Chapter

Priming the Pathway: Combining Oxytocin and Behavioral Intervention to Improve Outcomes in Autism Spectrum Disorder

Katherine Kuhl Meltzoff Stavropoulos and Elizabeth Baker

Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social-communication deficits and the presence of restricted interests and/or repetitive behaviors. There are currently no psychopharmacological agents approved to treat core symptoms of ASD. As such, behavioral interventions are the most effective method for improving symptoms. In the current chapter, we propose that administering the neuropeptide oxytocin in conjunction with evidence-based behavioral interventions may lead to improved outcomes in social-communication for children with ASD. From a mechanistic perspective, we hypothesize that oxytocin may "prime" social reward circuitry in the brain, thereby allowing behavioral interventions designed to increase social motivation/initiation to be more effective. Extant literature related to theories of ASD, oxytocin administration in children with ASD, and behavioral intervention outcomes are reviewed, and considerations for individual characteristics (e.g., genetics, oxytocin availability, age, behavioral profile, etc.) that may affect efficacy are discussed.

Keywords: Autism spectrum disorder (ASD), Social Motivation, Oxytocin, Intervention, Reward, outcomes, neuroscience

1. Introduction

It is estimated that 1 in 59 children in the United States has a diagnosis of Autism Spectrum Disorder (ASD) [1], which is characterized by life-long social communication deficits and the presence of restricted interests and/or repetitive behaviors [2]. Though all individuals with ASD meet common diagnostic criteria, they display a wide spectrum of behavioral manifestations, thus producing a wide array of heterogeneous phenotypes. As such, a multitude of behavioral interventions exist to address common symptoms of ASD, many of which have been tailored to address the heterogeneity of the disorder. Behavioral interventions are currently one of the most effective methods for improving social-communication skills, as no medications have been approved to "treat" social communication behaviors in ASD.

In the current chapter, we propose that administering the neuropeptide oxytocin in conjunction with evidence-based behavioral interventions may lead to improved outcomes in social-communication for children with ASD. Specifically, we propose

that oxytocin administration may "prime" social reward circuitry in the brain, allowing behavioral interventions designed to increase social motivation/initiation to be more effective. This theoretical model draws from the following research: (1) the social motivation hypothesis of ASD, (2) animal and human literature related to oxytocin, (3) studies of oxytocin levels in children with ASD, (4) behavioral changes after oxytocin administration in children with ASD, (5) neural changes after oxytocin administration in children with ASD, and (6) neural changes after behavioral interventions in children with ASD.

Subsequent sections will briefly review these research areas. We propose that taken together, the aforementioned literature provides a theoretical basis for combining oxytocin administration with behavioral interventions to improve social-communicative outcomes for children with ASD.

2. Social motivation hypothesis of ASD

The social motivation hypothesis posits that early impairments in social attention (due to social stimuli being less rewarding for individuals with ASD compared to their neurotypical peers) set a series of negative developmental consequences in motion. Initial impairments in social attention--which often manifest as decreased orienting to one's own name, diminished eye contact, and decreased social initiations in early life--lead to fewer opportunities for social learning, which in turn lead to deficits in social communication, social skills, and social-cognitive development [3, 4]. The proposed neural mechanisms underlying the social motivation hypothesis are the reward centers in the brain including the amygdala, ventral striatum, and orbito-frontal cortex [4]. Importantly, social motivation is thought to involve both oxytocin and the dopaminergic reward pathways [5, 6]. Given the hypothesized role of oxytocin in social motivation, it is not surprising that oxytocin has been considered as a potential mechanism for understanding social deficits in ASD--and that oxytocin administration has been considered as a potential therapeutic agent.

3. Oxytocin overview

Oxytocin is a neuropeptide produced in the hypothalamus [7]. Colloquially referred to as the "love hormone," oxytocin has been implicated in the formation of pair bonds in a variety of species, including rats and prairie voles [8–10]. As such, oxytocin has been extensively studied and utilized for its effects on social cognition and prosocial behaviors [11–13]. It has been hypothesized that interactions between oxytocin and the dopaminergic reward system support social affiliative behaviors and social bonds [14]. Further evidence of the connection between oxytocin and the dopamine reward system comes from overlap in locations of receptor binding sites and neuronal fibers [15]. Furthermore, oxytocin cells in the hypothalamus have been found to express dopamine receptors [16]. Importantly for neurodevelopmental disorders such as ASD, oxytocin is developmentally regulated and its receptors are malleable, particularly in response to parent-child interactions [17, 18].

In contrast to other conditions in which both behavioral and medical treatments are supported by empirical evidence, no medication is currently approved to improve core symptoms of ASD. Although two pharmaceutical medications, risperidone and aripiprazole, have been approved by the Federal Drug Administration for use in ASD, they do not address core symptoms. Rather, they have been approved to treat ancillary symptoms of ASD, such as aggression and irritability [19]. Due to the lack of pharmacological interventions to address the core symptoms of ASD, there

has been a focus on compounds that directly address social communication symptoms. Given oxytocin's role in prosocial behaviors, exogenous administration of the neuropeptide has been considered as a potential therapeutic agent in ASD.

3.1 Oxytocin levels in ASD

Modahl and colleagues [20, 21] were the first to provide evidence of reduced levels of oxytocin in children with ASD. Specifically, the authors found that compared to their neurotypical peers, oxytocin does not increase prior to the onset of puberty in individuals with ASD. This suggests that oxytocin is less available to individuals with ASD during development [21]. Our understanding of oxytocin in individuals with ASD has since been shaped by research that suggests deficits in oxytocin may reveal the pathogenesis of ASD. No known mechanistic pathway exists to form a substantial link between the neuropeptide and development of ASD, but studies support the idea that lower concentrations of oxytocin are strongly related to social impairments [22].

Early studies of the endocrine system have found that oxytocin release occurs differently in children with ASD compared to their neurotypical peers, suggesting that oxytocin may be disrupted early in development in children with ASD [23]. Oxytocin blood plasma levels increase throughout neurotypical development, while children with ASD exhibit lower levels of plasma oxytocin [24] that are stable over time [21]. Therefore, disruptions of the oxytocin system may possibly occur early in life in individuals with ASD, resulting in cascading consequences.

4. Oxytocin administration in children with ASD

4.1 Behavioral findings

To our knowledge, eight studies have been conducted to measure behavioral results of oxytocin administration for children with ASD [22, 24–33]. Though the current chapter focuses on children, see the meta-analysis by Ooi and colleagues [32] for a review of randomized control trials of oxytocin administration in both children and adults. See **Table 1**.

In 2010, Guastella and colleagues [25] completed a double-blind placebo-controlled study with 16 adolescent boys with ASD (ages 12-19). 45 minutes after oxytocin (or placebo) administration, participants completed the Reading the Mind in the Eyes Task, or RMET [33]. Compared to placebo, oxytocin improved performance on the REMET for 60% of participants. When the authors split REMET items into "easy" and "hard" categories, the effect of oxytocin was particularly significant for "easy" items. This was the first investigation of the results of oxytocin administration to children/adolescents, and suggested that oxytocin improves emotion recognition in a group of males with ASD.

Tachibana and colleagues [26] measured behavioral changes associated with an open label (participants knew they were receiving oxytocin), single arm (no placebo condition) long-term oxytocin administration in 8 boys with ASD (ages 10-14). Participants received intranasal oxytocin twice a day for approximately 7 months. Oxytocin dosage was increased in a stepwise fashion every 2 months (from an initial dose of 8 IU to 24 IU). Outcome measures were scores on the Autism Diagnostic Observation Schedule—Generic (ADOS-G; [34]), Aberrant Behavior Checklist (ABC; [35]), and Child Behavior Checklist (CBCL; [36]). ADOS-G scores for items comprising the "communication," and "social interaction" sub-scales and the sum of both sub-scales were significantly improved after oxytocin administration. No change in ADOS-G scores related to play/imagination of restrictive/

Authors	Study Design & Participants	Oxytocin Administration and Dosage	Primary Outcomes
Guastella et al. [25]	Double-blind placebo-controlled design. 16 ASD (all male) • M_{age} = 14.88 yrs., SD_{age} = 2.42 yrs.	A single dose of oxytocin and a placebo nasal spray 1 week apart. (a) OXT nasal spray and (b) placebo containing all ingredients except active oxytocin puff per nostril contained 3 IU. Older participants (aged 16 –19, n = 5) received a dose of 24 IU (4 puffs per nostril, 3 IU per puff). Those aged 12 to 15 years n = 11 received 75% dose of the adult dose at 18 IU (3 puffs per nostril, 3 IU per puff).	Oxytocin improved performance on the REMET (particularly on "easy" items) compared to placebo.
Tachibana et al. [26]	Open label, single arm long-term design. 8 ASD (all male) • M_{age} = 11.93 yrs., SD_{age} = 1.32 yrs.	Intranasal oxytocin twice a day for approximately 7 months; dosage was increased in a stepwise fashion every 2 months (from an initial dose of 8 IU to 24 IU). Placebo was inserted between the dosing steps as a washout period. Concentration of OXT in the nasal spray was changed so that a total of 6 puffs/dose twice a day was maintained throughout the protocol.	Communication and social interaction scores on ADOS-G were significantly improved after oxytocin administration.
Anagnostou et al. [27]	Single arm, open label design. 15 ASD (11 male, 4 female) • M_{age} = 13.8 yrs., SD_{age} = 2.4 yrs.	Twice per day (morning and night) for 12 weeks; 24 IU total a day	Improvements on the following measures: ABC; SRS, BASC social skills and functional communication subscales, Let's Face It! Skills Battery, Irony and Empathy Task, Strange Stories Task, CASI, RBS-R, and C-YBOCS
Dadds et al. [28]	Double-blind, placebo controlled randomized controlled design. 38 ASD (all male). 19 in OXT group; 19 in placebo group • OXT: M_{age} = 10.74 yrs., SD_{age} = 2.38 yrs. • PLACEBO: M_{age} = 11.79 yrs., SD_{age} = 2.82 yrs.	Treatment group: intranasal spray contained: oxytocin, mannitol, glycerine, methyl parraben, propyl, parraben and purified water. Placebo contained all ingredients except the active oxytocin and mannitol. 5-day trial. Each nostril received a 12 IU dose (6 IU per puff) for a total of 24 IU/day.	No significant benefit of oxytocin versus placebo on SSRS, SRS, or an emotion recognition task.

