sloan, 2007), the authors found that a single intranasal dose of oxytocin increased facial expressivity in both groups. Further work investigating

facial expressivity specifically is needed to clarify the effects of oxytocin on this deficit in schizophrenia.

8.2 Non-social cognition

The association between cognition and functional outcomes in schizophrenia is well-documented (Green et al., 2000), but current treatments do not successfully address these deficits (Feifel et al., 2012a). Non-social cognitive deficits are widespread in individuals with schizophrenia, affecting visual and verbal learning and memory, attention/vigilance, working memory, reasoning and problem solving, and information processing speed (J. W. Young and Geyer, 2015). Given that social and non-social cognition interact and influence one another (Pessoa, 2008), it is not surprising that oxytocin has been linked to multiple aspects of non-social cognition in animals, including cognitive flexibility and spatial and episodic memory (Chini et al., 2014). Animal work suggests that low dosages of exogenous oxytocin improve memory when administered specifically during consolidation (see Chini et al., (2014) for a review). In the few studies conducted in healthy humans, however, oxytocin administration has generally resulted in no effect, or even an impairing effect, on various non-social memory tests (Bruins et al., 1992; Heinrichs et al., 2004; Herzmann et al., 2012) (notably, oxytocin has not been administered during the memory consolidation period, nor have a range of dosages been explored in the human literature). The relationship between oxytocin and cognition in healthy humans remains poorly understood, but no apparent benefit of oxytocin administration has been observed thus far.

However, there is some evidence of positive effects of oxytocin on aspects of memory in schizophrenia. Feifel et al. (2012) found that chronic oxytocin treatment improved short-term verbal memory but not long-term verbal memory or working memory as assessed by the California Verbal Learning Test (Delis, 2000) and the Letter Number Sequence task (Wechsler, 1997). In a within-subject study of 21 patients with schizophrenia, Michalopoulou et al. (2015) examined the effect of a single dose of 24 IU of oxytocin versus placebo on working memory and processing speed using the Digit Span and Digit Symbol Coding (DSC) tasks, respectively. The Digit Span task, which tests the “executive component” of working memory that involves maintenance and manipulation of information, is known to be more sensitive to deficits seen in schizophrenia (Kim, 2004). While oxytocin had no effect on processing speed, it did significantly improve the executive component of working memory. Cacciotti-Saija et al. (2015) and Guastella et al. (2015), however, used The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998) to test other aspects of non-social cognition (immediate memory, language, visuospatial/constructional, attention, delayed memory); neither study found an effect of oxytocin. Taken together, these findings suggest that oxytocin's effects on non-social cognition may be highly selective and beneficial only in the setting of specific underlying cognitive deficits. Whether oxytocin has pro-cognitive effects or observed changes in performance are secondary to reduction in other symptoms of schizophrenia remains to be determined; studies conducted thus far have small sample sizes and used only a limited cognitive battery. It is essential that future work investigate whether oxytocin has effects on specific domains of non-social cognition known to be impaired in schizophrenia.

8.3 Olfaction

Olfactory cues play a role in a variety of mammalian social processes, such as emotion contagion, bonding, and mate selection (Stevenson, 2010). Individuals with schizophrenia have been found to have widespread olfactory deficits including impairments in odor identification, sensitivity, and discrimination that tend to worsen over the course of the illness and are present in unaffected family members (Moberg et al., 2014). Furthermore, deficits in odor identification have been shown to correlate with negative symptoms (Malaspina and Coleman, 2003; Moberg et al., 2006). These findings have led to interest in olfactory deficits as an endophenotype of schizophrenia. However, little is understood about the underlying neurobiology of olfactory impairment and there are currently no treatments to address these deficits.

Studies in animals and humans suggest that oxytocin plays a role in olfactory-based social processing. Animal studies have linked oxytocin signaling with olfactory and social functions (Larrazolo-Lopez et al., 2008; Wacker and Ludwig, 2012). Oxytocin receptors are found in the olfactory bulbs of rodents and sheep, and oxytocin is necessary for retaining olfactory social memories (Wacker and Ludwig, 2012). Furthermore, oxytocin receptors have been found in high concentrations on human olfactory neurons (Loup et al., 1991), and oxytocin has been implicated in modulating olfactory memory in the limbic system of rodents (L. J. Young and Wang, 2004). A study by Strauss et al. (2015) directly investigated the association between plasma oxytocin, social functioning, and olfaction in a sample of 39 individuals with schizophrenia and 21 healthy controls. Lower endogenous oxytocin levels predicted poorer olfactory identification as assessed by the University of Pennsylvania Smell Identification test (UPSIT) (Doty et al., 1984). The authors also observed an association between lower oxytocin levels and greater severity of negative symptoms. These findings suggest a possible relationship between oxytocin and olfactory deficits in schizophrenia.

