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Research Review: Social motivation and oxytocin in autism – implications for joint attention development and intervention

Katherine K. M. Stavropoulos, and Leslie J. Carver
Department of Psychology, University of California, San Diego, CA, USA

Background and scope: The social motivation hypothesis (SMH) suggests that individuals with autism spectrum disorders (ASD) are less intrinsically rewarded by social stimuli than their neurotypical peers. This difference in social motivation has been posited as a factor contributing to social deficits in ASD. Social motivation is thought to involve the neuropeptide oxytocin. Here, we review the evidence for oxytocin effects in ASD, and discuss its potential role in one important social cognitive behavior. **Methods:** Systematic searches were conducted using the PsychINFO and MEDLINE databases and the search terms 'oxytocin' and 'autism'; the same databases were used for separate searches for 'joint attention', 'intervention', and 'autism', using the same inclusion criteria as an earlier 2011 review but updating it for the period 2010 to October 2012. **Findings:** Several studies suggest that giving oxytocin to both individuals with ASD and neurotypical individuals can enhance performance on social cognitive tasks. Studies that have attempted to intervene in joint attention in ASD suggest that social motivation may be a particular obstacle to lasting effects. **Conclusions:** The review of the evidence for the SMH suggests a potential role for oxytocin in social motivation deficits in ASD. Because of its importance for later communicative and social development, the focus here is on implications of oxytocin and social motivation in the development of and interventions in joint attention. Joint attention is a central impairment in ASD, and as a result is the focus of several behavioral interventions. In describing this previous research on joint attention interventions in ASD, we pay particular attention to problems encountered in such studies, and propose ways that oxytocin may facilitate behavioral intervention in this area. For future research, integrating behavioral and pharmacological interventions (oxytocin administration) would be a worthwhile experimental direction to improve understanding of the role of oxytocin in ASD and help optimize outcomes for children with ASD. **Keywords:** Autism spectrum disorders, behavioral interventions, social motivation hypothesis.

Introduction

Atypicalities in social behavior and social cognition are a central characteristic of autism spectrum disorders (ASD). Although it is clear that individuals with autism are impaired in multiple aspects of social behavior, the basis for these concerns has been the subject of debate. Effective strategies for intervening in social deficits in ASD can be improved by an understanding of the mechanisms behind the deficits, as well as effective behavioral treatments. Ideally, treatments would integrate knowledge that has proven effective in the lab, and our growing understanding of the neural basis of ASD.

The social motivation hypothesis (SMH) (Dawson, 2008; Dawson & Bernier, 2007; Dawson et al., 2002, 2005; Grelotti, Gauthier & Schultz, 2002) has been proposed as an explanation for social deficits in ASD. According to the SMH, children with ASD lack motivation to engage in social activities (joint attention, eye gaze) because they find these activities less rewarding than neurotypical individuals do. Brain reward circuits in neurotypical individuals are activated by social rewards such as faces (Kampe, Frith, Dolan & Frith, 2001; Vrtička, Andersson, Grandjean, Sander & Vuilleumier, 2008). In contrast, in ASD, reward centers are less activated for social stimuli than in controls (Kohls et al., 2012; Scott-Van Zeeland, Dapretto, Ghahremani, Poldrack & Bookheimer, 2010). It is not yet clear whether reward deficits in ASD are specific to social rewards, or reflect a general reward processing deficit (Dichter, Richey, Rittenberg, Sabatino & Bodfish, 2012; Dichter, Felder, et al., 2012). The SMH is the first theory to suggest that the lack of social motivation itself leads to later autism symptomology including abnormal brain responses to faces (McPartland, Dawson, Webb, Panagiotides & Carver, 2004), language and communication problems (Charman, 2003), and impaired joint attention ability (Charman, 2003; Mundy, 1995; Mundy, Sigman, Ungerer & Sherman, 1986), rather than that abnormal social brain function precedes and causes the symptoms of autism.

If there is a deficit in social motivation in ASD, a likely candidate mechanism is abnormality in the function of the neuropeptide oxytocin. Oxytocin has been implicated in several aspects of social behavior in animals (e.g. Liu & Wang, 2003) and humans (e.g. Guastella, Mitchell & Dadds, 2008), and likely plays a role in social reward systems (e.g. Baskerville & Douglas, 2010). Here, we examine the literature on the SMH in ASD, and the possible role of oxytocin in

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it. As a 'test case', we examine the putative role of oxytocin and social motivation in a specific social cognitive behavior, joint attention. Impairments in joint attention are one of the earliest and clearest signs of ASD. It is important to note that while this review will focus specifically on joint attention, there are many other problems in ASD that are relevant to social motivation. In a recent review, Dawson, Bernier and Ring (2012) discussed the role of oxytocin in a different facet of social behavior: social orienting.

First, we will describe the role of oxytocin in social motivation. Next, we will review the recent research on oxytocin levels and genetics in individuals with ASD. We next describe the effect of oxytocin administration in people with ASD and typical development. We will discuss how social motivation may contribute to the development of joint attention in both neurotypical individuals and those with ASD. Next, we describe behavioral interventions that have attempted to improve joint attention in individuals with ASD. This review will discuss behavioral interventions insofar as they relate to the SMH and the potential role of oxytocin. It is not written to evaluate clinical practice, but rather to review interventions that have attempted to improve joint attention, relate them to the SMH and oxytocin, and discuss implications of oxytocin findings for interventions.

Method

Systematic searches were conducted using the PsychINFO and MEDLINE databases and the search terms 'oxytocin' and 'autism'. The search was limited to empirical peer reviewed articles on human populations that were written in English. Forty studies fit these criteria. We examined the reference sections of the remaining studies to check for papers missed by the original search. Of these, we included ten papers that administered oxytocin to humans and measured social behaviors as a direct outcome. Papers that administered oxytocin but did not measure social behaviors (e.g. Kirsch et al., 2005) were not included.