Authors	Study Design & Participants	Oxytocin Administration and Dosage	Primary Outcomes
Guastella et al. [29]	Double-blind placebo-controlled design. 50 ASD (all male); 26 in OXT group, 24 in placebo • OXT: M_{age} = 13.85 yrs., SD_{age} = 1.54 yrs. • PLACEBO: M_{age} = 14.00 yrs., SD_{age} = 2.04 yrs.	Intranasal oxytocin or placebo, 2 times per day for 8 weeks. Older participants (aged 16–19, n = 5 in each group) received a dose of 24 IU. Those aged 12 to 15 years received 75% of the adult dose at 18 IU.	No improvements related to oxytocin were observed on primary outcome measures (SRS or CGI-Improvement scale).
Yatawara et al. [30]	Double-blind, randomized, placebo-controlled crossover (A/B, B/A) design. 31 ASD (27 male, 4 female).15 in OXT then placebo group; 16 in placebo then OXT group • OXT first: M_{age} = 5.7 yrs., SD_{age} = 1.5 yrs. • PLACEBO first: M_{age} = 6.7 yrs., SD_{age} = 1.8 yrs.	Intranasal oxytocin or placebo twice per day for 5 weeks, followed by a 4 week wash-out period, and then received either oxytocin or placebo (whichever they did not receive in the first phase) twice per day for 5 weeks. 24 IU total per day; 12 IU in morning and 12 IU at night.	Social-communication skills (SRS) improved significantly after oxytocin versus placebo. Ratings on the CGI were significantly better after oxytocin versus placebo.
Parker et al. [22]	Double-blind, randomized, placebo-controlled design. 32 ASD (27 males, 5 females). 13 in OXT group; 14 in placebo group • OXT: M_{age} = 9.35 yrs., SD_{age} = 2.34 yrs. • PLACEBO: M_{age} = 8.13 yrs., SD_{age} = 1.87 yrs.	Treatment group: Syntocinon nasal spray; Placebo group: placebo solution consisted of all the ingredients used in the active solution except the oxytocin compound. Participants' parents then were provided with a 4-week drug supply and were responsible for their child's continued twice daily dosing (24 IU per dose, 4 IU per puff, 48 IU/day) at home.	ASD participants who received oxytocin had greater improvements on the SRS compared to ASD participants who received the placebo. Pre-treatment plasma oxytocin negatively predicted the magnitude of improvement on the SRS (i.e., participants who had lower concentrations of oxytocin pre-treatment demonstrated the largest improvements in SRS scores).
Strathearn et al. [31]	Randomized, double-blind, placebo-controlled crossover design. 16 ASD • M_{age} = 12.8 yrs., SD_{age} = 3.4 yrs. • 16 TD • M_{age} = 13.2 yrs., SD_{age} = 3.2 yrs.	One nasal solution (oxytocin or placebo) on Visit 1 and the alternate solution on Visit 2. Participants 16 years and older received 24 IU oxytocin (10 puffs alternating between nostrils 2.4 IU). Participants aged 12–15 years received 7 puffs (16.8 IU), and participants aged 8–11 years received 5 puffs (12 IU total).	After nasal oxytocin was administered to ASD participants, differences in visual preference for structured/systemized images between ASD and TD participants was eliminated.

Table 1.
Behavioral results of oxytocin administration in children with ASD.

repetitive behaviors (RRBs) were observed. No significant changes were observed for the ABC or CBCL after oxytocin administration though some scores improved at a trend level. The authors note that oxytocin administration appeared to specifically affect social communication and interaction, but did not affect RRBs or play. However, the study was open label, single arm. Therefore, caution is needed when interpreting these findings.

Anagnostou and colleagues [27] administered intranasal oxytocin to 15 male and female adolescents (ages 10-17) twice per day for 12 weeks in a single arm, open label design. Participants completed a follow-up session 12 weeks after discontinuation of oxytocin administration. Though the authors measured change on a variety of behavioral measures related to social function, social cognition, anxiety, and repetitive behaviors, the aim of the study was to measure the safety of varying dose levels of oxytocin in this population. Safety results suggested that .4 IU/kg twice per day for 12 weeks produced no serious or severe adverse events. Using the Clinical Global Improvement-Social (CGI), almost half of the sample were classified as "responders" at 12 weeks, and most responders at 12 weeks maintained improvements 12 weeks after the end of the study (e.g. 24 weeks from the beginning of the study). At 12 weeks, significant improvements were observed for the following measures: ABC [35], Social Responsiveness Scale (SRS; [37]), Behavioral Assessment System for Children (BASC; [38]) social skills and functional communication subscales, Let's Face It! Skills Battery (LFI; [39]), Irony and Empathy Task [40], Strange Stories Task [41], Child and Adolescent Symptom Inventory (CASI; [42]), Repetitive Behavior Scale-Revised (RBS-R; [43]), Child Yale-Brown Obsessive-Compulsive Scale (C-YBOCS; [44]). At 24 weeks, significant improvements were observed for the following measures: BASC functional communication T-Score, RMET [33]--difficult items, Irony and Empathy Task, and C-YBOCS. The authors note that not all children demonstrated behavioral improvements in response to oxytocin administration, and that more information is needed about individual differences in response to oxytocin. Nevertheless, a broad array of measures was, on average, shown to increase after oxytocin administration.

Dadds and colleagues [28] completed a 5-day double-blind, placebo controlled, randomized controlled trial with 38 boys with ASD (ages 7-16). This study is unique as it combined oxytocin administration with consecutive parent-child interaction training sessions over a period of 4 days. The authors did follow-up testing 3 months after the completion of the 5-day intervention. The parent-child interaction training consisted of emotion recognition training using the Mindreading (MR) program [45], and short video clips demonstrating successful client interactions (e.g. eye contact, body language, responsiveness). Outcomes included parent-child interaction tasks (free play, emotion talk, and an "I love you" task in which a parent expresses positive emotions and the child's response is recorded), and parent-questionnaire measures (Social Skills Rating Scale, or SSRS, [46]; SRS, [37]), and an emotion recognition task (UNSW Facial Emotion Task, [28]). Analysis of the parent-child interaction tasks, parent rating scales, and emotion recognition tasks indicated behavioral improvements over time in both the placebo and oxytocin groups, but no significant benefit of oxytocin versus placebo. We note that although this study combined oxytocin and behavioral intervention, the intervention was not one previously validated for improving core symptoms of ASD, and the study timeline was short (5 days).

Guastella and colleagues [29] completed a double-blind placebo-controlled trial with 50 male participants with ASD (ages 12-18). Participants received either placebo or oxytocin nasal spray twice a day for 8 weeks. Participants were assessed again 3 months after completion of the study. Primary outcome measures were the SRS [37] and clinician ratings on the Clinical Global Impressions--Improvement scale

(CGI-Improvement). Secondary outcome measures included the Developmental Behaviour Checklist, or DBC [47] and Repetitive Behavior Scale-Revised, or RBS [43], RMET [33], the Diagnostic analysis of nonverbal accuracy, or DANVA [48], and Biological Motion [49]. No improvements related to oxytocin were observed on the primary or secondary outcome measures.

Yatawara and colleagues [30] completed a double-blind, randomized, placebo-controlled crossover (A/B, B/A) design trial in 31 children with ASD (ages 3-8). Children received intranasal oxytocin or placebo twice per day for 5 weeks, completed a 4-week wash-out period, and then received either oxytocin or placebo (whichever they did not receive in the first phase) twice per day for 5 weeks. Primary outcome measures were scores on the SRS [37], and scores on the RBS-R [43]. Secondary outcome measures were changes in ADOS scores, scores on the DBC [50], clinician-rated clinical global impressions-improvement scale [51], and the Caregiver Strain Questionnaire [52]. Results indicated that parent-rated social-communication skills (SRS) improved significantly after oxytocin versus placebo. Ratings on the CGI were significantly better after oxytocin versus placebo. To our knowledge, this study includes the youngest sample of children with ASD to receive oxytocin versus placebo in a randomized, double-blind trial. This work provides behavioral evidence of symptom reduction in ASD in response to prolonged oxytocin administration.