Two studies have investigated the effects of intranasal oxytocin administration on olfactory deficits in schizophrenia. Lee et al. (2013) found that chronic oxytocin administration improved odor identification of pleasant, but not unpleasant, odors. Woolley et al. (2015) administered a single dose of 40 IU of oxytocin or placebo in a within-subject study in 31 individuals with schizophrenia and 34 age-matched healthy controls. The authors selected an olfactory detection threshold test to minimize confounding effects of higher order cognitive processes (detection thresholds do not require subjects to engage in memory retrieval or verbal labeling), and the synthetic fragrance compound lyral, as patients with schizophrenia have shown specific deficits in lyral detection (Turetsky et al., 2009). Oxytocin significantly and selectively improved detection of lyral in individuals with schizophrenia, but not in healthy participants. These preliminary findings suggest that the oxytocin system may play a role in the olfactory deficits in schizophrenia, but further work is needed to determine whether exogenous oxytocin could offer therapeutic benefit for such impairment.

9. Conclusions and agenda for future research

Schizophrenia represents a complex collection of neuropsychiatric disorders, and multiple neurotransmitter and neuropeptide systems have been implicated in its pathophysiology and symptomology. Recent investigations highlighting oxytocin's role in the deficits associated

with schizophrenia, along with its high level of tolerability when administered intranasally, have led to excitement about its potential as a therapeutic. Thus far, however, clinical studies have yielded inconsistent findings that limit our ability to draw clear conclusions about oxytocin's utility. The heterogeneity of results seen in the literature is not surprising given that the neurobiological underpinnings of both schizophrenia and the human oxytocin system are inadequately characterized at this point. Furthermore, issues such as the use of various clinical assessment tools, differences in dosing and administration protocols, and failure to account for individual factors affecting oxytocin sensitivity have likely contributed to heterogeneity both between and within studies. In particular, antipsychotic dosage may be an important predictor of response to oxytocin in schizophrenia that has seldom been included in published reports.

Improved understanding of social cognition as a multidimensional construct has facilitated a closer examination of oxytocin's effects, and suggests that it may impact one specific domain, mentalizing. There are other intriguing findings regarding oxytocin's effects non-social cognition, olfaction, and facial expressivity that also warrant further exploration. Alvares et al. (2016) suggest that the current phase of oxytocin research be considered an “enlightenment” following the initial burst of interest and, subsequently, a period of disillusionment. This enlightenment should ideally be characterized by improvements in the consistency and rigor of research.

To meet our goal of elucidating oxytocin's role in schizophrenia and determining whether it has a place among therapeutics, future work must address limitations in the literature described in this review. First, assessment tools comprised of objective, specific symptom measures should be employed to quantify outcomes. As oxytocin's potential to improve negative symptoms is a particular area of interest, we recommend that future studies use the CAINS or BNSS, rating scales that reflect our current understanding of this domain. However, given that exclusive use of symptom rating scales to capture oxytocin effects has clear drawbacks, additional assessment tools should be incorporated into clinical trials. Measures that focus on signs linked to the neurobiological underpinnings of specific deficits, rather than subjective experiences, may allow for more thorough and precise evaluation of oxytocin's effects. For example, TASIT, which uses immersion in real-world social situations to assess deficits in specific domains of social cognition, may capture important changes that symptom rating scales do not. Objective facial expressivity coding, such as the system developed by Kring and Sloan (Kring and Sloan, 2007), is another example of a tool that may prove more useful in capturing clinically relevant oxytocin effects (e.g., as used in (Woolley et al., 2017)). Second, improved intranasal drug delivery systems, standardized administration protocols, and dose-response curves would likely increase consistency in oxytocin system engagement and allow for appropriate comparisons between studies. Specifically, replacing standard nasal spray bottles with newer devices that offer more consistent drug delivery (e.g. OptiNose (Djupesland, 2013), Impel (Lochhead and Thorne, 2012)) and using standardized instructions for administration (as outlined by Guastella et al. (2013) may significantly decrease heterogeneity introduced by administration protocols in oxytocin studies. In addition, the optimal dosages and treatment duration for intranasal oxytocin must be established. Trials that directly compare multiple dosages as well as acute

versus chronic effects are essential to rigorously evaluating oxytocin as a potential therapeutic for schizophrenia.