For our discussion of joint attention and interventions targeting joint attention, searches were conducted using PsychINFO and MEDLINE with the search terms 'joint attention', 'intervention', and 'autism'. The search was limited to empirical peer-reviewed articles written in English. 76 peer reviewed articles remained for consideration. White et al. (2011) published an excellent and comprehensive review summarizing behavioral interventions that focused on joint attention in ASD up through 2010. The authors searched in multiple online databases, and used the following criteria for inclusion: papers must utilize an intervention for joint attention, use joint attention as a dependent variable, utilize experimental control, and have at least one child with ASD in the study. The authors found 27 articles that met the above criteria for review. The current review utilized the same inclusion criteria as White et al. (2011). To avoid redundancy with White et al. (2011), we included studies from 2010 to October 2012 (the time of manuscript submission), as well as studies from White et al. (2011) that were particularly relevant to the SMH and joint attention.

Oxytocin's role in social motivation

Although this review will focus on oxytocin and its role in social motivation, it is important to note that oxytocin does not work alone to modulate social behaviors. Gordon, Martin, Feldman and Leckman (2011) reviewed oxytocin's relation with the neuropeptide arginine vasopressin, and how both interact with sex hormones and the hypothalamic-pituitary-gonadal axis to affect sexual, maternal, and adult bonds. For the purposes of this review, we will focus on the neurochemical oxytocin and its interactions with dopamine in the putative social motivation system.

Dopamine is the primary neurotransmitter involved in the reward system (Schultz, 1998). Functional magnetic resonance imaging (fMRI) research has shown that areas involved in the dopamine reward pathway (e.g., the ventral striatum) are activated in neurotypical adults when pictures of faces are shown (Cacioppo, Norris, Decety, Montelone & Nusbaum, 2009). This suggests that the dopamine reward circuit responds to social stimuli. This study also measured brain activity of lonely participants compared to non-lonely participants, and found that lonely individuals show less activity of the ventral striatum reward pathway in response to faces compared to non-lonely individuals. Thus, social stimuli might be more rewarding for some people than for others. For example, if people who find social stimuli less rewarding may be more likely to become lonely (Cacioppo et al., 2009). Alternatively, of course, it may be that spending a great deal of time alone leads to a reduction in oxytocin levels. However, if low oxytocin levels lead to social isolation, this may explain one aspect of social function in ASD. Perhaps individuals with ASD find social stimuli less rewarding (because of differences in the reward pathways in the brain), and therefore are not motivated to seek out those interactions. This failure to find social stimuli rewarding could in turn contribute to symptoms of autism.

Bell, Nicholson, Mulder, Luty and Joyce (2006), measured plasma oxytocin levels of individuals with different personality traits. People with low levels of reward dependence, as assessed using the Temperament and Character Inventory, also had low levels of oxytocin. Another study found similar results for reward dependence, and found that women who were more likely to express and share emotions with friends showed higher oxytocin levels (Tops, Van Peer, Korf, Wijers & Tucker, 2007). These studies support the hypothesis that oxytocin plays an important role in social behaviors, and that oxytocin

is related to variations in personal characteristics related to social rewards.

The dopamine reward system is activated in response to eye contact (Kampe et al., 2001) and smiling supportive faces (Vrtička et al., 2008). However, research involving nonhuman mammals has shown that dopamine alone might not account for social motivation. Oxytocin might be involved in social behavior and rewards via the mesocorticolimbic dopamine circuit (Dawson, 2008; Insel & Frenald, 2004; Neuhaus, Beauchaine & Bernier, 2010). Oxytocin is a peptide synthesized in the hypothalamus and released into the blood stream via the posterior pituitary (Insel, O'Brien & Leckman, 1999). Neuropeptides such as oxytocin might modulate the dopamine reward pathway when social interactions occur (Baskerville & Douglas, 2010; Young, Liu & Wang, 2008). In female prairie voles, blocking oxytocin receptors in the nucleus accumbens prevented partner preference induced by dopamine agonists. Conversely, blocking dopamine receptors in the nucleus accumbens prevented partner preference induced by oxytocin agonists (Liu & Wang, 2003). The animal literature suggests that an association between dopamine and oxytocin could also exist in humans.

There is an extensive literature on oxytocin in animals (Liu & Wang, 2003; Ferguson, Young, Hearn, Insel & Winslow, 2000; for a review see Modi & Young, 2012). As these studies examine oxytocin function in animals, they do not directly inform the question of how oxytocin dysfunction may be related to ASD. Thus, we will not discuss them further here. In addition, although this review will discuss oxytocin as it is relevant to social dysfunction in ASD, others have written excellent reviews on oxytocin and other aspects of social behavior, including parenting and romantic bonds (e.g. Feldman, 2012). This review will focus on oxytocin and its relationship to the reward system, but it is important to note that other neuropeptides, including vasopressin, have also gained attention as potentially important for social behavior in humans. For an in-depth review of studies that have administered either oxytocin or vasopressin and measured various aspects of social behavior, see Zink and Meyer-Lindenberg (2012).

We will next consider evidence that supports the hypothesis that oxytocin is deficient or different in individuals with ASD compared to neurotypical individuals.

Evidence for deficient/different oxytocin levels in ASD

Initial papers looking at oxytocin levels in individuals with ASD measured blood plasma levels of oxytocin. In a study of plasma oxytocin levels in children with autism and neurotypical peers, Modahl et al. (1998), found that children with autism had lower oxytocin levels than controls. The relationship between oxytocin levels and social functioning was different for neurotypical children than those with ASD. Neurotypical children who had higher oxytocin levels scored higher on social interaction scales, while children with ASD with higher oxytocin levels were more impaired in social and linguistic development (Modahl et al., 1998). However, plasma levels of oxytocin were measured, which are thought to provide a less direct measure of neuropeptide levels than cerebral spinal fluid (CSF). Furthermore, the ASD and control groups were not matched for verbal or nonverbal measures of IQ, or on measures of daily living, communication, or socialization. The control group scored significantly higher on these measures than the ASD group (Modahl et al., 1998). There was also large variability in oxytocin levels in the sample (e.g. there were children with ASD with high levels of oxytocin, and neurotypical children with low levels of oxytocin).

Individuals with ASD not only may have lower levels of oxytocin, they also show differences in an alternative peptide form of oxytocin (the extended form of oxytocin, oxytocin-X, with a three amino acid extension, Gainer, Lively & Morris, 1995). Oxytocin-X becomes oxytocin through enzymatic activity (Green et al., 2001). Individuals with ASD showed higher levels of oxytocin-X compared to neurotypical individuals, but lower levels of oxytocin, resulting in a large oxytocin-X/oxytocin ratio difference between the two groups (Green et al., 2001). In neurotypical children, oxytocin, but not oxytocin-X was positively associated with age. In contrast, there was a positive association between oxytocin-X and age in the sample of children with ASD. Although these studies are suggestive of a relation between the synthesis of oxytocin from oxytocin-X and ASD, they are very preliminary. Participants from Modahl et al. (1998) were used in this study, and, as described above, ASD participants were not matched with the comparison group on IQ, vocabulary, communication, socialization, and daily living abilities. Furthermore, as these studies used the same participants, one must consider their results as one piece of evidence rather than a replication of findings.