Parker and colleagues [22] completed a double-blind, randomized, placebo-controlled trial with 32 children with ASD (ages 6-12). Children received either intranasal oxytocin or placebo twice per day for 4 weeks. The primary outcome measure was scores on the SRS [37]. Secondary outcome measures included scores on the RBS-R [43] and Spence Children's Anxiety Scale [53]. Additionally, authors measured plasma oxytocin concentrations both before and after participation in the trial, as well as expression of genes related to oxytocin receptors (Oxytocin Receptor Gene, OXTR, and Vasopressin Receptor 1a; V1AR). Results suggested that children who received oxytocin demonstrated greater improvements on the SRS compared to those receiving placebo. Additionally, pre-treatment plasma oxytocin negatively predicted the magnitude of improvement on the SRS. That is, individuals who had the lowest concentrations of oxytocin pre-treatment demonstrated the largest improvements. The authors hypothesized conflicting findings of previous oxytocin trials may be attributable to variability in pre-treatment concentrations of oxytocin. That is, previous trials did not measure pre-treatment oxytocin concentrations which may have reduced their ability to accurately measure improvement. When the authors did not include pre-treatment oxytocin, concentration findings were non-significant. In fact, inclusion of these pre-treatment "biomarkers" improved the statistical models by 43%, which underscores the importance of measuring individual variability in pre-post measurement designs.

Strathearn and colleagues [31] completed a double-blind, placebo-controlled crossover study with 16 children with ASD and 16 neurotypical children (ages 8-19). Participants completed an eye tracking paradigm on two occasions: once after receiving oxytocin and the other after receiving a placebo nasal spray. The authors measured participants' eye gaze while viewing images that varied on how organized or structured they were. The authors' primary focus was whether or not oxytocin affected eye gaze patterns when viewing stimuli that varied on levels of systemization. Results demonstrated that after oxytocin administration, children and adolescents with ASD displayed a decreased preference for highly systemized stimuli, whereas neurotypical children and adolescents displayed increased preference for systemized images. Overall, when participants received placebo, children and adolescents with ASD displayed more of a preference for systemized stimuli compared to their neurotypical peers. After both groups received oxytocin this difference was no longer significant (e.g. participants with ASD looked more similar to their

neurotypical peers, and neurotypical children and teens looked more similar to their peers with ASD). The authors concluded that oxytocin administration may have differential effects on individuals with and without ASD, but that oxytocin appears to decrease preference for highly organized (e.g. systemized) stimuli in ASD.

Overall, studies of the behavioral effects of oxytocin in children in ASD are mixed, with some investigations observing significant behavioral changes [22, 25–27, 30, 31], whereas others find no evidence for change as a function of oxytocin versus placebo administration [28, 29]. A likely explanation for these disparate findings is outlined by Parker and colleagues [22]. The authors noted that measuring participant's plasma oxytocin levels provided a critical "biomarker" for predicting a given individual's response to oxytocin administration. Most studies do not measure oxytocin concentration prior to administration and therefore may miss individual differences which significantly impact outcomes. Parker and colleagues [22] noted that without the addition of pre-administration plasma oxytocin concentration into their predictive models, their results would have indicated no difference between oxytocin and placebo. When pre-administration oxytocin levels were included, their models were improved by 43%. This underscores why it is critical to consider biological differences in individuals *prior* to administration of oxytocin in order to more accurately understand variability within samples of children with ASD. When such individual differences are considered, behavioral effects of oxytocin may be more detectable, and/or may help us understand which children are most likely to benefit from oxytocin.

4.2 Neuroscience findings

To our knowledge, only 3 studies have investigated the effects of oxytocin on brain activity in children with ASD [54–56]; see [57] for a review. See **Table 2**.

Gordon and colleagues [54] used functional magnetic resonance imaging (fMRI) to measure brain activity after oxytocin versus placebo in 17 children and adolescents with ASD (ages 8-16.5) using a randomized, double-blind, crossover design. Forty-five minutes after administration of either oxytocin or placebo, participants completed an fMRI emotion recognition task based on the RMET [33]. In a control fMRI condition, participants were asked to label the category of automobile presented in pictures. Findings suggested enhanced brain activity after oxytocin administration in brain areas hypothesized to be critical to reward (dorsal and ventral striatum), social attention and cognition (posterior cingulate, inferior parietal lobule, posterior superior temporal sulcus), and reasoning about mental states (medial prefrontal cortex). In addition, several brain regions were less active during nonsocial judgements after oxytocin administration. Interestingly, the effect of oxytocin on brain activity in response to social judgements differed as a function of symptom severity. Children with ASD with less severe symptoms (measured with the SRS) exhibited more 'typical' brain activity after oxytocin administration compared to children with ASD with more severe symptoms. Taken together, the authors hypothesized that oxytocin may increase the reward value and/or salience of social stimuli for children with ASD while simultaneously decreasing the salience of nonsocial information.

Gordon and colleagues [55] employed a randomized, double-blind, placebo-controlled crossover design with 20 children with ASD (ages 8-16.5). Participants completed an fMRI scan twice: once receiving oxytocin and the other after receiving placebo nasal spray. The authors measured participants' brain activity in response to two social perception tasks: a biological motion task and an affective voices task. The authors' primary aim was to measure whether oxytocin increased brain activity in areas related to the reward system and the connections between reward and social brain regions (e.g.

Authors	Participants and Oxytocin Administration	Design and Stimuli/ Paradigm	Major Findings
Gordon et al. [54]	21 ASD (3 females; 18 males) • M_{age} = 13.2 yrs., SD_{age} = 2.7 yrs. Intranasally. Older participants (16 – 19 yrs.) received a dose of 24 IU (4 puffs per nostril); 15 yr olds received 18 IU (3 puffs per nostril); Younger participants (7 - 11 yrs.) received 12 IUs, (1 puff per nostril); or placebo. Testing was repeated on consecutive study visits. Order was randomized.	Randomized, double-blind, cross-over design. fMRI. Reading the Mind in the Eyes Test (RMET). Participants were instructed to label the mental state of each facial picture, or label the category of automobile images.	Social condition: Enhanced activity in the dorsal and ventral striatum, premotor cortex, posterior cingulate, inferior parietal lobule, and posterior STS in response to oxytocin compared to placebo.
Gordon et al. [55]	20 ASD (3 females) • M_{age} = 13.2 yrs., SD_{age} = 2.8 yrs. Intranasally. Older participants (16 – 19 yrs.) received a dose of 24 IU (4 puffs per nostril); 15 yr olds received 18 IU (3 puffs per nostril). Younger participants (7 - 11 yrs.) received 12 IUs, (1 puff per nostril); or placebo. Testing was repeated on consecutive study visits. Placebo or oxytocin was randomized at the first visit and participants received the opposite nasal spray at the second visit.	Randomized, double blind, placebo-controlled crossover design. fMRI. Participants passively viewed a biological motion paradigm (human motion and scrambled motion) and listened to a vocal affect perception paradigm (angry voices and happy voices).	Biological motion condition: enhanced response in the right posterior superior temporal sulcus (pSTS) after oxytocin compared to placebo administration. Negative vocal affect condition: Enhanced activation in right brainstem and right amygdala after oxytocin versus placebo administration.
Greene et al. [56]	28 ASD (2 females, 26 males) • M_{age} = 13.4 yrs., SD_{age} = 2.4 yrs. Intranasally. 3 puffs per nostril (Syntocinon), each puff contained 4 IU of oxytocin, for a total of 24 IU, or placebo containing the same inactive ingredients. Nostrils were alternated between puffs over the course of several minutes. Two scan sessions were scheduled at least 72 hours apart from one another. Order of oxytocin and placebo were counter-balanced.	Placebo-controlled double-blind design. fMRI. Participants completed an incentive delay task with nonsocial (money) or social rewards (smiling face).	Anticipation of nonsocial reward: Increased activity in right nucleus accumbens (NAcc), right frontal pole, left ACC, left superior frontal cortex, bilateral orbital frontal cortex (OFC) after oxytocin versus placebo administration. Increased functional connectivity during nonsocial reward anticipation (between the right NAcc and the right FP) after oxytocin versus placebo. Nonsocial reward outcome: Decreased frontostriatal functional connectivity between left ACC, bilateral postcentral gyrus, left inferior front gyrus, left precentral gyrus, and left medial frontal gyrus after oxytocin vs placebo administration.

Table 2.
Neuroscience results after oxytocin administration in children with ASD.

mesocorticolimbic pathways and communication between this pathway and socially-relevant brain regions) compared to placebo. Results were consistent with the author's hypotheses: oxytocin enhanced neural responses to biological versus random motion in the posterior superior temporal sulcus (pSTS), and in the amygdala and hippocampus in response to angry versus happy voices. Across both fMRI tasks, oxytocin increased neural connectivity both within reward regions and between the reward pathway and regions associated with social perception. The authors concluded that oxytocin administration appeared to enhance salience/reward of social stimuli (as measured in the biological motion task), but also increased the salience of negative social stimuli (as measured by the affective voices task).

Greene and colleagues [56] conducted a placebo-controlled, double-blind study with 28 children and adolescents with ASD (ages 10-17). Participants completed an fMRI incentive delay task on two occasions: once after receiving oxytocin, and once after receiving a placebo nasal spray. The fMRI task involved both social and non-social reward conditions so the authors could compare the effects of oxytocin versus placebo on brain activity related to both social and nonsocial rewards. Results demonstrated that compared to placebo, oxytocin increased brain activity in the caudate nucleus, left anterior cingulate cortex, frontal pole, insular cortex, and orbito-frontal cortex in the nonsocial reward versus social reward condition. Additionally, the authors found a positive relationship between symptom severity (measured using the SRS; [37]) and activation in the frontal pole and anterior cingulate during nonsocial reward anticipation, and between symptom severity and activation in the precentral gyrus and left caudate during nonsocial reward processing. Interestingly, these findings do not support the hypothesis that oxytocin selectively enhances reward-related brain activity to social stimuli, but rather may be associated with increased reward anticipation and processing for nonsocial stimuli. The authors hypothesize that reward-related effects of oxytocin may be sensitive to task-specific features, and noted that their findings strengthen the body of evidence that oxytocin acts on the brain's reward system.