Finally, perhaps the greatest challenge arises from the complexity of the oxytocin system itself, and our limited understanding of the mechanisms by which it modulates neural circuits at the individual level. Continued efforts to map the expression of OXTR receptors in the human brain (Freeman et al., 2017), as well as clarifying the effects of OXTR genotype and epigenetic signatures, are critical to identifying factors that predict responsiveness to oxytocin at the individual level. Furthermore, key potential moderators, such as age, sex, context of administration, and use of antipsychotic medications, must be considered in the design and data analysis phases of future trials. Elucidating the mechanisms underlying oxytocin's effects and understanding why individuals may be more or less responsive to exogenous oxytocin requires that we move beyond conducting efficacy trials. An approach that focuses instead on target identification and engagement will likely yield more informative findings that ultimately clarify oxytocin's role in schizophrenia treatment. Through this approach, oxytocin-induced changes in behavior can be linked to functional impact on neural systems (e.g., as in Aoki et al. (2014)). Studies designed to test specific targets of oxytocin treatment will provide essential insights regarding oxytocin's mechanisms of action.

To determine whether oxytocin has a role in the treatment of schizophrenia, future investigations must tackle multiple challenges. In addition to the issues discussed in this review, it is critical to highlight the fact that oxytocin has been tested as an add-on to stable treatment regimens in all clinical schizophrenia studies conducted thus far. The multiple limitations of addon designs and particular challenges of examining oxytocin effects in schizophrenia using this approach have been well-articulated in the review by Shilling and Feifel (2016). As the authors discuss, only monotherapy RCTs can test the hypothesis that oxytocin has inherent therapeutic properties in schizophrenia. Without trials that directly test the efficacy of oxytocin in the absence of antipsychotics, we are at risk of failing to capture oxytocin effects and dismissing a much-needed potential treatment. While moving forward is a daunting task, the disease burden of schizophrenia and lack of adequate treatments are critical issues in mental health. Thorough exploration of oxytocin's potential as a therapeutic remains a worthy pursuit.

Acknowledgments

Role of funding sources: This work was supported by the Career Development Award # CX000758 from the United States Department of Veterans Affairs, Office of Research and Development, Clinical Science Research and Development program, and the National Institutes of Mental Health Grant R25 MH60482. The funders did not play any role in decision to publish or preparation of the article.

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Highlights

- Studies of oxytocin in schizophrenia have yielded mixed results.
- Study design and individual differences may account for this heterogeneity.
- Oxytocin may improve specific deficits not captured in many studies.
- Future studies should employ precise, objective outcomes to capture oxytocin effects.

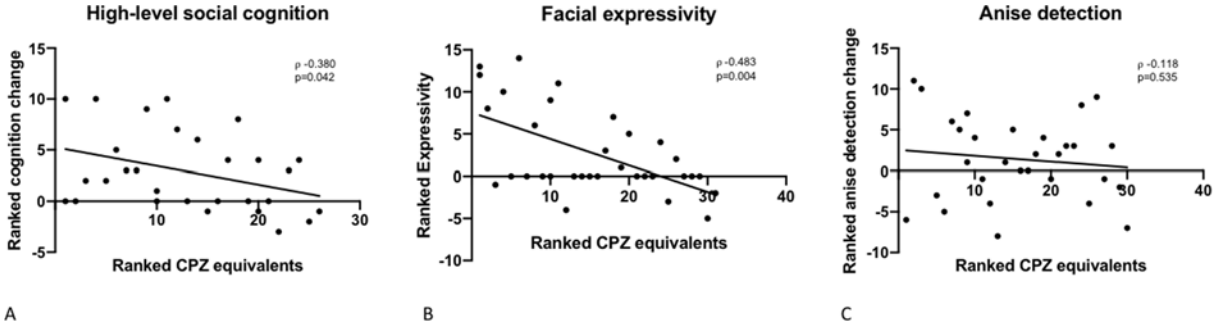

Fig. 1. Relationships between oxytocin effects and antipsychotic dosage

The magnitude of oxytocin-induced changes in high-level social cognition (A), and facial expressivity (B), are significantly associated with lower antipsychotic dosage. Anise odor detection (C) is not significantly associated with lower antipsychotic dosage, although the relationship is in the right direction.

