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From Behavior to Biology: Examining Oxytocin and Social Cognition in Preschoolers with and without Autism Spectrum Disorder

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Abstract

Oxytocin (OXT) has been implicated in the social difficulties evidenced in autism. Given this, the current study characterized OXT concentration levels and social cognition in preschoolers, ages 3-5, with either ASD (n=18) or typical development (TD; n=21). The two samples did not differ in OXT concentration levels, however, children with ASD had significantly lower social cognitive ability. Within the TD sample, sad emotion recognition was the largest significant predictor of OXT levels. Within the ASD sample, aggressive interpersonal acts in play accounted for the largest variance in predicting OXT concentration. Results do not support the "OXT deficit hypothesis" in ASD but suggest that oxytocin may have unique relationships with social cognition across diagnostic categories.

Keywords: Autism spectrum disorder; Oxytocin; Social cognition; Emotion recognition

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Introduction

A strong research base has led to the understanding of the behavioral deficits evident in ASD and how they present across development. An important next step in order to meaningfully target these deficits is to characterize the biological underpinnings of social cognitive impairment in ASD as compared to typical development. Most recently, a burgeoning literature has begun to emerge, which implicates the hormone oxytocin (OXT), a nine-amino neuropeptide synthesized in the hypothalamus, in playing a role in the social difficulties individuals with autism and other disorders face [1,2]. The implication of OXT in social behavior has led to various studies in which OXT is used pharmacologically as an intervention option. However, in total, these studies show mixed results, which has left some questioning the efficacy and importance of OXT in human social cognitive ability and development [3]. Given this, the proposed study aimed to characterize peripheral OXT concentration levels and social cognitive ability in preschool children, ages 3-5, who either have a diagnosis of ASD or are typically developing (TD). The findings extend the field's current understanding of OXT release across typical and atypical development and its relationship to other developmental factors.

The OXT System and Human Sociality

On the whole, the origins of human social behavior have been theorized to have multiple genetic and physiological factors that have interacted with the environment over thousands of years [1,4]. One such factor that has garnered support in its role in human social development is oxytocin (OXT) [4]. OXT has been implicated in social processes such as selective social and pair bonding, social communication, empathy, feelings of reciprocity, expressing emotions and understanding other's mental and emotional states, modulating social stress, mother-infant interactions, lactation, gestation, and even the biological processes underpinning birth [4-6].

In humans, OXT is synthesized in cells located most predominately in the hypothalamus, in particular, the paraventricular nucleus (PVN) and supraoptic nuclei of the hypothalamus [5]. Further, OXT can be released from the brain into general circulation and the peripheral nervous system [4]. Levels of OXT vary across species and individual differences in hormone expression are common [1,4]. Most individual variation relates to traits, such as personality factors, or the presence of certain disorders, such as autism, schizophrenia, and genetic syndromes such as Williams syndrome [4,7,8].

OXT Concentration Levels in ASD: Previous Research

A handful of studies have measured OXT concentration levels

across children and adolescents with ASD through varied methods of either saliva and/or blood samples [8-15]. The earliest study conducted by Modahl et al. [8] suggested that an all-male ASD sample had significantly lower plasma OXT levels than the typically developing group. Further, lower peripheral OXT levels were associated with lower scores on measures of social cognitive behavior, as measured by the Vineland Adaptive Behavior Scales (VABS). Green et al. [12] extended these findings by measuring plasma OXT and OT-X, a precursor molecule of oxytocin, to better understand if there were changes in oxytocin peptide formation in males with ASD. Results showed that the ASD group had significantly lower OXT plasma levels and significantly higher precursor molecule OT-X levels as compared to the typical control group, suggesting a disruption in the production of OXT from OT-X precursor molecules. Al-Ayadhi et al. [10] and Miller et al. [13] both incorporated female participants into their samples and found contradictory results. Al-Ayadhi et al. [10] found decreased levels of OXT in the ASD group as compared to the TD control group. Conversely, Miller et al. [13] showed no significant effects of diagnosis on OXT levels. However, across all participants, a significant gender effect was found in that females showed significantly higher levels of OXT as compared to males across this age range [13]. Parker et al. [14] extended this work in the largest characterization study to date which found no significant differences between groups; however, oxytocin expression was related to social cognitive ability across both ASD and TD development. A further examination of OXT concentration across different diagnostic categories was done by Taurines et al. [15], who compared baseline levels in children with ASD, attention deficit hyperactive disorder (ADHD), and a typical control group, ages 6-17. This study showed that children with ASD had levels that did not differ from the TD group and were higher than the ADHD group. In regard to the age range examined in the current study, Feldman et al. [11] is the only project to date that has measured peripheral OXT levels through saliva collection in a sample of preschoolers diagnosed with ASD. In that study, children with ASD showed lower baseline OXT levels as compared with the typical control group [11]. Overall, OXT characterization findings show that children with ASD have either normal or decreased levels of peripheral OXT, which may vary as a function of gender or disorder severity. These mixed findings have led some researchers to posit an "OXT deficit hypothesis" in ASD, which is not fully supported by the field [3]. However, a large limitation in integrating these results, as detailed above, is that studies have used different methodologies in terms of sample characteristics, collection of samples for analysis and OXT extraction procedures. Further, across studies, other variables that impact OXT expression, such as time of day, have also not been controlled for. Given this variability, studies are needed that use validated measures of OXT, well characterized and representative samples, and control for variables across typical and atypical development. To this end, the current study proposed to investigate peripheral OXT concentration levels and social cognitive ability in children with ASD and typical development (TD). Describing OXT levels and social cognition, as they relate to both behavior and disorder type, will aide in our understanding of the OXT system, its relation to social functioning, and its potential use as a treatment option.