Taken together, these findings provide further evidence that intranasal oxytocin administration appears to act on the neural reward system. However, evidence is mixed regarding whether oxytocin specifically acts on the social reward system [54, 55] or the reward system more broadly [56]. It is likely that differences in neuroscience tasks, as well as differences in regions of interest, and participant sample characteristics may explain disparate findings. Importantly for our theoretical framework, intranasal oxytocin administration appears to impact the reward system in children with ASD. This provides an empirical basis for our hypothesis that combining a pharmacological agent with behavioral interventions that act on similar brain regions/networks may improve outcomes related to social initiation and communication.

5. Behavioral Interventions in ASD

Given the heterogeneous behavioral manifestations of ASD, it is not surprising that multiple behavioral interventions have been developed to improve social communication and decrease challenging behaviors [58–60]. Multiple systematic reviews have been published on the success of behavioral interventions for children with ASD (e.g. [61–64]), and an extensive review is beyond the scope of the current chapter. Of primary relevance to the current chapter are behavioral interventions designed to increase the salience, relevance, and reward value of social interactions in order to improve social-communicative symptoms.

This section will briefly review two of these behavioral interventions, specifically the Early Start Denver Model (ESDM) and Pivotal Response Training (PRT) as both of these interventions are based on principles of Applied Behavioral Analysis (ABA) but emphasize naturalistic teaching strategies to promote generalization. Note, however, that there are other naturalistic interventions grounded in ABA principles (e.g. Incidental Teaching [65]; Reciprocal Imitation Training, or RIT [66, 67]; Parent-training programs, such as Project ImPACT [68]; Joint attention Interventions, such as JASPER [69, 70], and others).

5.1 Early start denver model (ESDM)

ESDM is an empirically validated, manualized intensive early intervention program designed for children between the ages of 1-4 [60, 71]. ESDM uses teaching strategies including: interpersonal exchange and positive affect, engagement with real-world activities and materials, adult responsivity and sensitivity, and focus on both verbal and nonverbal communication. These strategies are grounded in ABA principles including operant conditioning, shaping, and chaining. Importantly, ESDM is not conceptualized as a behavioral intervention that must occur in a table-top or structured situation, nor is it a "one size fits all" approach. Each child's program is individualized, and parent's roles are emphasized. Parents are taught ESDM strategies and encouraged to utilize them during daily activities (e.g. feeding, bath time, play). In a 2010 randomized controlled trial, Dawson and colleagues compared the efficacy of ESDM versus treatment as usual (TAU) over a 2-year period [60]. Results found significant improvements in cognitive abilities in the ESDM group compared to TAU. These group differences appeared driven by improvements in both expressive and receptive language in the ESDM group. Additionally, significant group differences were observed in adaptive behaviors. Whereas children in the ESDM group remained steady in their adaptive behaviors across time, children in the TAU group exhibited lower scores across time when compared to their neurotypical peers. This difference appeared driven by increasing gaps between the TAU group and their neurotypical peers in a variety of adaptive skills, whereas children in the ESDM group displayed improvement in their communication abilities. A recent meta-analysis corroborates the efficacy of ESDM in improving cognition and language for children with ASD [72].

5.2 Pivotal response training (PRT)

Pivotal response training (PRT), sometimes referred to as Pivotal Response Teaching or Pivotal Response Therapy, is a naturalistic behavior intervention based on principles of ABA. The underlying assumption of PRT is that children's challenges can be improved with behavioral and environmental manipulations including reinforcement, contingencies, consequences, and extinction [73]. The term "pivotal" is important as it refers to pivotal behaviors that, when targeted, can lead to improvements in other areas of behavior not specifically targeted. The behaviors/function areas most commonly targeted in PRT are: motivation, initiation, responding to multiple cues, and self-management [74, 75]. To increase motivation, teaching strategies include: following the child's lead, offering choices, providing clear opportunities for response, varying tasks, including both maintenance and acquisition tasks, contingent and natural reinforcement, and reinforcing all attempts at target skills [73, 74]. Similar to ESDM, PRT emphasizes the importance of implementing the intervention in the child's natural environment and the involvement of parents and other caregivers in the intervention [73]. Results of a systematic review indicate that PRT is largely effective at increasing self-initiation

and improving language, communication, and play skills in children with ASD [76]. A 2016 meta-analysis concluded that PRT is effective at teaching behaviors to children with ASD [77].

6. Neuroscience findings after behavioral intervention in ASD

Despite a wealth of research examining the behavioral utility of empirically-based interventions for children with ASD, there is a relative paucity of literature utilizing neuroscience as an outcome measure or predictor of behavioral intervention response (see [78] for a review). To our knowledge, seven studies have been published using neuroscience as either an outcome measure or predictor of response for an empirically supported behavioral intervention designed to help with core symptoms of ASD. See **Table 3**.

The first published paper using neuroscience as an outcome measure was Dawson and colleagues in 2012 [79]. 29 children with ASD (ages 48-77 months) participated in the study and were randomly assigned to either receive two years of ESDM intervention or two years of treatment as usual, TAU. Compared to toddlers in the community intervention, those who received ESDM demonstrated faster neural signatures of attention (the Nc ERP component) when viewing faces versus objects. Interestingly, when brain activity patterns of the two groups of toddlers with ASD were compared to brain activity of neurotypical (TD) toddlers, the ESDM and TD groups exhibited increased cortical activation when viewing faces versus objects, whereas toddlers in the TAU group evidenced more cortical activation when viewing objects vs. faces. The authors concluded that participation in ESDM appeared to lead to "normalization" of attention to faces. However, the authors did not include measures of brain activity prior to intervention, so they were unable to directly infer whether participation in ESDM significantly changed brain activity from pre to post intervention.

Voos and colleagues [80] used fMRI to measure brain activity in two five-year-olds with ASD before and after four months of PRT. The fMRI paradigm involved watching point-light displays that were either attached to an adult who performed actions (e.g. biological motion) or scrambled light displays created with random selections of light points (scrambled motion). When measuring brain activity from brain areas implicated in ASD from previous research [81], the authors found that one participant had increased brain activity after intervention in the left fusiform gyrus and left dorsal prefrontal cortex, and the other participant had greater activation in the left ventrolateral prefrontal cortex, right posterior superior temporal sulcus, and fusiform gyrus. All of these brain regions have been previously implicated as relevant to processing social stimuli and biological motion. Despite the small sample size, the results suggest that PRT can increase brain activity in important regions associated with social stimuli.

Ventola and colleagues [82] also measured brain activity before and after participation in PRT. 10 children with ASD (aged 4-7) completed an fMRI biological motion task both before and after 16 weeks of PRT. 5 neurotypical children were tested twice (once at "baseline" and once 16 weeks later) but they did not receive PRT. Based on activity in the parietal temporal sulcus (pSTS) at baseline compared to neurotypical participants, children with ASD were separated into two groups: hypo- and hyper-active. Children with hypo-activation were hypothesized to have decreased social motivation (evidenced by hypoactivity in the pSTS compared to neurotypical children), and children with hyper-activation were hypothesized to be hypersensitive to stimuli (evidenced by hyperactivity in the pSTS compared to neurotypical children). After PRT, children in the hypo-active

Authors	Participants	Intervention, Neuroscience Methodology, & Task	Neuroscientific Findings
Dawson et al. [79]	15 ASD in ESDM group • M_{age} = 54.1 mo., SD_{age} = 4.9 mo. 14 ASD in the TAU group • M_{age} = 54.1 mo., SD_{age} = 7.8 mo. 17 TD participants • M_{age} = 55.7 mo., SD_{age} = 4.5 mo.	ESDM; 2 for years; 20 hours/ week ERP Participants viewed images of faces and toys.	Faster Nc and increased cortical activation to faces vs. objects in the EDSM group. Faster Nc and increased cortical activation to objects vs. faces in the TAU group.
Voos et al. [80]	2 ASD (1 male, 1 female), each 5 years old	PRT; 16 weeks; 8– 10 hours/ week fMRI Participants viewed biological motion clips and scrambled motion clips.	During biological motion: Participant 1 (female): Increased activity in the fusiform gyrus (FG) and dorsolateral prefrontal cortex (dlPFC). Participant 2 (male): Increased activity in the posterior superior temporal sulcus (pSTS), ventrolateral prefrontal cortex (vlPFC), and FG.
Ventola et al. [82]	10 ASD (8 male, 2 female) Hypoactive group (3 male, 2 female): • M_{age} = 5.3 yrs., SD_{age} = .27 yrs. Hyperactive group (5 male): • M_{age} = 5.66 yrs., SD_{age} = 1.02 yrs.	PRT; 16 weeks; 7 hours/week fMRI Participants viewed biological motion clips and scrambled motion clips.	During biological motion: Initially hypoactive group: increased activation in the ventral striatum (VS) and right posterior superior temporal sulcus (pSTS) Initially hyperactive group: decreased activation in right pSTS, amygdala, thalamus, and hippocampus.
Van Hecke et al. [83]	28 ASD in the immediate treatment group (22 male, 6 female) • M_{age} = 14.1 yrs., SD_{age} = 1.3 yrs. 29 ASD in the waitlist control (WLC) group (23 male, 6 female) • M_{age} = 13.3 yrs., SD_{age} = 1.7 yrs. 30 TD (28 male, 2 female) • M_{age} = 13.3 yrs., SD_{age} = 1.3 yrs.	PEERS; 14 weeks; 1.5 hours/week EEG Continuous resting EEG	Immediate treatment: Increased left-dominant gamma asymmetry during resting state EEG after intervention vs. pre-intervention (more similar to TD). WLC: no change.
Venkataraman et al. [88]	19 ASD (13 males, 6 females) • M_{age} = 5.87 yrs., SD_{age} = 1.09 yrs.	PRT; 16 weeks; 7 hours/week fMRI Participants viewed biological motion clips and scrambled motion clips.	During biological motion, reduction in connectivity between the posterior cingulate cortex (PCC) and orbital frontal cortex and an increase in connectivity between the PCC and regions of ventral occipital temporal extrastriate cortex.