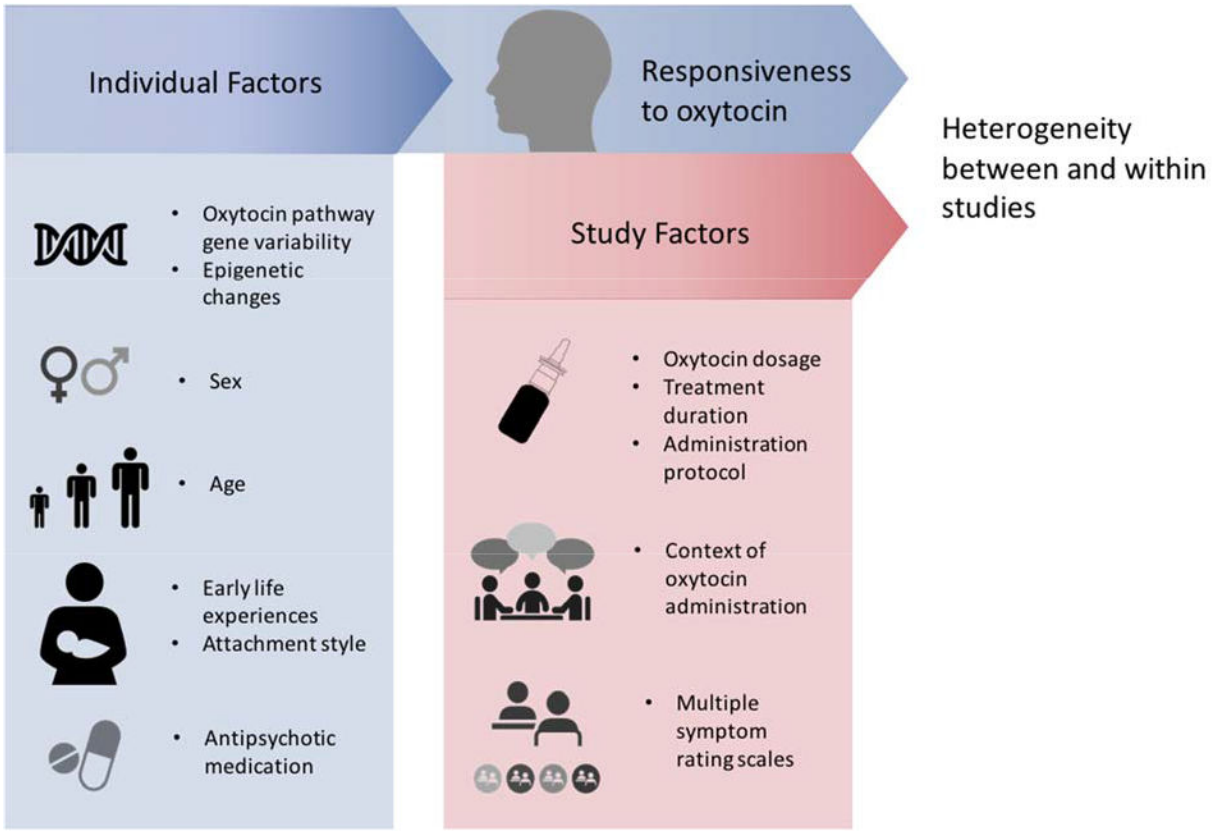

Fig. 2. Sources of heterogeneity in studies of oxytocin in schizophrenia

Individual factors affect responsiveness to exogenous oxytocin, which, combined with study factors, lead to heterogeneous results.