Research Methodology

Participants

Thirty-nine children (18 ASD; 21 TD) between the ages of 3-5 years participated in the current study. Recruitment of participants followed a series of matching guidelines to ensure a more homogenous ASD sample that could be compared to the TD comparison group in terms of basic demographics. Specifically, all participants were between 3 years 0 months to 5 years 11 months of age. Further, ASD is known to be more common in males than females, with current estimates suggesting that diagnosis is 4.5 times more common in boys than in girls [16]. Given this, the gender split of the ASD sample reflected this general population difference with 14 male participants (77.8%) in the current study. Within the TD group, gender was split more evenly to reflect the general population, with 13 male participants (61.9%). In terms of cognitive and language ability, participants were assessed using the Visual Reception Subscale of the Mullen Scales of Early Learning (MSEL) and the Peabody Picture Vocabulary Test (PPVT). Results show that the ASD group scored within the low average range in terms of receptive language ability (M=82.07; SD=17.93) and within the below average range for cognitive functioning (M=31.13; SD=9.33). This suggests that the ASD sample used in the current study fell within a moderate range of functioning but were not severely impacted by their diagnosis and other developmental concerns. Lastly, in terms of both behavior and temperament, parents of both the ASD and TD groups completed an eligibility survey which asked questions that assessed their child's level of problem behaviors and their temperament in social situations. Further, a mix of children, with both outgoing and introverted social tendencies across both the ASD and TD groups were recruited to participate in the current study.

Inclusion/exclusion criteria

The To be included in the study, participants must have been minimally verbal, able to sit at a table for short periods of time, and independently partake in the assessment tasks in the current study (i.e., able to point, focus attention towards a task). Participants were excluded from the study if they were currently enrolled in an oxytocin trial, taking medication that altered mood or behavior, or presented with severe behavioral issues that would impact the ability to be assessed. Individuals with ASD were required to provide documentation of a primary diagnosis of ASD from a pediatrician, clinical psychologist, psychiatrist, or pediatric neurologist prior to enrollment. All children included in the TD group had no previous diagnosis of developmental, behavioral, mental, or learning disorder or disability.

Recruitment

Local recruitment and enrollment of participants occurred on a rolling basis over the course of 12 months. Participants with ASD were recruited through the greater Cleveland area ASD organizations, local preschools and daycare programs, and assessment clinics associated with UH Developmental Pediatrics and The Cleveland Clinic Learner Autism Center. Typically developing children were recruited through established

relationships with local school districts and preschools and through posting to the online Case Western Community Board.

Measures

Parent report of child

Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord 2003): Brief instrument completed by a parent or caregiver that evaluates communication skills and social functioning in screening for an autism spectrum disorder. In the current study, this measure was used as a confirmation of elevated ASD concerns within the autism sample as compared to the TD group, with a score above 15 indicated clinical levels of autism symptomology. All participants included in the study met this cut-off criterion.

In-person child assessments

Saliva collection & OXT extraction: One saliva sample from each child participant was collected during the laboratory visit approximately 15 minutes after arrival and the consent process. The saliva sample collection occurred between 8-10am to account for the cyclical nature of peripheral OXT release. Specifically, it is known that peripheral OXT levels peak at 1200 hours, and this amount significantly differs from 0600, 1800, and 2400 hours [17]. To control for this factor, participant's saliva collections did not significantly differ in regards to time of day.

Saliva was collected via cotton swab, placed in Sallivette containers, and subsequently stored at -80 degrees Celsius in Mather Memorial Building on CWRU's campus until shipment to Emory University for extraction procedures, per validated and replicated procedures [18,19]. Extracted values for OXT concentration levels were provided specifically through the Emory Biomarkers Core lab [18,19]. Multiple studies have shown that salivary OXT measured by immunoassay are reliable biomarkers, stable over time, and correlate with hormone related processes. Salivary OXT is associated with plasma OXT and genetic variability in OXTR receptor gene, which suggests coordination between central and peripheral activity on the oxytocin/vasopressin neuropathway [11,20]. OXT levels in pg/mL (pictogram/milliliter) were obtained for each participant.

Peabody picture vocabulary test, Fourth edition (PPVT-4; Dunn & Dunn, 2007): An individually administered measure of receptive vocabulary for standard American English for ages 2 years 6 months to 90+ years. The measure has shown good validity and reliability across both typical and atypical populations (Dunn & Dunn, 2007). Overall receptive language ability is reported as a Standard Score (M=100; SD=15).

Mullen scales of early learning-visual reception subscale (MSEL; Mullen, 1995): An individually administered assessment which measures functioning in infants and children up to 68 months of age across 5 domains (gross motor, visual reception, fine motor, expressive language, and receptive language). In the current study, only the visual reception subscale was administered and T-scores for this scale are reported given that previous research has shown that it is a valid and reliable indicator of early cognitive ability across typical and atypical populations [21].

Effect in play scale-preschool version [22] (APS-P) The APS-P is a standardized play task designed to measure various dimensions of children's pretend play. It has been validated for preschool children ages 4-5 years, however it has been used in children as young as three with no group differences based on age [23,24]. In this task, various toys are laid out on a table (cups, stuffed animals, toy car) and children are provided with a story stem and instructions to play with the toys and talk out loud for a 5-minute period.