Authors	Participants	Intervention, Neuroscience Methodology, & Task	Neuroscientific Findings
Yang et al. [89]	20 ASD (13 male, 7 female) • M_{age} = 5.90 yrs., SD_{age} = 1.07 yrs.	PRT; 16 weeks; 7 hours/week fMRI Participants viewed biological motion clips and scrambled motion clips.	Pre-intervention brain activity in the following areas while viewing biological motion predicted behavioral improvements on the SRS from pre- to post-intervention. (1) social perception (fusiform gyrus, inferior temporal gyrus, middle temporal gyrus), (2) social attention (inferior parietal gyrus, superior parietal lobule), (3) emotion regulation and reward (orbitofrontal cortex, ventrolateral prefrontal cortex, anterior insula), and (4) social reward (putamen, pallidum, amygdala, hippocampus, ventral striatum)
Baker et al., [90]	7 ASD (6 male, 1 female) • M_{age} = 13.88 yrs., SD_{age} = 2.21 yrs. 7 TD (6 male, 1 female) • M_{age} = 13.46 yrs., SD_{age} = 2.29 yrs.	PEERS; 16 weeks; 1.5 hours/week ERP Participants completed a reward task with feedback that was social (face) or nonsocial (arrow) with correct or incorrect feedback (face: smile vs frown; arrow: upward vs downward).	Increased neural sensitivity to both social and nonsocial rewards (RewP amplitude) after versus before intervention.

Table 3.
Neuroscience outcome measures of behavioral interventions in children with ASD.

group had increased brain activity in the pSTS and ventral striatum when viewing biological motion, and decreased ventral striatum activity in response to scrambled motion. Children in the hyperactive group evidenced decreased brain activity in the pSTS, amygdala, thalamus, and hippocampus when viewing biological motion. The authors' hypothesized that participation in PRT differentially affected brain activity of children depending on their baseline characteristics (e.g. children who displayed too little brain activity in response to social stimuli evidenced increased brain activity after intervention, whereas children who displayed too much brain activity in response to social stimuli evidenced decreased activity after intervention).

Van Hecke and colleagues [83] used electrophysiology (EEG) to measure brain activity before and after participation in a randomized control trial of the Program for the Education and Enrichment of Relational Skills (PEERS; [84, 85]) versus a waitlist control (WLC) condition. PEERS is an empirically validated, manualized program which focuses on making and keeping friends for adolescents with ASD [86].

35 adolescents (13-14 years old) with ASD were randomly assigned to receive PEERS, 31 were randomly assigned to WLC, and 30 neurotypical (TD) adolescents were assessed prior to the intervention for comparison purposes. The authors measured brain activity patterns during "resting state" during which adolescents were instructed to focus on a fixation point for three minutes. Of particular interest was patterns of brain activity in the right versus left hemispheres as previous research suggests that individuals who have left-hemisphere dominance have higher approach motivation and positive affect compared to those with right-hemisphere dominance who are often characterized as withdrawn [87]. Prior to intervention, the two groups of teens with ASD evidenced less left-dominant asymmetry compared to the TD group. When comparing post-intervention brain activity of teens who received PEERS to brain activity in the TD group, differences in left-hemispheric dominance were no longer observed. Differences between the WLC group and the TD group were still observed after the 14-week intervention period (during which the WLC group did not receive intervention). These findings suggest that participation in PEERS (compared to a waitlist condition) significantly changed patterns of brain activity to be increasingly left-hemisphere dominant, which is more similar to patterns observed in neurotypical teens.

Venkataraman and colleagues [88] used a Bayesian probabilistic model to characterize fMRI activity in 19 children with ASD (mean age 5.87 years) before and after 16 weeks of PRT. Similar to Ventola et al. [82], the fMRI paradigm involved watching two types of light displays: biological motion and scrambled motion. The probabilistic model allowed the authors to measure PRT-induced changes in neural connectivity between neural regions of interest. Results indicated both reduced connectivity between the posterior cingulate cortex (PCC) and orbitofrontal cortex and increased connectivity between the PCC and areas of the ventral occipital temporal extrastriate cortex. These results are interesting given that the PCC is known for its role in social cognitive processes, the orbitofrontal cortex has been implicated in reward processes, and the ventral occipital and temporal cortices play a role in processing socially meaningful stimuli (including biological motion). These findings suggest that PRT causes a shift, in which connectivity between the PCC and orbitofrontal cortex is decreased while PCC and the ventral occipital-temporal cortex connection is strengthened.

Yang and colleagues [89] utilized fMRI as a pre-intervention predictor of intervention response in 20 children with ASD (mean age 5.90 years). The authors measured brain activity during a biological motion paradigm prior to 16 weeks of PRT. Results demonstrated that pre-intervention brain activity in areas implicated in: (1) social perception (fusiform gyrus, inferior temporal gyrus, middle temporal gyrus), (2) social attention (inferior parietal gyrus, superior parietal lobule), (3) emotion regulation and reward (orbitofrontal cortex, ventrolateral prefrontal cortex, anterior insula), and (4) social reward (putamen, pallidum, amygdala, hippocampus, ventral striatum) while viewing biological motion predicted behavioral improvements on the SRS from pre- to post-intervention. For all 4 regions, greater levels of pre-intervention brain activity were associated with increased behavioral improvements from pre- to post- intervention. Results from this study suggest that neuroscience methods may be able to predict which children are most likely to benefit from a specific intervention, as well as underscoring the importance of brain regions associated with social perception, emotion regulation, and reward for understanding how interventions may affect brain circuitry in ASD.

Baker and colleagues [90] used event-related potentials (ERP) to measure brain response to reward in ASD adolescents before and after participation in the PEERS

program compared to a typically developing sample. Response to social and nonsocial rewards were measured using the reward-related positive component (RewP) in seven adolescents with ASD and seven TD adolescents, aged 10 to 17 years. Prior to intervention, patterns of reward-related brain activity (RewP mean amplitude) did not differ between groups. However, after intervention the ASD group demonstrated an enhanced sensitivity to rewards, regardless of social or nonsocial condition, compared to the TD group. Additionally, ASD participants with less robust responses to social rewards prior to the start of the PEERS intervention demonstrated the most gains in social behaviors (as measured via SRS-2 [91]; Social Skills Improvement System, [92]. Findings from this study suggest an enhancement of the neural response to rewards after teens with ASD receive training in social skills and additionally that teens with attenuated responses to social rewards may gain the most benefit from intervention.

Taken together, these seven studies provide evidence for two critical concepts: (1) *Behavioral Intervention* can significantly change patterns and/or magnitude of brain activity in response to social stimuli for children with ASD, and (2) *Neuroscience* may be able to predict individual levels of behavioral intervention response and could eventually be used to advance "precision medicine" (e.g. to predict who is most likely to benefit from a specific intervention). The first concept is central to our theoretical framework, as it suggests that participation in empirically based interventions changes brain activity in children with ASD--particularly in response to social stimuli and in brain areas/patterns of activity related to social perception and reward. Neural changes in the reward system and other areas of the "social brain" after interventions provides an empirical basis for our hypothesis that the addition of pharmacological compounds that enhance brain activity/responses in those same regions might lead to increased benefits for children with ASD.

7. Current research combining oxytocin and behavioral interventions in ASD

Although there are no published studies (to our knowledge) that have conducted double-blind, placebo-controlled trials combining oxytocin administration with an empirically validated behavioral intervention in ASD, two trials are currently underway and recorded on ClinicalTrials.Gov (identifiers NCT02918864 and NCT03370510). We also note that a large-scale multi-site trial of the behavioral effects of oxytocin versus placebo is underway by the Study of Oxytocin in Autism to Improve Reciprocal Social Behaviors (SOARS-B; clinical trial identifier NCT01944046). One paper describing the rationale and methods for the trial has been published [93].

8. Does timing matter?

As noted above, we hypothesize that empirically based behavioral interventions designed to increase social-communication skills such as social initiation/motivation are more likely to be enhanced by oxytocin administration than interventions focused on other aspects of ASD (e.g. disruptive behaviors, anxiety). Such interventions are typically aimed towards young children (i.e. ESDM was developed for children ages 1-4) due to the targeted skills. We hypothesize that age is likely to play an important role in the efficacy of combining oxytocin with behavioral interventions

such that younger children are more likely to benefit due to: (a) Early interventions in ASD often focus on improving social motivation and initiation, whereas interventions for older children are less likely to have such an emphasis. As oxytocin has been shown to affect the reward system, behavioral interventions designed to increase the reward value of social stimuli are likely to be the best candidates for this framework. (b) Increased neural plasticity in younger ages and the negative neuro-developmental sequelae described in the social motivation hypothesis. That is, young children have been hypothesized to benefit more from early intervention for ASD compared to older children due to neural plasticity, and the social motivation hypothesis posits that decreased reward value of social stimuli early in life leads to a negative cascade of developmental consequences [5, 94]. It therefore seems likely that younger children are best positioned to benefit from combining behavioral intervention with oxytocin because early interventions may disrupt this negative developmental cascade and help children move back towards a typical trajectory. (c) Accumulating evidence that interventions for ASD are likely to be more effective if started earlier in life [94–96]. It is unclear, however, exactly how age will affect our theoretical model. Future research should pay close attention to how and if age is a predictor when measuring outcomes of combining oxytocin and behavioral intervention in ASD.