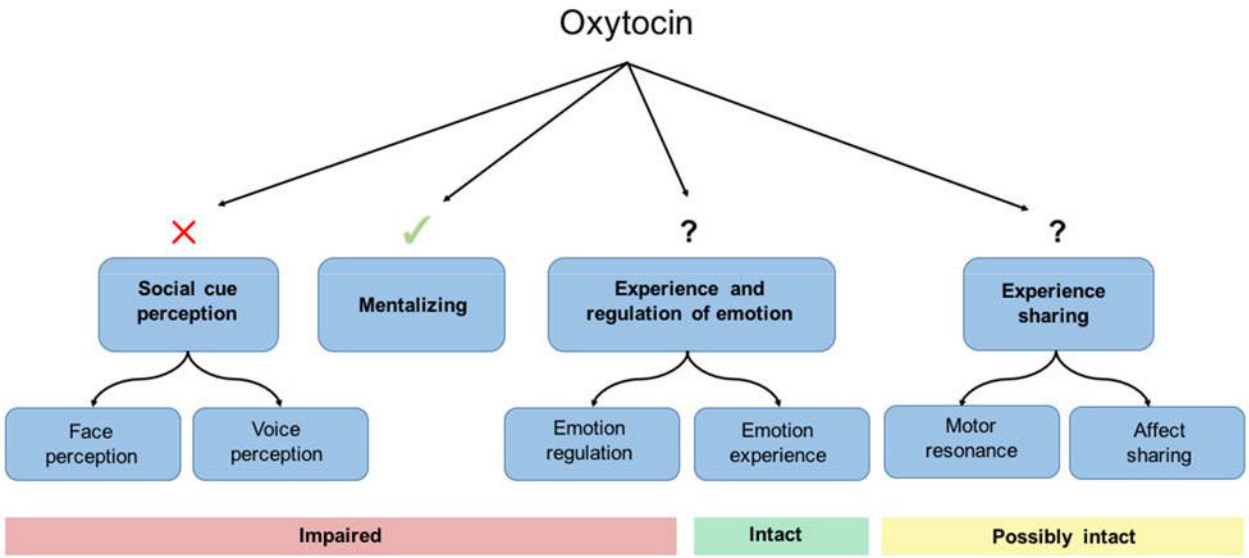

Fig. 3. Social cognitive processes in schizophrenia (adapted from Green et al. 2015) and potential oxytocin effects

In studies of oxytocin effects on social cognition in schizophrenia, oxytocin does not consistently influence social cue perception deficits. However, more promising effects are seen on mentalizing deficits. Oxytocin effects on the other domains of social cognition, experience and regulation of emotion and experience sharing, have not yet been investigated.

Table 1

Studies evaluating oxytocin effects on symptom rating scales.

Authors	N	Gender	Mean age (SD)	Duration	Design	Setting	Dosing	Administration	Symptom measures	Outcomes
Cacciotti-Sajia et al., 2015	52 SZ OT=27, PL=26	M+F	OT: 21.5 (4.2) PL: 22.3 (4.4)	6 weeks	Between	Outpt	24 IU BID	Self	SAPS SANS	OT did not improve positive symptoms Increased use of OT correlated with less severe negative symptoms
Dagani et al., 2016	32 SZ	26 M 6F	30.4 (6.7)	16 weeks	Within	Outpt	40 IU daily	Self	PANSS	OT did not improve positive, negative, or general symptoms
Davis et al., 2014	27 SZ OT=13, PL=14	M	OT: 37 (10.8) PL: 37 (10.8)	6 weeks	Between	Outpt	40IU 2× per week	Supervised	BPRS CAINS	OT did not improve positive or negative symptoms
Feifel et al., 2010	15 SZ	M+F	48 (8.9)	3 weeks	Within	Outpt	40IU BID	Self	PANSS	OT improved positive and negative symptoms
Gibson et al., 2014	14 SZ OT=8, PL=6	M+F	OT: 38.9 (7.22) PL: 35.6 (9)	6 weeks	Between	Outpt	24IU BID	Self	PANSS	OT improved negative symptoms
Lee et al., 2013	28 SZ OT=13, PL=15	M+F	OT: 44.7 (11.7) PL: 35.1 (8.2)	3 weeks	Between	Inpt/Outpt	20IU BID	Self	BPRS SANS	OT improved negative symptoms in inpatients only
Modabbernia et al., 2013	40 SZ OT=20, PL=20	M+F	OT: 32.3 (7.4) PL: 33.2 (6.9)	8 weeks	Between	Inpt	40IU BID	Supervised	PANSS	OT improved positive and negative symptoms
Pedersen et al., 2011	20 SZ OT=11, PL=9	M+F	OT: 39.0 (11.2) PL: 35.8 (9.5)	2 weeks	Between	Inpt/Outpt	24IU BID	Self	PANSS	OT improved positive symptoms, general psychopathology, & paranoia

Table 2

Studies evaluating oxytocin effects on social cognition.