The child's play is scored from the videotape using a criterion-based rating scale. For this study, a modified version of the APS-P scoring system was used, which included 8 original variables in addition to 7 variables created to better measure a wide range of pretense ability and interpersonal domains in pretend play. The original variables included ones that captured cognitive processes in play, specifically: (1) Imagination, (2) Organization of the storyline, and (3) Comfort in playing with the toys. These variables were all scored on a 1-5 scale; 1 being the lowest ability in that domain. Original variables that measured affective processes included: (1) Frequency of Affect, a total frequency count of affect units expressed within the play narrative and (2) Variety of Affect, a total count of the number of affect categories out of 11 possible categories expressed during the play. Further, for each 20-second interval, the rater indicates which of three types of play (No Play; Functional Play; Symbolic Play) was the predominant activity i.e., occurred for greater than or equal to 10 seconds within each 20-second interval. No Play was defined as the child not moving or interacting with the toys. Functional Play was coded when a child made simple, repetitive muscle movements with the toys or used them in a functional nature, such as stacking the cups, bouncing the ball, or pushing the car. Lastly, Symbolic Play was defined as any instance of using toys in an unusual manner, substituting an object for another, or using the object in any way other than how it is intended.

The 7 additional variables included two which aimed to measure more detailed and sensitive levels of pretense and imagination ability in pretend play. The first was a frequency count of the number of symbolic substitutions a child displayed during the 5-minute play task. A symbolic substitution was defined as when a child used a toy in a way that was similar to the properties of the toy, yet still imagined it was something else. For example, the ball as a sun or the cup as a bowl. This occurred when the object used for a substitution shared some type of overlap in its shape, size, or consistency with the imagined object. The second variable measured the frequency count of the number of symbolic transformations a child made during the 5-minute play period. A symbolic transformation was defined as when a child used a toy in a completely "as-if" manner that did not relate to the original properties of that toy. For example, using a cup as a rocket ship or imagining that there are other objects present (i.e., the table is the road; over here is the house). The other 5 variables all measured aspects relating to interpersonal processes in pretend play, namely: (1) frequency count of personification of the toys (i.e., any instance of when human attributes were ascribed to the toys during the 5-minute play task), (2) frequency count of the number of cooperative/nurture interactions that

occur between the toys, (3) frequency count of the number of aggressive/negative interactions that occur between the toys, (4) frequency count of the number of neutral interactions that occur between the toys, and (5) frequency count of the total number of interpersonal acts included in their play period.

Taken together, the cognitive domain encompassed 8 variables-Imagination, Comfort, Organization, Time in No Play, Time in Functional Play, Time in Symbolic Play, Frequency of Substitutions, and Frequency of Transformations. The Affective Domain encompassed 2 variables-Affect Frequency and Affect Variety. Lastly, the Interpersonal Domain encompassed 5 variables-frequency of Personifications, Frequency of Aggressive Interpersonal Acts, Frequency of Nurture/Affectionate Interpersonal Acts, Frequency of Neutral Acts, and Total Number of Interpersonal Acts.

Kaugars & Russ et al. [22] have developed a detailed scoring manual for the original 8 variables included in the APS-P. Zyga, Dimitropoulos, and Russ created an additional coding system for the symbolic and interpersonal variables. Interrater reliability across all variables is high, consistently in the 0.80s and 0.90s. Internal consistency for the affect scores on the APS-P using the Spearman-Brown split-half reliability is also high (0.85). The APS-P has a growing body of validity studies demonstrating associations with theoretically relevant criteria [22-26].

Facial Affect Comprehension Evaluation (FACE) [27]: The picture labeling task from the facial affect comprehension evaluation was used in the current study. This task, created for use in preschool children as young as 3 years of age, used a total of 18 pictures of adult and child faces with different expressions relating to happy, sad, angry, scared, surprised, disgusted, and ashamed. The experimenter verbally provided the child with the list of possible feelings and described the meaning of each (e.g., "Ashamed is when you did something wrong and your mommy yells at you, you feel ashamed"). Each picture was then presented to the child and he/she was asked to label each one with an emotion word by pointing to the list of provided options. No feedback on incorrect trials was provided for this task. The task is scored as to provide mean ability on each emotion presented along with total accuracy across all emotions, aggregate scores assessing ability in regards to negative versus positive emotion identification, and a total ability score. This task has shown to be a reliable measure of preschool children's ability to recognize and label emotions (ages 3-6 years) and significantly correlates with other measures of emotional understanding, such as emotional listening and learning tasks [28].

Social cognitive tasks [29]: Three domains were measured as part of the social cognitive observation tasks. All tasks were video recorded for later coding analysis.

Joint attention: measured a child's ability to follow the gaze of an adult examiner using a gaze-following task [30]. A child's ability to redirect attention to a focal object was scored along a 4-point scale for 8 consecutive trials: (1) Immediately follows point (2) After name prompt (3) Delayed/After object being labeled and (4) Did not follow point. A composite score was created based on mean scores across the 8 trials for each participant.