9. Conclusions

Taken together, considering extant research findings from behavioral and neural effects of oxytocin administration along with those on brain activity in response to behavioral interventions in children with ASD suggests that both oxytocin and behavioral interventions lead to measurable changes in regions of the "social brain" and reward network. These findings, combined with those suggesting that oxytocin administration may improve social-communication in children with ASD, provide the empirical basis of our hypothesis [57] that combining oxytocin administration with behavioral interventions may improve outcomes related to social-communication. We hypothesize that the administration of oxytocin prior to each session of an intervention may "prime" the neural reward system to be maximally responsive to the behavioral skills taught during the intervention session. Due to the central role of the reward system in our theoretical model we hypothesize that this combined approach may be most effective for social-communicative skills requiring social motivation (e.g. social initiation/approach) and be maximally beneficial for young children. See **Figure 1** for hypothesized neural mechanisms underlying the efficacy of combining interventions with oxytocin to improve outcomes.

It is important to note, however, that this approach is unlikely to be equally effective in all children with ASD. As with all interventions, there does not appear to be any "one size fits all" approach to help children with ASD. It will be critical to measure and characterize individual differences that may explain variability in treatment efficacy from *biological* (e.g. levels of oxytocin concentration in plasma/saliva before and after oxytocin administration, genetic expression of candidate genes relevant for oxytocin; OXTR, VAP1, brain activity in response to social stimuli prior to oxytocin administration, age), *behavioral* (e.g. social communicative symptom profile prior to oxytocin administration), and *psychological* (e.g. co-occurring diagnoses such as ADHD, anxiety, etc.) standpoints. Such individual differences will likely be central to our understanding of how, why, and for whom this combined approach will be maximally effective.

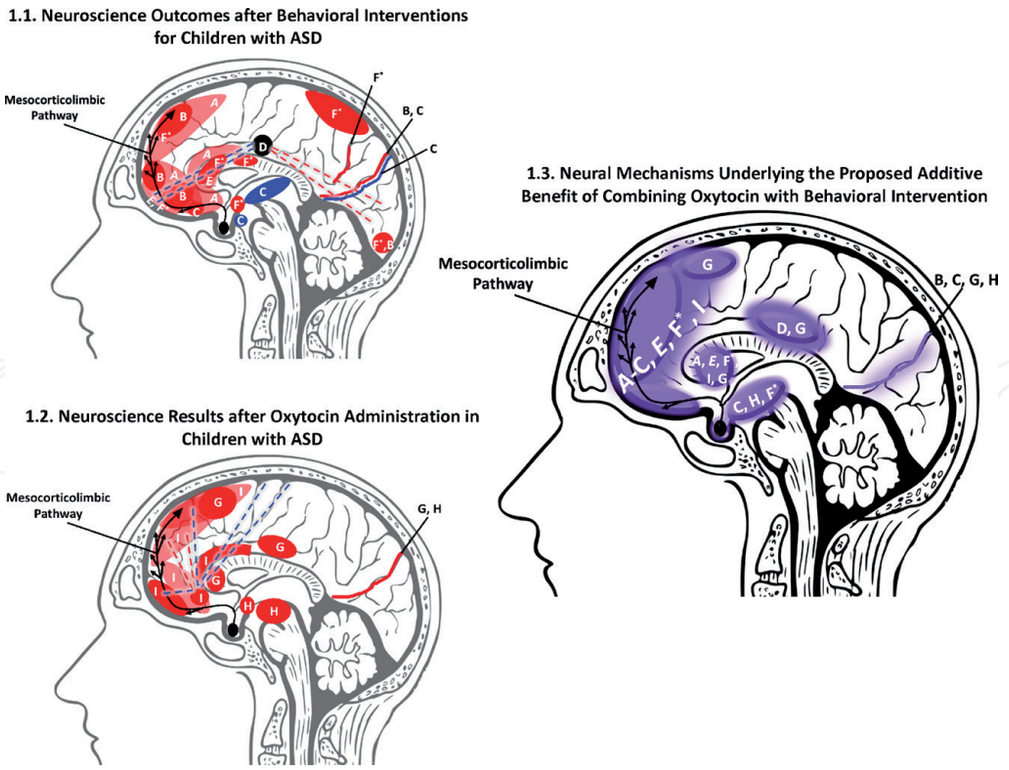

Figure 1

(1.1) *Neuroscience Outcomes after Behavioral Intervention for Children with ASD. This figure depicts results from studies which measured brain activity before and after behavioral intervention. The brain areas highlighted in red indicate increased brain activity after behavioral intervention, whereas regions shown in blue indicate decreased brain activity after behavioral intervention. Results related to neural connectivity are shown with a dotted line. A. Dawson et al. [79], proposed neural generators of the Nc component (Reynolds & Richards, 2005) are highlighted (medial frontal gyrus, inferior frontal gyrus, anterior cingulate cortex); B. Voos et al. [80] (fusiform gyrus, dorsolateral prefrontal cortex, posterior superior temporal sulcus (pSTS), ventrolateral prefrontal cortex (vlPFC)); C. Ventola et al. [82], ventral striatum (VS), pSTS, amygdala, thalamus, and hippocampus; D. Venkataraman et al. [88], reduction in connectivity between the posterior cingulate cortex (PCC) and orbital frontal cortex (OFC) and an increase in connectivity between the PCC and regions of ventral occipital temporal extrastriate cortex; E. Baker et al. [90], proposed neural generators of the RewP component (Carlson et al., 2011 & Proudfit, 2015) are highlighted (ventral striatum, dorsal striatum, OFC, medial frontal cortex); F*. Yang et al. [89], activity in the following pre-intervention brain areas were used to predict behavioral improvements: fusiform gyrus, inferior temporal gyrus, middle temporal gyrus, inferior parietal gyrus, superior parietal lobule, OFC, ventrolateral prefrontal cortex, anterior insula, putamen, pallidum, amygdala, hippocampus, ventral striatum. *This study used neuroscience measures prior to intervention as a predictor of intervention success, whereas the other studies used neuroscience measures pre- and post-intervention.* ***(1.2)*** *Neuroscience Results after Oxytocin Administration in Children with ASD. This figure depicts results from studies that have measured brain activity after oxytocin administration. Results related to neural connectivity are shown with a dotted line (red dotted line indicates increased connectivity, blue dotted line indicates decreased connectivity). G. Gordon et al., [55] (dorsal and ventral striatum, premotor cortex, posterior cingulate, pSTS); H. Gordon et al. [56] (pSTS, right amygdala, right brain stem); I. Greene et al., [56] (right nucleus accumbens (NAcc), right frontal pole (FP), left anterior cingulate cortex (ACC), left superior frontal cortex, bilateral OFC, functional connectivity during nonsocial reward anticipation (between the right NAcc and the right FP); frontostriatal functional connectivity between left ACC, bilateral postcentral gyrus, left inferior front gyrus, left precentral gyrus, and left medial frontal gyrus).* ***(1.3)*** *Neural Mechanisms Underlying the Proposed Additive Benefit of Combining Oxytocin with Behavioral Intervention. This figure depicts the proposed additive benefits of combining oxytocin administration with behavioral interventions for children with ASD. Brain regions that have been implicated in both behavioral intervention and oxytocin administration are labeled. We propose that oxytocin administration will "prime" neural structures related to reward and/or social information processing, which will make behavioral intervention sessions more effective.*

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Author details

Katherine Kuhl Meltzoff Stavropoulos* and Elizabeth Baker
University of California, Riverside, Riverside, California, USA

*Address all correspondence to: katherine.stavropoulos@ucr.edu

References

[1] Maenner M J 2020 Prevalence of autism spectrum disorder among children aged 8 years — autism and developmental disabilities monitoring network, 11 sites, United States, 2016 *MMWR Surveill Summ* **69**

[2] American Psychiatric Association 2013 *Diagnostic and statistical manual of mental disorders* (Washington, DC: American Psychiatric Publishing)

[3] Dawson G, Webb S J and McPartland J 2005 Understanding the nature of face processing impairment in autism: insights from behavioral and electrophysiological studies *Dev Neuropsychol* **27** 403-24

[4] Chevallier C, Kohls G, Troiani V, Brodkin E S and Schultz R T 2012 The social motivation theory of autism *Trends Cogn Sci* **16** 231-9

[5] Dawson G 2008 Early behavioral intervention, brain plasticity, and the prevention of autism spectrum disorder *Dev Psychopathol* **20** 775-803

[6] Stavropoulos K K M and Carver L J 2013 Research Review: Social motivation and oxytocin in autism – implications for joint attention development and intervention *Journal of Child Psychology and Psychiatry* **54** 603-18

[7] Gainer H, Altstein M and Whitnall M H 1987 The cell biology and development of vasopressinergic and oxytocinergic neurons *Prog. Brain Res.* **72** 153-61

[8] Magon N and Kalra S 2011 The orgasmic history of oxytocin: Love, lust, and labor *Indian J Endocrinol Metab* **15** S156-61

[9] Carter C S and Porges S W 2013 The biochemistry of love: An oxytocin hypothesis *EMBO reports* **14** 12-6

[10] Modi M E and Young L J 2012 The oxytocin system in drug discovery for autism: Animal models and novel therapeutic strategies *Horm Behav* **61** 340-50