These results suggest that individuals with ASD have differences in the enzymatic activity that converts oxytocin-X to oxytocin in typical individuals, which could be the result of defects in the genes controlling oxytocin synthesis, the oxytocin gene itself, or genes that regulate developmental changes in activity. Although these studies must be interpreted with caution, they provided important preliminary evidence for differences in oxytocin between typical individuals and those with ASD, and have served to motivate later research on this topic.

Genetic studies

There are multiple studies that shed light on potential genetic mechanisms that may be responsi-

ble for the differences in oxytocin in individuals with ASD. Studies have largely focused on two genes, the oxytocin receptor gene (OXTR), and a gene hypothesized to be involved in oxytocin release (CD38) (Ebstein et al., 2009; Lerer et al., 2010; Munesue et al., 2010; Reibold et al., 2011).

Several studies investigating the relation between ASD and OXTR have found correlations between single nucleotide polymorphisms and ASD symptoms (Campbell et al., 2011; Ebstein et al., 2009; Jacob et al., 2007; Lerer et al., 2008; Liu et al., 2010; Walum et al., 2012; Wu et al., 2005; Ylisaukko-oja et al., 2006; Yrigollen et al., 2008; For a review of the relation between single nucleotide polymorphisms of the OXTR and various psychiatric disorders including ASD, depression, and anxiety, see Brüne, 2012). However, several studies that have found relations between ASD and OXTR alleles have not corrected for multiple comparisons, and one that did (e.g. Campbell et al., 2011) found that effects were not maintained after corrections were applied. As has been described by Sullivan (2007), there are risks of false positive significant results in genetic association studies where correction of the significance threshold to account for the number of tests conducted is not applied. Of the papers mentioned above, only Ebstein et al. (2009), Liu et al. (2010), and Yrigollen et al. (2008) adjusted *p*-values for multiple comparisons. Lerer et al. (2008, 2010), used a similar, albeit slightly less conservative technique of correcting for multiple comparisons but accounting for correlations between markers. As Lerer et al. (2010) point out, this technique increases power, but results should nevertheless be interpreted somewhat cautiously. Jacob et al. (2007) does not discuss correction for multiple comparisons, but because the authors only tested two a priori identified single nucleotide polymorphisms, this potential confound is likely not applicable to this study. Similarly, Reibold et al. (2011), examined CD38 expression, and a priori identified single nucleotide polymorphism, so the concerns about multiple comparisons likely do not apply. Campbell et al. (2011) undertook the largest-scale study of single nucleotide polymorphisms, observed phenotypes, and ASD. Although the authors found multiple nominally significant results, they point out that none of the results would survive corrections for multiple comparisons. The results of these studies can be interpreted as preliminary evidence for association between alterations in the OXTR gene and ASD, and provide useful future directions for research associating genetic results with observable phenotypes of ASD. Future studies should be careful to employ rigorous statistical controls to confirm this finding.

Not all studies find relations between single nucleotide polymorphisms and ASD (e.g. Tansey et al., 2010; Wermter et al., 2009). In independent samples from Portugal and the UK, Tansey et al. (2010) did not find a relation between any significant single nucleotide polymorphism on the OXTR gene and ASD that survived statistical correction for multiple comparisons. The authors suggest heterogeneity of participants as one reason for lack of replication from previous studies. The two samples did not utilize the same inclusion criteria, however, which might also have affected the outcome (Tansey et al., 2010).

Other studies have suggested that oxytocin genes are associated with reward dependence, and fMRI activation in response to social stimuli (Tost et al., 2010). Finally, a genetic study of ASD suggested that over methylation of OXTR could be responsible for gene silencing in some patients (Gregory et al., 2009). Although these genetic studies are by no means conclusive evidence that the OXTR or CD38 genes are causally related to ASD, they do suggest that it is important to study oxytocin in ASD. Given the diversity of genetic results, epigenetic approaches may be a beneficial avenue for future research in pharmacological treatment for ASD.

This section has briefly reviewed genetic studies concerning oxytocin and ASD. Other studies have investigated single nucleotide polymorphisms on oxytocin-related genes in neurotypical individuals (e.g. Chen & Johnson, 2011; Sauer, Wörner, Kirsch, Montag & Reuter, 2012; Walum et al., 2012), as well as genetic studies of arginine vasopressin and ASD. Those studies are outside the scope of the current review, but are discussed in other reviews (e.g. Ebstein, Knafo, Mankuta, Hong Chew & San Lai, 2012; Skuse & Gallagher, 2011)

Effects of oxytocin administration on social behavior

Studies of oxytocin levels and genetic studies suggest that deficits in oxytocin function should be considered as a possible contributor to social dysfunction in ASD. Table 1 summarizes the human oxytocin administration studies that measured social behaviors. In neurotypical individuals, several studies show that social behavior is enhanced under oxytocin administration. These include recognition of emotions (Domes, Heinrichs, Michel, Berger & Herpertz, 2007), gaze to the eye region of the face (Gamer, Zurowski & Büchel, 2010; Guastella, Mitchell, et al., 2008), the salience of positive social memories (Guastella, Mitchell & Mathews, 2008), and the effects of social reinforcement on learning (Hurlemann et al., 2010). Neurotypical individuals given oxytocin show increased trust during a social computer game (Kosfeld, Heinrichs, Zak, Fischbacher & Fehr, 2005). Oxytocin also decreases amygdala response to fearful scenes and faces (Gamer et al., 2010; Kirsch et al., 2005). These studies provide important information about the role of oxytocin in social behavior in neurotypical individuals. However, in neurotypical individuals, effects of oxytocin

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Table 1 Studies that have examined effects of oxytocin on social behavior