Empathy: measured a child's responsiveness to the feigned distress of an adult examiner. At standard points during the task, the examiner would pretend to hurt her knee and finger, as well as drop and ostensibly break her favorite toy. A frequency count of the number of times the child engaged in each of the 6 domains below was recorded for each task (hurt finger, hurt knee, and broken toy). Then, a score was given based on each task's frequency counts on 5-point scale ("very untrue" of the child's behavior to "very true" of the child's behavior). The six items scored on each task included: (1) Provides comfort (2) Offers help (3) Glances at examiner (4) Asks what is wrong (5) Expresses feeling sorry (6) Shows no upset.

Cooperation: measured the child's engagement in helping an adult experimenter complete a sequence of actions. First, the child was asked to help the experimenter hold up a napkin as to act as a "trampoline" for a stuffed animal rabbit to jump on. Second, the child was invited to help the experimenter complete a sequence of actions in which she rolled a ball down a tube and asked the child to help her hold the tube and catch the ball at the bottom. For the child to be successful, they could not just imitate the experimenter, as in task one, but had to have engaged in a complementary behavior to achieve the goal. Each task was administered and scored over 2 trials. For the trampoline task, ratings from 1-4 were assigned based on the following criteria: 1=no success; 2=low engagement; 3=medium engagement; 4=high engagement. For the tube task, ratings from 1-4 were assigned based on the following criteria: 1=child makes no attempt; 2=no success; 3=some success; 4=complete success

The tasks have been validated within toddler to preschool age samples and shown mean inter-rater reliability of α=0.86 (ranging from 0.68 to 0.96). All items loaded significantly onto the same factor, explaining 47% of the variance, with item loadings ranging from 0.54 to 0.76, suggesting construct validity [29].

Procedure

Scheduled visits began between 8-10am, to account for time of day and the cyclical nature of OXT release. To obtain a baseline sample of OXT, the child was asked to chew on a cotton swab (Salivette) (approx. 15 minutes after arrival and consent process). Then the child underwent cognitive and social cognitive assessments, including the PPVT-4 to assess receptive language ability, the MSEL to assess cognitive ability, the APS-P to assess pretend play ability, FACE to assess emotional understanding and recognition, and a series of Social Cognitive Tasks that measure a child's ability to respond to cues of joint attention, empathy, and cooperation. Parents completed the SCQ to assess autism symptomology during the visit as well.

Results

Data coding & interrater reliability

The SCQ, PPVT, MSEL, FACE, and videos of the APS-P, and social cognitive tasks were scored based on standardized manuals by undergraduate and graduate research assistants who were trained in the coding systems by the first and second authors.

Interrater reliability for all video coded tasks (APS-P; social cognitive tasks) was assessed. Independent coders, blind to conditions, rated 20% of each of these video recorded tasks. Intra-class correlations (ICC) were calculated based on a single measures, absolute agreement, two-way mixed effects model to assess the degree of consistency between coders for each task. The resulting ICCs for the APS-P and social cognitive tasks were Excellent (IRR=0.75-0.85) [31]. Raters had overall high levels of agreement and rated behaviors consistently across participants.

Demographics

Participants across the 2 groups did not differ on age (M=4.38; SD=0.85). However, there was a significant difference in receptive language ability (F=52.42; p=0.000) across the 2 groups as measured by the PPVT-4 and early cognitive ability (F=15.00; p=0.000) as measured by the visual reception subscale on the MSEL, with the ASD group scoring lower than the TD group. Further, the TD (61.9% male) sample had a more even split on gender whereas the ASD group (77.8% male) had a higher percentage of male participants which reflects the gender distribution in this disorder. The groups did not differ on race (majority Caucasian). One outlier was identified in the ASD group based on scores across language, cognitive, and social cognitive ability. This participant was excluded from all further analyses, leaving the total sample to include 17 children with ASD and 21 TD children. Lastly, given that language and cognitive ability differed between groups, all subsequent analyses controlled for cognitive ability. In regard to level of autism symptom severity, the ASD group scored significantly higher than the TD group (F=120.6; p=0.000) and fell above the cut-off score of 15, suggesting the presence of autism (**Table 1).**

Baseline OXT concentration levels

Within the ASD group, one value was identified as an outlier (pg/ml>149) and within the TD group, one sample was deemed corrupted and provided an invalid result. Overall, in the ASD sample, two values were thus excluded from any subsequent baseline analyses including OXT (1 outlier due to oxytocin level; 1 previously identified outlier) to bring the sample size to 16. In the TD sample, one sample was excluded from any subsequent baseline analyses including OXT, bringing the sample size to 20. A one-way, between-subjects ANOVA showed that the TD and ASD samples did not differ on their baseline levels of OXT expression (F=2.87; p=0.11) **(Table 2).**

Social cognitive ability

Pretend play (APS-P): A series of one-way, between-subjects ANCOVAs, controlling for cognitive ability, were conducted to better understand how global scores reflecting cognitive and affective ability in pretend play differed between the TD and ASD groups based on the standardized play task administered as part of the current study. Results showed that the two groups significantly differed on Imagination (F=7.91; p=0.008), Organization (F=10.07; p=0.003), Time Spent in Functional Play (F=6.84; p=0.01), Time Spent in Symbolic Play (F=5.25; p=0.03), number of Divergent Themes (F=8.03; p=0.008), Affect Frequency (F=5.41; p=0.03), and number of Personifications (F=11.55; p=0.002). For all variables except for Time Spent in Functional Play, the ASD group performed significantly lower than the TD group (**Table 3).**