[11] Domes G, Heinrichs M, Michel A, Berger C and Herpertz S C 2007 Oxytocin improves “mind-reading” in humans *Biological Psychiatry* **61** 731-3

[12] Hurlemann R, Patin A, Onur O A, Cohen M X, Baumgartner T, Metzler S, Dziobek I, Gallinat J, Wagner M, Maier W and Kendrick K M 2010 Oxytocin enhances amygdala-dependent, socially reinforced learning and emotional empathy in humans *J. Neurosci.* **30** 4999-5007

[13] Kosfeld M, Heinrichs M, Zak P J, Fischbacher U and Fehr E 2005 Oxytocin increases trust in humans *Nature* **435** 673-6

[14] Gordon I, Martin C, Feldman R and Leckman J F 2011 Oxytocin and social motivation *Dev Cogn Neurosci* **1** 471-93

[15] Baskerville T A and Douglas A J 2010 Dopamine and oxytocin interactions underlying behaviors: Potential contributions to behavioral disorders *CNS Neuroscience & Therapeutics* **16** e92-123

[16] Baskerville T A, Allard J, Wayman C and Douglas A J 2009 Dopamine–oxytocin interactions in penile erection *European Journal of Neuroscience* **30** 2151-64

[17] Shapiro L E and Insel T R 1989 Ontogeny of oxytocin receptors in rat forebrain: A quantitative study *Synapse* **4** 259-66

[18] Krol K M, Moulder R G, Lillard T S, Grossmann T and Connelly J J 2019 Epigenetic dynamics in infancy and the impact of maternal engagement *Science Advances* **5** eaay0680

[19] LeClerc S and Easley D 2015 Pharmacological therapies for autism spectrum disorder: A review *P T* **40** 389-97

[20] Modahl C, Fein D, Waterhouse L and Newton N 1992 Does oxytocin deficiency mediate social deficits in autism? *J Autism Dev Disord* **22** 449-51

[21] Modahl C, Green L A, Fein D, Morris M, Waterhouse L, Feinstein C and Levin H 1998 Plasma oxytocin levels in autistic children *Biological Psychiatry* **43** 270-7

[22] Parker K J, Oztan O, Libove R A, Sumiyoshi R D, Jackson L P, Karhson D S, Summers J E, Hinman K E, Motonaga K S, Phillips J M, Carson D S, Garner J P and Hardan A Y 2017 Intranasal oxytocin treatment for social deficits and biomarkers of response in children with autism *Proc Natl Acad Sci USA* **114** 8119-24

[23] Green L, Fein D, Modahl C, Feinstein C, Waterhouse L and Morris M 2001 Oxytocin and autistic disorder: Alterations in peptide forms *Biological Psychiatry* **50** 609-13

[24] Andari E, Duhamel J-R, Zalla T, Herbrecht E, Leboyer M and Sirigu A 2010 Promoting social behavior with oxytocin in high-functioning autism spectrum disorders *PNAS* **107** 4389-94

[25] Guastella A J, Einfeld S L, Gray K M, Rinehart N J, Tonge B J, Lambert T J and Hickie I B 2010 Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders *Biological Psychiatry* **67** 692-4

[26] Tachibana M, Kagitani-Shimono K, Mohri I, Yamamoto T, Sanefuji W, Nakamura A, Oishi M, Kimura T, Onaka T, Ozono K and Taniike M 2013 Long-term administration of intranasal oxytocin is a safe and promising therapy for early adolescent boys with autism spectrum disorders *Journal of Child and Adolescent Psychopharmacology* **23** 123-7

[27] Anagnostou E, Soorya L, Brian J, Dupuis A, Mankad D, Smile S and Jacob S 2014 Intranasal oxytocin in the treatment of autism spectrum disorders: A review of literature and early safety and efficacy data in youth *Brain Research* **1580** 188-98

[28] Dadds M R, MacDonald E, Cauchi A, Williams K, Levy F and Brennan J 2014 Nasal oxytocin for social deficits in childhood autism: A randomized controlled trial *J Autism Dev Disord* **44** 521-31

[29] Guastella A J, Gray K M, Rinehart N J, Alvares G A, Tonge B J, Hickie I B, Keating C M, Cacciotti-Saija C and Einfeld S L 2015 The effects of a course of intranasal oxytocin on social behaviors in youth diagnosed with autism spectrum disorders: A randomized controlled trial *Journal of Child Psychology and Psychiatry* **56** 444-52

[30] Yatawara C J, Einfeld S L, Hickie I B, Davenport T A and Guastella A J 2016 The effect of oxytocin nasal spray on social interaction deficits observed in young children with autism: A randomized clinical crossover trial *Molecular Psychiatry* **21** 1225-31

[31] Strathearn L, Kim S, Bastian D A, Jung J, Iyengar U, Martinez S, Goin-Kochel R P and Fonagy P 2018 Visual systemizing preference in children with autism: A randomized controlled trial of intranasal oxytocin *Development and Psychopathology* **30** 511-21

[32] Ooi Y P, Weng S-J, Kossowsky J, Gerger H and Sung M 2017 Oxytocin and autism spectrum disorders: A systematic review and meta-analysis of randomized controlled trials *Pharmacopsychiatry* **50** 5-13

[33] Baron-Cohen S, Wheelwright S, Hill J, Raste Y and Plumb I 2001 The "Reading the Mind in the Eyes" Test revised version: A study with normal adults, and adults with asperger

syndrome or high-functioning autism *Journal of Child Psychology and Psychiatry* **42** 241-51

[34] Lord C, Risi S, Lambrecht L, Cook E H, Leventhal B L, DiLavore P C, Pickles A and Rutter M 2000 The Autism Diagnostic Observation Schedule-Generic: A standard measure of social and communication deficits associated with the spectrum of autism *J Autism Dev Disord* **30** 205-23

[35] Aman M G, Singh N N, Stewart A W and Field C J 1985 The aberrant behavior checklist: A behavior rating scale for the assessment of treatment effects *Am J Ment Defic* **89** 485-91

[36] Achenbach T M and Edelbrock C 1991 Child behavior checklist *Burlington (Vt)* **7** 371-92

[37] Constantino J N and Gruber C P 2005 *Social Responsiveness Scale* (WPS)

[38] Reynolds C R and Kamphaus R W 1992 *Behavior Assessment System for Children* (Circle Pines, MN: American Guidance Service)

[39] Wolf J M, Tanaka J W, Klaiman C, Cockburn J, Herlihy L, Brown C, South M, McPartland J, Kaiser M D, Phillips R and Schultz R T 2008 Specific impairment of face processing abilities in children with autism spectrum disorder using the Let's Face It! Skills Battery *Autism Res* **1** 329-40

[40] Dennis M, Purvis K, Barnes M A, Wilkinson M and Winner E 2001 Understanding of literal truth, ironic criticism, and deceptive praise following childhood head injury *Brain and Language* **78** 1-16

[41] Happé F G E 1994 An advanced test of theory of mind: Understanding of story characters' thoughts and feelings by able autistic, mentally handicapped, and normal children and adults *J Autism Dev Disord* **24** 129-54

[42] Gadow K and Sprafkin J 2009 *The symptom inventories: An annotated bibliography*

[43] Bodfish J W, Symons F J, Parker D E and Lewis M H 2000 Varieties of repetitive behavior in autism: Comparisons to mental retardation *J Autism Dev Disord* **30** 237-43

[44] Scahill L, Riddle M A, McSwiggin-Hardin M, Ort S I, King R A, Goodman W K, Cicchetti D and Leckman J F 1997 Children's Yale-Brown obsessive compulsive scale: Reliability and validity *Journal of the American Academy of Child & Adolescent Psychiatry* **36** 9

[45] Baron-Cohen S 2007 *Mind reading: The interactive guide to emotions* (Jessica Kingsley Publishers)

[46] Gresham F M and Elliott S N 1990 *The Social Skills Rating System* (American Guidance Service)

[47] Tonge B J, Brereton A V, Gray K M and Einfeld S L 1999 Behavioural and emotional disturbance in high-functioning autism and asperger syndrome *Autism* **3** 117-30

[48] Nowicki S and Duke M P 2001 Nonverbal receptivity: The Diagnostic Analysis of Nonverbal Accuracy (DANVA) *Interpersonal sensitivity: Theory and measurement* The LEA series in personality and clinical psychology (Mahwah, NJ, US: Lawrence Erlbaum Associates Publishers) pp 183-98

[49] Moore D G, Hobson R P and Lee A 1997 Components of person perception: An investigation with autistic, non-autistic retarded and typically developing children and adolescents *British Journal of Developmental Psychology* **15** 401-23

[50] Einfeld S L and Tonge B J 1995 The Developmental Behavior Checklist: The development and validation of an instrument to assess behavioral and emotional disturbance in children and

adolescents with mental retardation *J Autism Dev Disord* **25** 81-104

[51] Guy W 1976 *ECDEU assessment manual for psychopharmacology* (Rockville, Md: U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs)

[52] Brannan A M, Heflinger C A and Bickman L 1997 The caregiver strain questionnaire: Measuring the impact on the family of living with a child with serious emotional disturbance *Journal of Emotional and Behavioral Disorders* **5** 212-22

[53] Spence S H, Barrett P M and Turner C M 2003 Psychometric properties of the Spence Children's Anxiety Scale with young adolescents *Journal of Anxiety Disorders* **17** 605-25

[54] Gordon I, Wyk B C V, Bennett R H, Cordeaux C, Lucas M V, Eilbott J A, Zagoory-Sharon O, Leckman J F, Feldman R and Pelphrey K A 2013 Oxytocin enhances brain function in children with autism *PNAS* **110** 20953-8