Study authors	Population, sample size (*N*), age (mean, *M*)	Administration	Dependent variable(s)	Results of oxytocin administration	Effect size
Andari et al., 2010;	HFAD, AS (*N* = 13) TD (*N* = 13) *M* = 26 years	Intranasal	1. Cooperation with computer partners in a computer game 2. Gaze to regions of the face	1. Demonstrated preference for 'good' versus 'bad' computer partner 2. Increased gaze to eye region of the face	–[a] –[a]
Bartz et al., 2010;	TD *N* = 27 *M* = 26.8 years	Intranasal	Accuracy of emotional /empathetic recognition as a function of autism quotient (AQ) scores	Individuals with low AQ scores did well on the empathy task regardless of oxytocin; whereas individuals with high AQ scores improved after oxytocin	–[a]
Domes et al., 2007;	TD *N* = 30 *M* = 25 years	Intranasal	Reading the Mind in the Eyes Test (REMET)	Improvement on items rated as 'difficult'	–[a]
Gamer et al., 2010;	TD *N* = 46 *M* = 28 years	Intranasal	1. Fixation to regions of emotional faces 2. Amygdala activity in response to emotional faces	1. More gaze changes toward eye region regardless of facial emotion 2. Dampened amygdala response to fearful faces; enhanced response to happy/neutral faces	–[a] –[a]
Guastella et al., 2010;	HFAD, AS *N* = 16 *M* = 14.8 years	Intranasal	REMET	Improvement on items rated as 'easy'	–[a]
Guastella, Mitchell, et al., 2008	TD *N* = 52 *M* = 19.80 years	Intranasal	Looking time and fixation to regions of neutral faces	Longer gaze + more fixations to the eyes	Fixation count to eyes placebo versus oxytocin: ES = .88 Gaze time to eyes placebo versus oxytocin: ES = 1.20
Guastella, Mitchell, and Mathews 2008;	TD *N* = 69 *M* = 19.98 years	Intranasal	Making 'remember', 'know' or 'new' judgment for new and previously seen happy, neutral, and angry faces	More likely to make 'remember' and 'know' judgments for previously seen happy faces, but not for neutral or angry faces	'know' = .608[b] 'remember' = .421[b]
Hollander et al., 2007;	ASD, AS *N* = 15 *M* = 32 years	Intravenous	Ability to identify and comprehend affective speech	1. Improved ability to identify and comprehend affective speech 2. Improvements lasted to session 2 if session 1 was oxytocin versus placebo	–[a] *d* = .66
Hurlemann et al., 2010;	TD *N* = 48 *M* = 25.9 years	Intranasal	1. Learning task with either social or nonsocial feedback	1. Improved learning when feedback is social	.848 main effect of oxytocin[b]
Kosfeld et al., 2005	TD *N* = 58 *M* = 22 years	Intranasal	Trust in a partner during an investment game (willingness to invest)	Increased willingness to invest with partner	.249[c]

ASD, autism spectrum disorder; HFAD, high functioning autistic disorder; AS, Asperger's syndrome; TD, typical development; RTMET, Reading the Mind in the Eyes Test.
[a]Authors did not report effect sizes, and we are unable to calculate effect sizes accurately from the published information.
[b]Authors did not report effect sizes. We calculated them with the information provided in the results section. Whenever there were multiple interactions, we calculated the effect size for the main effect.
[c]Authors did not report effect sizes. We calculated them with the information provided in the results section. Note that these effect sizes were calculated from a Mann–Whitney *U*-test, and will not be directly comparable to the other effect sizes reported above (e.g., Cohen's *d*). An effect size calculated this way considers .3 as a moderate effect size.

administration are seen only on difficult versions of tasks (Domes et al., 2007). For example, in the Reading the Mind in the Eyes Test (Baron-Cohen, Wheelwright, Hill, Raste & Plumb, 2001; Domes et al., 2007), intranasal doses of oxytocin improved neurotypical adults' performance, but only on items that had been identified in previous research as 'difficult' (Domes et al., 2007). There was no improvement on items identified as 'easy'. This is likely because the Reading the Mind through the Eyes Test was designed to measure severe impairments in mind reading (e.g. with individuals with ASD), and thus neurotypical adults already score highly on items rated as 'easy' (Domes et al., 2007).

Domes et al.'s (2007) results may be explained in part by changes in looking behavior to the face under oxytocin administration. Guastella, Mitchell, et al. (2008) administered intranasal oxytocin to neurotypical adults and measured both looking time and fixations to various regions of the face. Participants who received oxytocin had significantly longer gaze and more fixations to the eye region of the face compared to those who received placebo. Increased gaze to the eyes may have helped participants better identify ambiguous emotions in the Reading the Mind through the Eyes Test. Following the direction of eye gaze is an important preliminary component of joint attention (Scaife & Bruner, 1975). Because there is significant evidence that people with ASD tend to look less at eyes than neurotypical controls (Jones, Carr & Klin, 2008; Klin, Jones, Schultz, Volkmar & Cohen, 2002), results from the Guastella, Mitchell, et al. (2008) study have provocative implications for ASD, and particularly the joint attention deficits reported in children with ASD.

Administering oxytocin to individuals with ASD

Studies that have administered oxytocin to individuals with ASDs are relatively limited. Of those that exist, there is a range of procedures that have been utilized. In general, results of these studies suggest that oxytocin improves performance on social tasks relative to placebo. These tasks include: recognition of affective speech (Hollander, Bartz, Chaplin & Phillips, 2007), the Reading the Mind through the Eyes Test (Guastella et al., 2010), and social cooperation in an online computer game (Andari et al., 2010). Andari et al. (2010) had adult participants play a cooperative ball tossing game with fictitious partners who were programmed to have 'neutral', 'bad', or 'good' traits depending on the amount they cooperated (i.e. passing the ball back). In a baseline measure, participants with ASD or Asperger's syndrome did not distinguish between the characteristics of the partners, throwing the ball equally often to each of the players regardless of their programmed behavior. In contrast, control participants tended to throw the ball exclusively to cooperative partners by the end of the game. When participants with ASD or Asperger's syndrome were given intranasal doses of oxytocin, their performance became more comparable to neurotypical participants in that they preferred to interact with the good compared to bad partner (Andari et al., 2010). Participants with ASD or Asperger's syndrome also showed increased gaze fixation on socially relevant areas of the face (e.g. the eyes) after oxytocin administration. The results of this study suggest that, like controls, individuals with ASD or Asperger's syndrome improve on social tasks after oxytocin administration. However, even after oxytocin administration, individuals with ASD or Asperger's syndrome spent less time gazing at the face and eye region compared to neurotypical participants. Although oxytocin increased the time spent gazing at the face and eyes in individuals with ASD or Asperger's, performance was still different from controls. Furthermore, because the neurotypical participants were not tested with oxytocin, it is difficult to contextualize the improvements seen in individuals with ASD or Asperger's syndrome. For example, the results of the study cannot tell us how neurotypical individuals might perform on these tasks with oxytocin, and whether the groups would differ on eye gaze measures before and after oxytocin administration.