Emotion Recognition (FACE): A series of one-way, between-subjects ANCOVAs, controlling for cognitive ability, were conducted to better understand how emotion recognition and understanding differed between the TD and ASD groups. Results showed that the two groups significantly differed in their ability to recognize Happy (F=11.07; p=0.002), Angry (F=4.97; p=0.03), Surprised (F=9.60; p=0.004), Positive Emotions (F=8.75; p=0.006), Negative Emotions (F = 8.98; p = 0.006), Total Accuracy by each emotion (F=16.39; p=0.000), and Total Ability across positive and negative emotional categories (F=17.57; p=0.000). For all variables, the ASD sample scored significantly lower than the TD sample **(Table 4).**

Joint attention, empathy, and cooperation (Social cognitive tasks): A series of one-way, between-subjects ANCOVAs, controlling for cognitive ability, were conducted to better understand how social cognitive ability relating to joint attention, empathy, and cooperation differed between the TD and ASD groups. Results showed that the two groups significantly differed on Joint Attention (F=4.12; p=0.05), Empathy (F=5.51; p=0.03), and Cooperation (F=18.33; p=0.000). For all variables, the ASD sample scored significantly lower than the TD sample. **(Table 4).**

Table 1: Participant demographics.

Variables	TD (n = 21)	ASD (n = 17)	F-Value	p-value
Age	4.47 (0.90)	4.27 (0.81)	0.483	0.49
Gender (%male)	13 (61.9%)	14 (77.8%)	0.896	0.35
PPVT	118.86 (12.61)	82.07 (17.93)	52.42	0.000**
MSEL-VRS	47.57 (14.39)	31.13 (9.33)	15.00	0.000**
Autism Severity (SCQ)	4.10 (1.89)	17.88 (5.21)	120.6	0.000**

PPVT: Peabody Picture Vocabulary Test; MSEL-VRS: Mullen Scales of Early Learning-Visual Reception Subscale; SCQ: Social Communication Questionnaire; †trending; *p<0.05; **p<0.01

Table 2: Baseline oxytocin across groups.

Variables	TD (n=20)	ASD (n=16)	F-Value	p-value
OXT Concentration (pg/ml)	54.38 (18.19)	65.62 (15.73)	2.87	0.11

*p<0.05; **p<0.01

Table 3: Pretend play ability across groups (APS-P).

Variables	TD (n = 21)	ASD (n = 17)	F-Value	p-value
Imagination	3.95 (0.74)	2.60 (1.18)	7.909	0.008**
Organization	3.67 (0.66)	2.33 (1.11)	10.07	0.003**
Comfort	3.57 (0.87)	3.33 (0.72)	0.552	0.46
No Play (%time)	3.19 (6.59)	4.80 (9.13)	0.001	0.97
Functional Play (%time)	31.33 (24.7)	61.87 (25.4)	6.840	0.01*
Symbolic Play (%time)	64.62 (27.5)	33.33 (26.7)	5.249	0.03*
Divergent Themes	3.05 (2.00)	0.80 (1.08)	8.034	0.008**
Transformation Frequency	0.52 (0.68)	0.20 (0.56)	0.714	0.40
Substitution Frequency	1.43 (0.81)	0.73 (0.70)	1.630	0.21
Affect Frequency	14.43 (6.74)	7.33 (5.43)	5.408	0.03*
Affect Variety	4.29 (1.85)	2.47 (1.77)	3.577	0.07†
Neutral Interpersonal Acts	1.10 (1.76)	0.47 (0.74)	2.760	0.11
Aggressive Interpersonal Acts	2.43 (2.71)	0.80 (1.82)	2.743	0.11
Nurturing Interpersonal Acts	0.43 (0.75)	0.00 (0.00)	3.170	0.08†
Personifications	4.19 (2.34)	1.13 (1.51)	11.55	0.002**
Number of Characters	5.38 (2.13)	3.40 (2.17)	2.097	0.16

†Trending; *p<0.05; **p<0.01

Table 4: Social cognitive ability across groups.

Variables	TD (n=21)	ASD (n=17)	F-Value	p-value
Facial Affect Comprehension Evaluation (FACE)				
Happy	93.71 (13.3)	53.30 (45.0)	11.07	0.002**
Sad	72.62 (26.1)	47.50 (36.2)	2.703	0.11
Angry	81.00 (33.5)	50.00 (47.1)	4.973	0.03*
Scared	39.62 (34.4)	26.60 (26.4)	0.405	0.53
Surprised	61.90 (41.6)	20.00 (35.0)	9.595	0.004**
Disgusted	64.30 (35.9)	30.00 (35.0)	3.698	0.07†
Ashamed	9.50 (25.6)	0.00 (0.00)	1.232	0.28
Total Accuracy	62.57 (11.9)	36.10 (19.4)	16.39	0.000**
Positive Emotions	81.00 (20.5)	50.00 (35.6)	8.752	0.006**
Negative Emotions	91.19 (6.42)	78.50 (13.3)	8.981	0.006**
Total Ability	88.19 (5.50)	70.50 (15.4)	17.57	0.000**
Social Cognitive Tasks				
Joint Attention[a]	1.02 (0.06)	1.56 (0.85)	4.122	0.05*
Empathy	2.81 (0.46)	2.28 (0.62)	5.513	0.03*
Cooperation	3.86 (0.20)	3.07 (0.60)	18.33	0.000**

[a]Reverse scored; †Trending; *p<0.05; **p<0.01

TD sample comparison

Correlational analyses were used to examine the relationship between OXT concentration levels and variables relating to pretend play ability (APS-P), emotional understanding (FACE), and social cognitive ability within the TD group. First, in regards to pretend play, results show a significant positive correlation between baseline OXT concentration level and Functional Play (r=0.53; p=0.02) and significant negative correlations between baseline OXT and Symbolic Play (r=-0.53; p=0.02) and Aggressive Interpersonal Acts (r=-0.54; p=0.02). Third, a significant positive correlation was found between baseline OXT concentration level and Sad emotion recognition (r=0.58; p=0.009). Fourth, a significant positive correlation was found between baseline OXT concentration level and Joint Attention (r=0.53; p=0.02).