[55] Gordon I, Jack A, Pretzsch C M, Vander Wyk B, Leckman J F, Feldman R and Pelphrey K A 2016 Intranasal oxytocin enhances connectivity in the neural circuitry supporting social motivation and social perception in children with autism *Sci Rep* **6** 35054

[56] Greene R K, Spanos M, Alderman C, Walsh E, Bizzell J, Mosner M G, Kinard J L, Stuber G D, Chandrasekhar T, Politte L C, Sikich L and Dichter G S 2018 The effects of intranasal oxytocin on reward circuitry responses in children with autism spectrum disorder *Journal of Neurodevelopmental Disorders* **10** 12

[57] Baker E and Stavropoulos K K M 2020 The effects of oxytocin administration on individuals with ASD: Neuroimaging and behavioral evidence *Progress in Molecular Biology and Translational Science* Autism vol 173, ed M Ilieva and W K W Lau (Elsevier) pp 209-38

[58] Eldevik S, Hastings R P, Hughes J C, Jahr E, Eikeseth S and Cross S 2009 Meta-analysis of early intensive behavioral intervention for children with autism *Journal of Clinical Child & Adolescent Psychology* **38** 439-50

[59] Kasari C and Lawton K 2010 New directions in behavioral treatment of autism spectrum disorders *Curr Opin Neurol* **23** 137-43

[60] Dawson G, Rogers S, Munson J, Smith M, Winter J, Greenson J, Donaldson A and Varley J 2010 Randomized, controlled trial of an intervention for toddlers with autism: The Early Start Denver Model *Pediatrics* **125** e17-23

[61] Reichow B, Barton E E, Boyd B A and Hume K 2012 Early intensive behavioral intervention (EIBI) for young children with autism spectrum disorders (ASD) *Cochrane Database Syst Rev* **10** CD009260

[62] Howlin P, Magiati I, Charman T and MacLean J 2009 Systematic review of early intensive behavioral interventions for children with autism *Am J Intellect Dev Disabil* **114** 23-41

[63] Dawson G and Burner K 2011 Behavioral interventions in children and adolescents with autism spectrum disorder: A review of recent findings *Curr Opin Pediatr* **23** 616-20

[64] Schreibman L, Dawson G, Stahmer A C, Landa R, Rogers S J, McGee G G, Kasari C, Ingersoll B, Kaiser A P, Bruinsma Y, McNerney E, Wetherby A and Halladay A 2015 Naturalistic developmental behavioral interventions: Empirically validated treatments for autism spectrum disorder *J Autism Dev Disord* **45** 2411-28

[65] Hart B M and Risley T R 1968 Establishing use of descriptive adjectives in the spontaneous speech of disadvantaged preschool children *J Appl Behav Anal* **1** 109-20

[66] Ingersoll B 2010 Brief report: Pilot randomized controlled trial of reciprocal imitation training for teaching elicited and spontaneous imitation to children with autism *J Autism Dev Disord* **40** 1154-60

[67] Ingersoll B and Schreibman L 2006 Teaching reciprocal imitation skills to young children with autism using a naturalistic behavioral approach: Effects on language, pretend play, and joint attention *J Autism Dev Disord* **36** 487-505

[68] Ingersoll B and Wainer A 2013 Initial efficacy of Project ImPACT: A parent-mediated social communication intervention for young children with asd *J Autism Dev Disord* **43** 2943-52

[69] Kasari C, Freeman S and Paparella T 2006 Joint attention and symbolic play in young children with autism: a randomized controlled intervention study *J Child Psychol Psychiatry* **47** 611-20

[70] Kasari C, Paparella T, Freeman S and Jahromi L B 2008 Language outcome in autism: Randomized comparison of joint attention and play interventions *Journal of Consulting and Clinical Psychology* **76** 125

[71] Rogers S J and Dawson G 2009 *Early start denver model curriculum checklist for young children with autism* (Guilford Press)

[72] Fuller E A, Oliver K, Vejnoska S F and Rogers S J 2020 The effects of the Early Start Denver Model for children with autism spectrum disorder: A meta-analysis *Brain Sciences* **10** 368

[73] Koegel R L and Koegel L K 2006 *Pivotal response treatments for autism: Communication, social, & academic development* (Baltimore, MD, US: Paul H Brookes Publishing)

[74] Koegel R L, Koegel L K and Carter C M 1999 Pivotal teaching interactions for children with autism *School Psychology Review* **28** 576-94

[75] Koegel R L, Koegel L K and McNerney E K 2001 Pivotal areas in intervention for autism *Journal of Clinical Child & Adolescent Psychology* **30** 19-32

[76] Verschuur R, Didden R, Lang R, Sigafoos J and Huskens B 2014 Pivotal response treatment for children with autism spectrum disorders: A systematic review *Rev J Autism Dev Disord* **1** 34-61

[77] Bozkus-Genc G and Yucesoy-Ozkan S 2016 Meta-analysis of pivotal response training for children with autism spectrum disorder *Education and Training in Autism and Developmental Disabilities* **51** 13-26

[78] Stavropoulos K K M 2017 Using neuroscience as an outcome measure for behavioral interventions in autism spectrum disorders (ASD): A review *Research in Autism Spectrum Disorders* **35** 62-73

[79] Dawson G, Jones E J H, Merkle K, Venema K, Lowy R, Faja S, Kamara D, Murias M, Greenson J, Winter J, Smith M, Rogers S J and Webb S J 2012 Early behavioral intervention is associated with normalized brain activity in young children with autism *J Am Acad Child Adolesc Psychiatry* **51** 1150-9

[80] Voos A C, Pelphrey K A, Tirrell J, Bolling D Z, Vander Wyk B, Kaiser M D, McPartland J C, Volkmar F R and Ventola P 2013 Neural mechanisms of improvements in social motivation after pivotal response treatment: two case studies *J Autism Dev Disord* **43** 1-10

[81] Kaiser M D, Hudac C M, Shultz S, Lee S M, Cheung C, Berken A M, Deen B, Pitskel N B, Sugrue D R, Voos A

C, Saulnier C A, Ventola P, Wolf J M, Klin A, Vander Wyk B C and Pelphrey K A 2010 Neural signatures of autism *Proc Natl Acad Sci U S A* **107** 21223-8

[82] Ventola P, Yang D Y J, Friedman H E, Oosting D, Wolf J, Sukhodolsky D G and Pelphrey K A 2015 Heterogeneity of neural mechanisms of response to pivotal response treatment *Brain Imaging Behav* **9** 74-88

[83] Van Hecke A V, Stevens S, Carson A M, Karst J S, Dolan B, Schohl K, McKindles R J, Remmel R and Brockman S 2015 Measuring the plasticity of social approach: A randomized controlled trial of the effects of the PEERS intervention on EEG asymmetry in adolescents with autism spectrum disorders *Journal of Autism and Developmental Disorders* **45** 316-35

[84] Laugeson E A and Frankel F 2011 *Social skills for teenagers with developmental and autism spectrum disorders: The PEERS treatment manual* (Routledge)

[85] Laugeson E A, Frankel F, Gantman A, Dillon A R and Mogil C 2012 Evidence-based social skills training for adolescents with autism spectrum disorders: The UCLA PEERS program *J Autism Dev Disord* **42** 1025-36

[86] Laugeson E A, Frankel F, Mogil C and Dillon A R 2009 Parent-assisted social skills training to improve friendships in teens with autism spectrum disorders *J Autism Dev Disord* **39** 596-606

[87] Mitchell A M and Pössel P 2012 Frontal brain activity pattern predicts depression in adolescent boys *Biological Psychology* **89** 525-7

[88] Venkataraman A, Yang D Y J, Dvornek N, Staib L H, Duncan J S, Pelphrey K A and Ventola P 2016 Pivotal response treatment prompts a functional rewiring of the brain among individuals with autism spectrum disorder *Neuroreport* **27** 1081-5

[89] Yang D, Pelphrey K A, Sukhodolsky D G, Crowley M J, Dayan E, Dvornek N C, Venkataraman A, Duncan J, Staib L and Ventola P 2016 Brain responses to biological motion predict treatment outcome in young children with autism *Transl Psychiatry* **6** e948

[90] Baker E, Veytsman E, Martin A M, Blacher J and Stavropoulos K K M 2020 Increased neural reward responsivity in adolescents with ASD after social skills intervention *Brain Sciences* **10** 402

[91] Constantino J N 2012 *Social Responsiveness Scale* (WPS)

[92] Gresham F M and Elliott S N 2008 *Social Skills Improvement System Rating Scales* (Pearson)

[93] Spanos M, Chandrasekhar T, Kim S-J, Hamer R M, King B H, McDougle C J, Sanders K B, Gregory S G, Kolevzon A, Veenstra-VanderWeele J and Sikich L 2020 Rationale, design, and methods of the Autism Centers of Excellence (ACE) network Study of Oxytocin in Autism to improve Reciprocal Social Behaviors (SOARS-B) *Contemp Clin Trials* **98** 106103

[94] Webb S J, Jones E J H, Kelly J and Dawson G 2014 The motivation for very early intervention for infants at high risk for autism spectrum disorders *International Journal of Speech-Language Pathology* **16** 36-42

[95] Zachor D and Ben-Itzchak E 2017 Variables affecting outcome of early intervention in autism spectrum disorder *J Pediatr Neurol* **15** 129-33

[96] Eldevik S, Hastings R P, Jahr E and Hughes J C 2012 Outcomes of behavioral intervention for children with autism in mainstream pre-school settings *J Autism Dev Disord* **42** 210-20