Guastella et al. (2010) had adolescents with ASD or Asperger's syndrome complete the Reading the Mind through the Eyes Test after taking either placebo or oxytocin. Participants showed significant improvement after oxytocin. Notably, this study was the first to administer oxytocin to young adolescents, and when analyses were restricted to individuals under 16 years of age, performance on the Reading the Mind through the Eyes Test still improved after oxytocin. However, when the items were separated into 'easy' and 'hard', improvements were significant only for 'easy' items. These results contrast with those of Domes et al. (2007), who found that while neurotypical adults showed significant improvement on the Reading the Mind through the Eyes Task after oxytocin, that improvement was significant only for items rated as 'hard'. As Domes et al. (2007) speculate, their result could be due to the fact that neurotypical adults are unlikely to improve further on items that they already perform extremely well on. Guastella et al. (2010), suggested that oxytocin might improve performance on tasks that are of medium difficulty (e.g. neither too hard nor too easy). One could speculate that because individuals with ASD or Asperger's syndrome find items rated as 'easy' to be somewhat difficult, and items rated as 'hard' to be extremely difficult, selective improvement could occur. Unfortunately, because Domes et al. (2007) only studied neurotypical adults, and Guastella et al. (2010) studied only adolescents with ASD or Asperger's syndrome, a direct comparison between the two studies is not possible.

In one within-subjects study, order effects were seen in an affective speech recognition task when

adults were given oxytocin during one session (either session one or two), and placebo during the other session (Hollander et al., 2007). Individuals who received oxytocin first maintained high levels of performance even during the later placebo session. In contrast, participants who were administered placebo in the first session showed decreased performance during their second, oxytocin session. This finding suggests two noteworthy things: administration of placebo or oxytocin during the first session improved performance relative to baseline; and performance was improved as a result of the *expectation* of receiving treatment in the placebo condition. However, when the first session injection was placebo, the improvements did not last until the second session, whereas those seen from oxytocin maintained even after the delay. Thus, there appear to be effects of oxytocin on the ability to recognize and remember affective speech even above the placebo effect. These order effects suggest that oxytocin administration has the potential to facilitate improvements in the ability to recognize affective speech that last beyond a single testing session.

These results have important implications for ASD interventions. If oxytocin is given before a behavioral intervention, improvement might continue throughout the intervention – and thus oxytocin should be administered *prior* to behavioral interventions. The Hollander et al. (2007) results also suggest that oxytocin affects the ability of individuals with ASD to correctly identify affective speech – which is an important aspect of social cognitive functioning.

However, because the Hollander et al. (2007) study was done with adults, it is difficult to make assumptions about whether oxytocin administration would have equally long-lasting results in adolescents or children with ASD. In addition, therapeutic use of oxytocin would require repeated administration over time and early in development. Currently, little is known about the effects of repeated doses of oxytocin in development.

One recent animal study looked at the effects of repeated oxytocin administration. Bales et al. (in press), repeatedly administered intranasal oxytocin to prairie voles from weaning to sexual maturity. As expected, initial oxytocin administrations led to increases in social behaviors. However, long-term administration led to deficits in partner preference behavior (Bales et al., 2012). These results suggest that oxytocin administration might have unexpected negative results over time. Relatedly Bales and Perkeybile (2012) reviewed the animal literature, and suggested that oxytocin and vasopressin administration may change how social experiences affect development. Although these papers are relevant to the animal literature, they point out the need for further research into repeated exposures of oxytocin, as well as research that will shed light on effects of early or repeated oxytocin exposure in humans.

The aforementioned studies suggest that oxytocin might mediate some social cognitive deficits seen in ASD. However, it should be noted that there have only been three completed studies that investigate the effects of oxytocin on social deficits in individuals with ASDs, and of those three, two of them were with adults. It is likely that many other studies will be completed soon. The website *clinicaltrials.gov* lists eight active and one completed study investigating the effects of oxytocin on individuals with ASD. Of these, four involve recruiting adolescents or children, and the other four are recruiting adults. From the information on the website, it appears as though none of the listed studies are administering oxytocin concurrently with a behavioral intervention with ASD, but are either measuring brain or behavior after a single administration of oxytocin, or giving oxytocin over time and measuring behavior afterwards (Clinicaltrials.gov, 2012).

We have reviewed results of oxytocin administration on social behaviors in both neurotypical individuals and those with ASD. We have limited the discussed studies to those that explicitly measured social behaviors rather than including those that discuss how social information is processed. For a review of all studies concerning oxytocin administration and social information processing, see Graustella and MacLeod (2012). For a review of studies administering oxytocin or vasopressin and using imaging methods, please see Zink and Meyer-Lindenberg (2012).

We have not discussed studies that have administered oxytocin to individuals with disorders other than ASD. Oxytocin administration has been preliminarily helpful in treating symptoms of schizophrenia (e.g. Feifel et al., 2010; Pedersen et al., 2011). For a review of the literature on oxytocin administration and schizophrenia, see MacDonald and Feifel (2012). Of particular note, Pedersen et al. (2011) found that intranasal oxytocin improved measures of social cognition in patients with schizophrenia, including theory of mind and recognition of suspicious faces. These results suggest that intranasal oxytocin might be helpful for social deficits seen in a variety of disorders, not only ASD.