Given that Functional Play, Symbolic Play, and Aggressive Interpersonal Acts on the APS-P, Sad emotion recognition on the FACE, and Joint Attention on the Social Cognitive Task significantly correlated with baseline OXT concentration levels at $r \geq 0.30$, $p<0.05$, a five step hierarchical multiple regression was conducted with baseline OXT concentration level as the dependent variable. Sad (FACE) was entered at step one of the regression given that it was shown to account for the most variance in regards to predicting baseline OXT levels. Subsequent variables were entered based on variance predicted, with later variables predicting less variance. The hierarchical regression revealed that at Step One, Sad (FACE) contributed significantly to the regression model (t=2.97, p=0.009) and accounted for 30.2% of the variation in baseline OXT concentration level. Introducing Aggressive Interpersonal Acts (APS-P) explained 18.4% of variation in baseline OXT levels and this change in R^2 was significant (t=-2.490, p=0.02). Adding Functional Play (APS-P), Symbolic Play

(APS-P) and Joint Attention to the regression model explained a non-significant portion of variance in baseline OXT concentration levels. Given this, Step Two was found to be the model of best fit with Sad (FACE) and Aggressive Interpersonal Acts (APS-P) serving as unique predictors which accounted for the most significant amount of variance in baseline OXT concentration level within the TD sample (**Table 5).**

Sample comparison

Correlational analyses were used to examine the relationship between baseline OXT concentration levels and variables relating to pretend play ability (APS-P), emotional understanding (FACE), and social cognitive ability within the ASD group. In pretend play, significant positive correlations were found between Affect Frequency (r=0.62; p=0.03), Divergent Storylines (r=0.60; p=0.04), Aggressive Interpersonal Acts (r=0.72; p=0.009), and Personifications (r=0.61; p=0.03) and baseline OXT concentration levels. No other significant correlations were found between baseline OXT concentration levels and variables relating to emotion recognition (FACE) or social cognitive ability in the ASD sample.

Given that Affect Frequency, Divergent Storylines, Aggressive Interpersonal Acts, and Personifications on the APS-P significantly correlated with baseline OXT concentration levels at $r \geq 0.30$, $p<0.05$, a four step hierarchical regression was conducted with baseline OXT concentration level as the dependent variable. Interpersonal Aggressive Acts (APS-P) was entered at Step One of the regression given that it was shown to account for the most variance in regards to predicting baseline OXT levels. Later variables entered into the model predicted less variance. Specifically, Aggressive Interpersonal Acts (APS-P) was entered at Step One, Personifications (APS-P) was entered at Step Two, Affect Frequency (APS-P) was entered at Step Three, and Divergent Storylines (APS-P) was entered at Step Four. The hierarchical regression revealed that at Step One, Aggressive Interpersonal Acts (APS-P) contributed significantly to the regression model (t=3.25, p=0.009) and accounted for 46.5% of the variation in baseline OXT concentration level. Introducing Personifications (APS-P), Affect Frequency (APS-P), and Divergent Storylines did not significantly predict baseline OXT concentration levels. These findings suggest that Step One is the model of best fit with Aggressive Interpersonal Acts (APS-P) accounting for the most significant amount of variance in baseline OXT concentration level within the ASD sample **(Table 6).**

Discussion

The current study aimed to characterize peripheral OXT concentration levels and social cognitive ability in preschoolers with ASD and typical development (TD) and understand how OXT levels related to these factors across diagnostic categories. A main finding was that the two samples did not differ in OXT concentration levels. Further, results indicated that children with ASD had significantly lower receptive language, cognitive ability, and lower scores in pretend play, emotion recognition, joint attention, cooperation, and empathy.

When evaluating how social cognitive factors related to OXT concentration levels, analyses showed that, within the TD sample, sad emotion recognition was the largest significant predictor of OXT concentration levels. Aggressive interpersonal acts in play also uniquely predicted a portion of the variance in OXT concentration levels. Within the ASD sample, aggressive interpersonal acts in play accounted for the largest portion of variance and was a unique significant predictor of OXT

Table 5: Summary of hierarchical regression analysis for predicting baseline OXT within TD sample (N=20).