Authors	N	Gender	Duration	Design	Setting	Dosing	Administration	Social cognition measures	Outcomes
Averbeck et al., 2012	Exp 1: 30 SZ, 29 HC Exp 2: 21 SZ	Exp 1: M +F Exp 2: M	Single dose	Exp 1: SZ vs HCs Exp 2: crossover	Outpt	24IU	Supervised	Hexagon emotion discrimination test	OT improved emotion recognition in SZ
Davis et al., 2013	23 SZ OT=11, PL=12	M	Single dose	Between	Outpt	40IU	Self	TASIT EPTT Half-PONS Ekman stimuli	OT improved high level social cognition in SZ No improvement in low level or overall social cognition
Fischer-Shofty et al., 2013	35 SZ 48 HC	M+F	Single dose	Within	Outpt	24IU	Supervised	IPT	OT improved kinship recognition in SZ
Goldman et al., 2011	13 SZ 11 HC	M+F	Single dose	Within	Outpt	10 IU 20IU	Supervised	Ekman stimuli (perceived intensity) Benton Facial Discrimination Test	10 IU decreased emotion recognition 20 IU improved emotion recognition in polydipsic SZ
Guastella et al., 2015	21 SZ	M	Single dose	Within	Outpt	24 IU	Supervised	DANVA FEEST RMET FBPSTL Hinting task Faux Pas Recognition	OT improved performance on higher order social cognition Improved paralinguistic subscomponent of DANVA
Horta de Macedo et al., 2014	20 SZ 20 HC	M	Single dose	Within	Outpt	48 IU	Supervised	Facial Emotion Matching	OT did not improve emotion matching in SZ or HCs
Shin et al., 2015	16 SZ 15 HC	M	Single dose	Within	Outpt	40IU	Supervised	Emotion Recognition Test (C-KFEE stimuli)	OT attenuated amygdala activity for emotional faces in SZ OT increased amygdala activity in HCs
Woolley et al., 2014	29 SZ 31 HC	M	Single dose	Within	Outpt	40 IU	Supervised	RMET TASIT	OT improved controlled social cognition in SZ

Table 3

Social cognition tasks used in studies of oxytocin in schizophrenia.

Task	Description	Domain assessed	Citation	Used by
Facial Affect Recognition Task	Still photographs of faces depicting basic emotions; participants select corresponding emotions from a list.	Social cue perception	Ekman and Friesen, 1976	Goldman et al., 2011
Emotion Matching Task	Still photographs of faces depicting basic emotions; participants select corresponding emotions from a list.	Social cue perception	Ekman and Friesen, 1978	Horta de Macedo et al., 2014
Facial Expression of Emotions Task (FEEST)	Still photographs of faces depicting basic emotions; participants select corresponding emotions from a list.	Social cue perception	Young et al., 2002	Guastella et al., 2015 Cacciotti-Sajia et al., 2014
Emotion Recognition (ER-40)	Still photographs of faces depicting basic emotions; participants select corresponding emotions from a list.	Social cue perception	Kohler et al., 2004	Gibson et al., 2014
Emotion Recognition Test	Still photographs of faces depicting basic emotions; participants select corresponding emotions from a list.	Social cue perception	Shin et al., 2015	Shin et al., 2015
Movie Stills Task	Stills from scenes depicting emotional interactions shown first with all facial expressions erased, second with facial expressions; participants select characters' emotions from a list.	Social cue perception	Adolphs et al., 2003	Cacciotti-Saija et al., 2014
Hexagon Emotion Discrimination Task	Still photographs of faces depicting basic emotions, including morphs between pairs of emotions; particpants select corresponding emotions from a list.	Social cue perception	Calder et al., 1996	Averbeck et al., 2011
Profile of Nonverbal Sensitivity (PONS)	2-second videos containing facial expressions, voice intonations, & bodily gestures of a female; participants select which of two labels best describes a situation that would generate the social cues.	Social cue perception	Rosenthal et al, 1979	Davis et al., 2014
Half-Profile of Nonverbal Sensitivity (Half-PONS)	Abbreviated version of PONS	Social cue perception	Rosenthal et al., 1979; Ambady et al., 1995	Davis et al., 2013
Reading the Mind in the Eyes Task (RMET)	Still photographs of eye region of faces; participants select corresponding emotion from a list.	Social cue perception	Baron-Cohen, 2001	Cacciotti-Saija et al., 2014 Woolley et al., 2014 Guastella et al., 2015 Gibson et al., 2014
Trustworthiness Task	Still photographs of faces; participants rate faces on	Social cue perception	Adolphs et al., 1998	Pedersen et al., 2011