Potential issues in intranasal oxytocin administration

Some questions about the efficacy of intranasal oxytocin administration exist. It is not clear whether oxytocin and other neuropeptides cross the blood–brain barrier when administered intranasally, although there is recent evidence that intranasal oxytocin appears in saliva (Weisman, Zagoory-Sharon & Feldman, 2012) and blood (Andari et al., 2010) for a short time after intranasal administration. Weisman et al. (2012) demonstrated that in neurotypical adults, intranasal oxytocin administration increases the amount of oxytocin in saliva after

15 min, reaches a peak 45 min after administration, and still not does return to baseline after 4 hr. This has important implications for the appropriate timeline for conducting experiments concerning intranasal oxytocin and social behaviors. Nine of the 10 studies reported in Table 1 measured social behaviors 45–50 min after intranasal oxytocin administration. The only exception (Hollander et al., 2007), administered oxytocin intravenously, and measured comprehension of affective speech at five separate time points as the amount of oxytocin administered was increased. Thus, the majority of studies have measured social behavior at the time of peak levels of oxytocin.

Churchland and Winkielman (2012) adeptly point out the error in assuming oxytocin has passed through the blood brain barrier based solely on reports of increased peripheral concentration of the peptide (e.g. in blood plasma). However, other studies report that peripheral and CSF levels of neuropeptides closely related to oxytocin (e.g. arginine vasopressin) are correlated (Born et al., 2002; Riekkinen et al., 1987). Studies have suggested that intranasal administration of neuropeptides, such as vasopressin, caused CSF levels to increase within 10 min of administration, and continued to rise for 80 min after administration (Born et al., 2002).

A more general issue with measuring plasma or CSF levels of oxytocin is that the amount of oxytocin in the blood or brain does not necessarily reflect whether oxytocin has reached the appropriate binding sites in the brain. Even if oxytocin reaches the brain via intranasal administration, there have not been any studies investigating *where* it goes, and whether it reaches the appropriate receptors (see Churchland & Winkielman, 2012; for a more in-depth discussion of this issue). Plasma and CSF measures of oxytocin may not reflect efficient oxytocin binding. If oxytocin receptors are damaged or the genes that control them are mutated, and oxytocin is available in the brain but not binding correctly, plasma and CSF measurements would not accurately represent the success or failure of oxytocin to bind, but only represent the net amount available in the brain. Further research on the location, timing, and binding of oxytocin after intranasal administration is necessary (Churchland & Winkielman, 2012). Such research would likely be possible with nonhuman primates, where concentrations of oxytocin in the brain could be measured after intranasal administration. While all of these limitations concerning intranasal oxytocin administration must be considered carefully, evidence in sum suggests that intranasal oxytocin administration succeeds in increasing oxytocin levels.

Social motivation and joint attention in ASD

We turn now to a case of social behavior that is impaired in ASD, and for which oxytocin may have important treatment implications. Joint attention is a crucial developmental milestone for typical social-cognitive development, and is among the most commonly identified deficits in ASD. Joint attention occurs when two people share attention to an object, location, or event in space. Joint attention allows information to be effectively conveyed from one person to another about an object without using language. In typical development, joint attention is thought to emerge during the second half of the first year of life, and is important for both successful language learning and later social cognition (Baldwin, 1991; Bates, 1979; Brooks & Meltzoff, 2005, 2008; Bruner, 1983; Corkum & Moore, 1998; Mundy & Gomes, 1998; Sigman & Kasari, 1995; Tomasello & Farrar, 1986). For reasons we will expand upon below, joint attention is an especially interesting test case for the SMH. A typical example of joint attention is the following scenario: An infant looks to his mother, up at a passing airplane, and back to her as if to indicate, 'look at that unusual thing in the sky!' This triadic interaction involving self (infant), other (mother), and their shared object of attention toward an object (airplane) is the defining feature of joint attention (Bakeman & Adamson, 1984; Scaife & Bruner, 1975; Tomasello, 1995). According to the SMH, individuals with ASD have impairments in joint attention because they find social activities less rewarding than neurotypical individuals. Given the evidence reviewed above that oxytocin may play a significant role in social behavior and social motivation, interventions focusing on joint attention that are combined with administration of oxytocin in may increase intrinsic social motivation and improve outcomes from joint attention interventions.

Although joint attention is often mentioned as a unified concept, it can be separated into two distinct subtypes that likely develop separately (Mundy & Gomes, 1998; Mundy, Sullivan & Mastergeorge, 2009). This differentiation is important because being able to respond to joint attention (i.e. following another person's gaze) likely develops earlier than initiating joint attention (i.e. seeking to share attention with another person through gaze that you initiate, Dunham & Moore, 1995). Joint attention can also serve multiple communicative functions (Gomez, Sarria & Tamarit, 1993; Mundy, Sigman & Kasari, 1993). *Imperative* joint attention occurs if a child points or gazes toward an object with the intention of requesting that object. *Declarative* joint attention occurs if a child points or gazes at an object with the intention of sharing his interest in that object with an adult (Gomez et al., 1993; Mundy et al., 1993). Using these distinctions, one could respond to a joint attention bid from another person that is either imperative or declarative, and also initiate joint attention for either of these two functions. As we will see in a subsequent section, these distinctions between two types of joint attention and

the two functions they serve are especially important when discussing joint attention difficulties in ASD.

Joint attention in children with ASD

Individuals with ASD are profoundly impaired in joint attention (Mundy, 1995; Mundy et al., 1986). This inability to share attention with another person is central to ASD and has been incorporated into the DSM-IV criteria for the disorder (American Psychiatric Association, 1994). Deficits in joint attention differentiate children with ASD from both neurotypical and other developmentally delayed children (Bacon, Fein, Morris & Waterhouse, 1998; Charman et al., 1998; Dawson, Meltzoff, Osterling & Rinaldi, 1998; Mundy et al., 1986; Sigman, Kasari, Kwon & Yirmiya, 1992).

However, individuals with ASD are not equally impaired in all aspects of joint attention. Initiating joint attention is more impaired, and predicts symptoms better, in ASD than responding to joint attention (Leekam, Lopez & Moore, 2000; Mundy et al., 1986, 1993, 2009; Sigman, Mundy, Sherman & Ungerer, 1986). Perhaps this is not surprising because responding to joint attention chiefly involves following another's gaze. One could argue that an object of another's attention is often rewarding on its own and that responding to joint attention therefore does not necessitate motivation that is purely social (Corkum & Moore, 1998). Initiating joint attention, on the other hand, requires one to be motivated to share something interesting with another individual – meaning that the motivation behind initiating joint attention is likely purely social in nature (Mundy, 1995; Mundy & Gomes, 1998; Tomasello, 1995).