Variables	B	t-value	p-value	R^2	Adjusted R^2	ΔR^2	Sig. ΔF
Step 1							
Sad	44.819	2.967	0.009**	0.341	0.302	0.341	0.009**
Step 2[b]							
Sad	37.612	2.780	0.013*	0.341	0.302	0.341	0.009**
Aggressive Interpersonal Acts	-3.315	-2.490	0.024*	0.525	0.466	0.184	0.024*
Step 3							
Sad	33.710	2.665	0.018*	0.341	0.302	0.341	0.009**
Aggressive Interpersonal Acts	-2.619	-2.046	0.059†	0.525	0.466	0.184	0.024*
Functional Play	28.176	1.943	0.071†	0.621	0.545	0.095	0.071†
Step 4							
Sad	32.762	2.575	0.022*	0.341	0.302	0.341	0.009**
Aggressive Interpersonal Acts	-2.994	-2.231	0.043*	0.525	0.466	0.184	0.024*
Functional Play	-18.232	-0.361	0.723	0.621	0.545	0.095	0.071†
Symbolic Play	-41.566	-0.960	0.353	0.644	0.542	0.023	0.353
Step 5							
Sad	25.095	1.767	0.103†	0.341	0.302	0.341	0.009**
Aggressive Interpersonal Acts	-2.718	-1.780	0.100†	0.525	0.466	0.184	0.024*
Functional Play	-8.118	-0.107	0.916	0.621	0.545	0.095	0.071†
Symbolic Play	-22.210	-0.358	0.726	0.644	0.542	0.023	0.353
Joint Attention	63.477	0.862	0.406	0.691	0.536	0.019	0.406

[b]Model of best fit; †trending; *p<0.05; **p<0.01

Table 6: Summary of hierarchical regression analysis for predicting baseline OXT within ASD Sample (N=16).

Variables	B	t-value	p-value	R^2	Adjusted R^2	ΔR^2	Sig. ΔF
Step 1[b]							
Aggressive Interpersonal Acts	12.134	3.252	0.009**	0.514	0.465	0.514	0.009**
Step 2							
Aggressive Interpersonal Acts	9.239	2.207	0.055*	0.514	0.465	0.514	0.009**
Personifications	5.805	1.344	0.212	0.595	0.505	0.081	0.212
Step 3							
Aggressive Interpersonal Acts	11.083	1.841	0.103	0.514	0.465	0.514	0.009**
Personifications	7.340	1.292	0.232	0.595	0.505	0.081	0.212
Affect Frequency	-1.166	-0.447	0.667	0.605	0.457	0.010	0.667
Step 4							
Aggressive Interpersonal Acts	8.907	1.530	0.170	0.514	0.465	0.514	0.009**
Personifications	13.445	1.993	0.086	0.595	0.505	0.081	0.212
Affect Frequency	-5.442	-1.432	0.195	0.605	0.457	0.010	0.667
Divergent Storylines	20.579	1.468	0.186	0.698	0.526	0.093	0.186

[b]Model of best fit; [†]trending; *p<0.05; **p<0.01

concentration. These findings suggest that relationships between OXT concentration levels and measures of social cognitive ability vary based on group membership.

Group comparison

OXT characterization: A first major aim of this study was to better understand OXT concentration levels in preschoolers with ASD and how these levels compared with typical developing children of the same age. Previous findings in the literature within the preschool age range [11] have posited an "OXT deficit hypothesis"in regard to individuals with autism [8,11,12]. Contradictory to this hypothesis, the current study found that preschoolers with ASD did not have lower OXT levels as compared to the TD group. This finding lends evidence towards the complex relationship between OXT and social cognitive functioning and its potential use as an indicator across diagnostic categories or populations rather than being solely specific to ASD. Building off this concept of complexity, more recent studies point to mixed findings that are beginning to question the "OXT deficithypothesis" in ASD. Whereas older studies found lower levels of OXT in individuals with ASD [8,10,12] more recent studies are showing no difference between diagnostic groups [13-15] or differences that are dependent on levels of cognitive and social impairment [9]. Notably, the results from a study conducted by Parker et al. [14] led the authors to suggest that OXT biology may not be uniquely related to autism, but may instead enact independent and accumulative influences on individual differences in human social functioning, which would also include the social deficits evidenced in ASD. Lastly, Taurines et al. [15] found a strong positive correlation (r=0.60; p=0.01) between OXT levels and ADOS severity scores in the ASD sample, suggesting that higher OXT related to more severe autism symptomology. The authors noted that proposing an OXT deficit or excess model for ASD seemed to be inadequate in fully describing findings from the literature and previous studies. Taurines et al. [15] posited that perhaps high OXT could potentially be understood as a secondary physiological effect from negative moods or stressors with a potential aim to moderate anxiety given that one of OXT functions is the regulation of social anxiety. This assumption that different levels of OXT can be impacted by factors outside of diagnostic category, such as comorbid conditions, levels of stress, and social cognitive ability, falls in line with the concept that the role OXT may play in ASD is more complex and further study of its expression across ages, levels of functioning, and diagnostic categories is warranted.

Behavioral characterization: This study further characterized social cognitive abilities between preschoolers with ASD and typically developing peers across domains relating to pretend play, emotion recognition, joint attention, empathy, and cooperation. Previous research has shown that children with ASD as young as 2 years old show a decreased ability to produce or engage in pretend or symbolic play [32-35], show a preference for non-speech versus motherese sounds when toddlers [36], visually attend less to social faces when circumscribed objects of interests are shown in tandem with these faces [37], show decreased skill in social interactions relating to less social bids and focus of engagement on other children [38], and decreased emotional understanding and recognition [39]. Overall, in the current study, these previous findings were replicated in that the ASD group scored significantly lower than the TD sample across all social cognitive measures as predicted. These findings provide further support that social cognitive deficits are evident in children with ASD even in this early age range [34,40]. These findings add to the literature in that many previous studies have characterized socioemotional deficits in preschoolers through the use of parent report or interviews. The current study's use of behavioral assessments in capturing skills relating to various domains such as pretend play, joint attention, cooperation, empathy, and emotion recognition provides more objective

evidence of the difficulties young children with autism may face. Further, given the more objective and quantitative nature of behavioral assessments, it may be important to use baseline findings to better tailor the needs of intervention to the child's specific difficulties or use these assessments as stronger outcome measures than parent report alone.