Task	Description	Domain assessed	Citation	Used by
	approachability or trustworthiness.			Gibson et al., 2014
Diagnostic Analysis of Non-Verbal Accuracy (DANVA)	Still photographs of faces & audio clips; participants use facial expressions, postures, gestures, & paralanguage to infer corresponding emotion from a list.	Social cue perception	Nowicki and Duke, 1994	Guastella et al., 2015
The Awareness of Social Inference Task (TASIT)	Brief audiovisual scenes depicting social interactions between 2-3 characters; participants answer yes/no questions regarding emotions, beliefs, & intentions following each scene.	Part I (EET): Social cue perception Part 2 (SI-M): Social cue perception Part 3 (SI-E): Mentalizing	McDonald et al., 2006	Davis et al., 2013 Davis et al., 2014 Woolley et al., 2014
Brune Theory of Mind Picture Stories Task	Cartoon picture story depicting an interaction between two characters; participants answer questions about characters' beliefs and intentions.	Mentalizing	Brune 2003	Pedersen et al., 2011 Gibson et al., 2014
False Belief Picture Sequencing Task (FBPST)	Cartoon picture story depicting an interaction between two characters; participants infer characters' beliefs in order to correctly sequence panels.	Mentalizing	Langdon et al., 1997; Langdon and Coltheart, 1999	Cacciotti-Saija et al., 2014 Guastella et al., 2015
FBPST: The Faux Pas Recognition Task	Brief written stories; participants evaluate whether a character said something they shouldn't have and, if so, why.	Mentalizing	Baron-Cohen et al., 1999	Cacciotti-Saija et al., 2014 Guastella et al., 2015
FBPST: Hinting Task	Brief written passages presenting a verbal exchange between characters involving hinting; participants evaluate intentions of the characters.	Mentalizing	Corcoran et al., 1995; Marjoram et al., 2005	Guastella et al., 2015
Emotional Perpective Taking Task (EPTT)	Still photographs depicting two characters in a social interaction with one character's face masked; participants infer emotional expression of masked face from two choices.	Mentalizing	Derntl et al., 2009	Davis et al., 2013
Interpersonal Perception Task	Brief audiovisual scenes depicting realistic social behavior; participants infer belief & intentions of characters to answer questions about their relationships following each scene.	Mentalizing	Costanzo and Archer, 1989	Fischer-Shofty et al., 2013
Empathic Accuracy Task	Brief audiovisual clips of characters discussing positive or negative autobiographical events; participants rate how positive/negative the character is feeling & how positive/negative they themselves are feeling.	Empathy/Mentalizing	Lee et al., 2011	Davis et al., 2014

Task	Description	Domain assessed	Citation	Used by
Empathy Quotient	Self-report questionnaire; participants rate their level of empathy across 40 items.	Empathy/Mentalizing	Baron-Cohen et al., 2004	Cacciotti-Saija et al., 2014
Interpersonal Reactivity Index (IRI)	Self-report measure consisting of four subscales, each addresses an aspect of empathy: Perspective Taking, Fantasy, Empathic Concern, Personal Distress.	Empathy/Mentalizing (Perspective Taking subscale)	Davis et al., 1983	Gibson et al., 2014
Ambiguous Intentions Hostility Questionnaire (AIHQ)	Brief written vignettes describing social situations; participants answer questions about intentions of the characters & how participants themselves would respond to the situation.	Attributional style/Mentalizing	Combs et al., 2007	Cacciotti-Saija et al., 2014 Gibson et al., 2014
Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT).	Assesses four components of emotional processing: Perceiving Emotions, Using Emotions to Facilitate Thinking, Understanding Emotions, and Managing Emotions.	Global emotional Intelligence/ Empathy/Social cue perception/ Mentalizing	Mayer et al, 2003	Davis et al., 2014 Brambilla et al., 2016