Based on this reasoning, the SMH (Dawson, 2008; Dawson & Bernier, 2007; Dawson et al., 2002, 2005; Grelotti et al., 2002) emphasizes initiating joint attention more than responding to joint attention skills. Similarly, individuals with ASD are impaired in both declarative and imperative joint attention, but show more profound problems with the declarative type, which can also be characterized as involving social motivation (Baron-Cohen, 1989, 1993; Mundy et al., 1986, 1993).

Improving joint attention skills in individuals with ASD

Because of its importance for later social and linguistic development, joint attention has been a focus of a great deal of intervention research. Research suggests that children with ASD who engage in joint attention gain language skills more rapidly than their peers who do not engage in joint attention over equivalent time periods (Bono, Daley & Sigman, 2004; Siller & Sigman, 2002). Furthermore, several studies suggest that relatively good joint attention skills early in development in children with ASD predicts better language and social outcomes up to several years later (Charman, 2003; Mundy, Sigman & Kasari, 1990; Sigman & Ruskin, 1999). Interventions for children with ASD that focus on nonverbal social communication skills lead to improvements in language and social skills in these children (see White et al., 2011 for review).

Interventions designed to improve joint attention in individuals with ASD

Interventions have sought to train individuals with ASD to engage in joint attention behaviors through various behavior modification procedures (e.g. discrete trial training, pivotal response training). Such interventions use principles of positive and negative reinforcement to increase desired behavior. As mentioned above, White et al. (2011) provide a thorough review of these interventions conducted prior to 2010. Table 2 summarizes studies of interventions to improve joint attention in individuals with ASD since 2010, and this section will review papers from Table 2, as well as those from White et al. (2011) that are particularly relevant to the scope of the current review.

Kasari, Freeman and Paparella (2006) and Kasari, Gulsrud, Wong, Kwon and Locke (2010), had children engage in 5–8 min of discrete trial training designed to improve initiating and responding to joint attention. This structured intervention was immediately followed by child-directed floor time designed to improve targeted skills in a less structured setting. In interventions like this, children are extrinsically reinforced for responding to and initiating joint attention bids, and generally show marked improvements in joint attention skills. However, many intervention studies fail to conduct follow-up sessions to assess whether skills gained during intervention are maintained, and those that did varied in duration (e.g. Ferraioli & Harris, 2011; Kaale, Smith & Sponheim, 2012). Of studies that did assess improvement at follow-up, often initiating joint attention skills did not last over time (e.g. Whalen & Schreibman, 2003), or were not as successfully improved as other primary outcome measures (e.g. Schertz, Odom, Baggett, & Sideris, 2012; Kasari et al., 2010; Landa, Holman, O'Neill & Stuart, 2011). Dysfunction in social motivation may explain the finding that joint attention intervention effects often do not last to follow-up. Because of the lack of intrinsic social motivation, extrinsic rewards are used, and when these rewards are no longer available, joint attention regresses. Studies that have attempted to use more naturalistic reinforcers, or that have attempted to generate intrinsic social motivation have shown better success on follow-up (e.g. Ingersoll, 2012; Isaksen & Holth, 2009; Naoi et al., 2008). However, even some studies that follow this model still report mixed levels of success (e.g. Taylor & Hoch, 2008). Only a few studies have attempted to teach responding to or initiation joint

Table 2 Studies that have examined the effects of joint attention interventions on individuals with autism spectrum disorders since 2010 [updating the studies reviewed in White et al. (2011)]

Study authors	Sample size, Age (mean, *M*)	Focus of intervention	Length (weeks)	Sessions per week	Significant improvement (effect size)	Follow-up?	Follow-up duration (months)	Effects maintained at follow-up
Ferraioli & Harris, 2011;	4 $M = 4.2$ years	Sibling JA	7–8	–	RJA IJA (2 participants only)[a]	Y	3	RJA, IJA (2 participants only)
Ingersoll, 2012;	14 intervention 13 control $M = 37.95$ months	Imitation intervention	10	3	IJA ($\eta^2_p = .16$)	Y	2–3	IJA
Kaale et al., 2012;	61 $M = 48.4$ months	Preschool intervention	8	10	JE with mothers ($d = .67$) IJA with teachers ($d = .44$)	N	–	
Kasari et al., 2010;	19 intervention 19 control $M = 30.83$ months	Caregiver JA	8	3	JE ($d = .87$) RJA ($d = .74$)	Y	12	JE, RJA
Landa et al., 2011;	24 intervention 24 control $M = 2$ years	IJA, SPA	24	4	IJA (trend) ($d = .89$)	Y	6	IJA (trend) ($d = 1.56$)
Lawton & Kasari, 2012;	9 intervention 7 control $M = 44.69$ months	IJA	6	2	IJA for classroom observation only ($d = 1.85$)	N	–	
Lawton & Kasari, 2012	20 JA intervention 16 symbolic play intervention 16 control $M = 42.01$ months	JAPA, JAPAU	5–6	7	No significant improvement at exit	Y	6, 12	JAPA (6 months: ES = 1.36; 12 months: ES = 1.52), JAPAU (6 months: ES = 1.16; 12 months: ES = 1.75) For JA vs. control[b]
Schertz, Odom, Baggett, Sideris, 2012	11 intervention 12 control $M = 26.11$ months	IJA, RJA	16–56 ($M = 28$)	1	RJA ($d = 1.39$)	Y	1, 2	RJA ($d = 1.18$)

JA, joint attention; RJA, responding to joint attention; IJA, initiating joint attention; SPA, shared positive affect; JAPA, joint attention with positive affect; JAPAU, joint attention with positive affect and utterances; JE, joint engagement.
[a]Authors did not report effect size, and *N* was too small to calculate effect size.
[b]Authors did not report effect size. Effect size was calculated with information given by the authors in the results section of published work.

attention without tangible extrinsic rewards, although Jones and Carr (2004), suggested it as a useful direction.

Isaksen and Holth (2009) attempted to deal with the problem of joint attention regression after interventions that utilize extrinsic motivation. They reinforced the smiling, nodding, and verbalization that typically occur after initiating joint attention behaviors. For example, an adult and a child with ASD were seated across from each other and various desirable toys were on the table. The adult's smiles and nods were used as a signal that the child could take a toy. When the adult was not smiling or nodding, any attempts to take a toy were blocked. In this way, the experimenters paired natural adult behavior with a rewarding activity. These types of social reinforcements motivate neurotypical children to engage in initiating joint attention behaviors (Isaksen & Holth, 2009; Jones & Carr, 2004; Whalen & Schreibman, 2003), are naturalistic, and will continue to be present after the intervention. Isaksen & Hoth measured joint attention behaviors after a 1-month follow-up interval and found that initiating joint attention skills maintained or improved for all four participants.