Social cognitive functioning and OXT Levels

Results showed that the relation between OXT levels and social cognitive ability did vary by group membership. Within the TD sample, emotion recognition and use of aggressive interpersonal acts in play accounted for the highest variance in predicting oxytocin. In the ASD sample, aggressive interpersonal acts in play also accounted for the highest variance in predicting baseline OXT, however in the opposite direction as that found in the TD sample. These findings fall in line with previous research in two main ways: (1) prior findings suggest a relationship between OXT and factors such as social interest and emotional understanding and expression and (2) the theory that OXT may not be uniquely related to ASD or one diagnostic category but rather related to individual differences across groups in a way that is nuanced and complex.

To the first point, multiple lines of research have shown the potential role of OXT in trust, altruism, social bonding, and human's ability to infer the emotional states of others [6], however, never in such a young population. Specifically, past findings have shown that the OXTR rs53576 allelic variation relates to deficits in empathy, attachment, and sensitive parenting [41]. In regard to emotion recognition and expressions, studies have shown that higher OXT expression is related to better classification of emotions displayed on faces and increased gaze to the eye region in human faces [6]. The findings in this study suggest that the relationship between OXT and socioemotional factors present early in development across both typical and atypical populations.

To the second point, current research suggests that the question should not be whether or not OXT relates to social cognitive factors but rather under what circumstances in that the effects of OXT are most often found to be moderated by contextual factors or by stable characteristics of the individual [42]. As shown in the results of this study, factors such as group membership, developmental trajectory, and severity of socioemotional deficits led to differences in how OXT related to various domains and measures. An interesting finding in the current study that has also been shown in previous research is the opposite nature of relationships between OXT and areas of functioning when comparing a TD sample against individuals with ASD. In the current study, it was found that aggressive interpersonal acts in play negatively correlated with baseline OXT levels in TD children but positively correlated with OXT in children with ASD. That is, for TD children, higher levels of aggressive interpersonal acts in their play related to lower OXT expression whereas, in ASD, higher interpersonal aggression related to higher OXT levels. This reversal of relationships provides evidence to the concept that the effects of oxytocin and its relationship with social cognition are nuanced. It may be that, for typically developing children, an expression of aggressive acts is less prosocial given higher overall social ability [38] which then would lead this factor to be negatively associated with OXT levels. However, in ASD, where social deficits are evident, the ability to express any type of interpersonal act, be it aggressive or otherwise, may show a true prosocial ability, which could lead to a positive relationship with OXT. A previous study conducted by Modahl et al. [8] also showed this reverse relationship in that elevated OXT was associated with higher scores on social and developmental measures in a typically developing sample of male children, ages 6-11 years. However, in the ASD sample, elevated OXT was associated with lower scores on these same measures. Other studies have shown these reverse relational patterns in regard to factors such as gender [13] and severity of diagnosis [9]. Taken together, the findings of this and previous studies suggest that more research needs to be done in better understanding the various circumstances and relationships that may be present between OXT and other domains of functioning, how context and person-dependent factors impact these relationships, and the thought that there may be distinct mechanisms of action for OXT within these various relationships or group differences.

Limitations and Future Directions

A few limitations should be noted in the present study when interpreting the results and determining future directions. One limitation is the small sample size, which yields low statistical power for detecting group differences. Relatedly, a large number of analyses were conducted given the small sample size. Bonferroni corrections were used when appropriate; however, it will be important for future studies, with larger samples sizes, to be conducted in order to replicate the current findings.

Another limitation to note is the cross-sectional nature of the current study which does not allow conclusions to be drawn about actual developmental change or change through time. This makes it difficult to understand the trajectory of OXT release and how it may relate and change with social cognitive ability. Future studies should extend the findings of the current study in characterizing OXT levels across developmental stages (i.e., infancy, toddler, preschool, and school-age periods) in a longitudinal design to obtain a better understanding of the course of OXT development.

Conclusion and Practical Significance

The prevalence rate of ASD continues to rise and the deficits associated with this disorder severely impact not only the affected child but the family system as a whole. Research into the molecular basis of ASD has begun to show a potentially important link between autism and the OXT system. However, current treatment models, both pharmacologically and behaviorally, show limited efficacy in targeting functioning across individuals with ASD. Vital next steps in this area include exploring the biology behind observable deficits, which will provide clarity on the nature of this disorder and begin to reveal what underlying mechanisms may be implicated in disorder development or as treatment targets. The findings from this study suggest that the relationship of OXT with social cognitive ability and disorder

category are complex and nuanced. Specifically, results do not support the concept of an "OXT deficit hypothesis" in children with ASD but rather show that oxytocin may have unique relationships with social cognitive variables across different groups and levels of functioning. Taken together, these findings suggest that further investigation of oxytocin and its relationship to social cognitive ability in the preschool period is warranted and may have large implications for early identification and treatment. Specifically, additional work may delineate that OXT levels do indeed vary as a function of the presence of disorder, implicating its measurement as a potential biomarker. Ultimately, continued research will aid in better understanding deficits evidenced in ASD and knowledge as to how to target these deficits earlier and more effectively, potentially with both biological and behavioral techniques [43,44].

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of Case Western Reserve University Institutional Review Board (IRB-2015-1240) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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