In summary, intervention studies demonstrate that children with ASD can improve their response to joint attention skills. However, initiating joint attention is much more challenging, most likely for motivational reasons. Studies such as those of Ingersoll (2012), Isaksen and Holth (2009), Naoi et al., (2008), and Taylor and Hoch (2008) are useful in their attempts to improve initiating joint attention without using extrinsic motivators, but their varied success underscores the difficulty of reinforcing social interactions for children with ASD. Finding a way to intrinsically motivate children with ASD to engage in initiating joint attention behaviors while they participate in interventions is important for long-term success.

Conclusions

This review has examined literature in the context of the SMH, including: oxytocin and ASD, administration of oxytocin and social behaviors, joint attention and ASD, and behavioral interventions to improve joint attention in ASD.

Although multiple neurotransmitters and neuropeptides have been implicated as candidates for improving intrinsic motivation for social interaction, oxytocin has consistently been seen as important for social motivation, interaction, and memory. Most of the literature linking oxytocin and social behavior derives from animal research, but there is a growing literature examining oxytocin administration in humans. Data from studies in which oxytocin has been administered to humans have strengthened the argument that oxytocin is important for social interaction. Because of the link between oxytocin and social behavior that has begun to emerge, oxytocin has begun to be used in interventions to improve social recognition in individuals with ASD.

Individuals with ASD have well-documented deficits in joint attention (Bacon et al., 1998; Charman et al., 1998; Dawson et al.,1998; Mundy et al., 1986; Sigman et al., 1992). Improving joint attention deficits is important for improving social and linguistic functioning of individuals with ASD (Bono et al., 2004; Charman, 2003; Koegel, 2000; Lord, 2000; Rogers & Lewis, 1989; Siller & Sigman, 2002), and therefore has been a focus of multiple behavioral interventions (e.g. see White et al., 2011; Table 2). Although these interventions have been somewhat successful in improving joint attention, one key underlying issue has been individuals with ASD's lack of intrinsic motivation to initiate joint attention and other social interactions (Jones & Carr, 2004; Whalen & Schreibman, 2003). Extrinsic rewards are often necessary for behavioral interventions to succeed, and when those are removed, individuals with ASD are no longer motivated to engage in joint attention behaviors, resulting in a failure of effects to maintain over the long term. Some theorists have proposed that increasing intrinsic motivation for social interaction might be a key component in improving symptoms of ASD (Dawson, 2008; Dawson & Bernier, 2007; Dawson et al., 2002, 2005; Grelotti et al., 2002).

However, one piece missing from the literature is integrating behavioral interventions and oxytocin administration in individuals with ASD. Behavioral interventions are important for increasing social behaviors, especially in young children with ASD. Oxytocin has been used experimentally to attempt to change social behaviors in ASD, but to our knowledge has not yet been used in a controlled treatments study, nor has it been used in combination with other intervention methods. By adding oxytocin administration to behavioral interventions, one important problem (lack of intrinsic motivation) that seems to hinder long-term success might be diminished. Interventions that combine behavioral interventions and oxytocin administration are crucial to long-term and generalized improvement of joint attention behaviors in young individuals with ASD (Dawson et al., 2012).

Experimental tests of such interventions would advance our understanding of how oxytocin mediates social symptoms of ASD in both the short and long term. Such experiments would need to be well-controlled, double-blind, and compare interventions plus oxytocin versus the same interventions with placebo. One issue would be when to administer oxytocin during the intervention, as well as what type of intervention to utilize. Multiple meta-analyses have emphasized the effectiveness of early intensive behavioral interventions (i.e. young children with ASD receiving 30–40 hr per week of structured behavioral interventions for over 2 years,

e.g. Reichow, 2012; Eldevik et al., 2009). Although these interventions require a large time investment, they are highly successful in improving a variety of behavioral skills, as well as improving IQ. To utilize oxytocin for behavioral interventions, however, it would likely be more practical to administer a more short-term intervention similar to those reported by White et al., 2010 and in Table 2.

Based on previous animal studies (Ferguson, Aldag, Insel & Young, 2001) as well as studies of the time course of oxytocin in saliva (Weisman et al., 2012) and order effects (Hollander et al. (2007), intervention should administer oxytocin about 45 min before each intervention session (rather than after or during sessions).

Directions for future research

We propose that two highly studied and important areas (behavioral intervention and studies on oxytocin administration) should be integrated to achieve optimal outcomes for children with ASD. Combining behavioral and pharmacological interventions has been highly successful in the alleviation of symptoms in other disorders (Hoffman et al., 2006; Ressler et al., 2004).

In the case of ASD, this novel approach to improving joint attention skills with both pharmacological and behavioral intervention is a necessary and worthwhile experimental direction. Theoretically, oxytocin administration will heighten patients' *intrinsic* motivation to engage in social interactions, and the behavioral interventions will facilitate and teach social interactions. By improving intrinsic motivation to engage in social interactions, behavioral interventions can use *only* social rewards, and cease using any extrinsic motivators. Because the rewards will be entirely social, and intrinsic motivation will be improved (via oxytocin), interventions should have long-lasting effects. Using behavioral interventions in combination with oxytocin administration should increase the chances of long-term success and an improved understanding of the role of oxytocin in ASD.

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Correspondence

Katherine K. M. Stavropoulos, Department of Psychology, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0109, USA; Email: kmeltzof@ucsd.edu

Key points

- The social motivation hypothesis posits that individuals with autism spectrum disorders (ASDs) are less motivated to engage in social behaviors than their neurotypical peers, and this lack of motivation leads to later atypicalities in social behavior and cognition.
- The neurochemical oxytocin has received attention as a potential mechanism for social atypicalities in ASD.
- Administering oxytocin to individuals with and without ASD has been effective at improving social cognition.
- We propose that future studies should combine oxytocin administration and behavioral interventions to optimize outcomes for various social cognitive behaviors in autism spectrum disorder.

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