Blood Oxytocin Concentration Positively Predicts Contagious Yawning Behavior in Children with Autism Spectrum Disorder

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Research suggests that children with autism spectrum disorder (ASD) may have reduced empathy, as measured by an impaired contagious yawn response, compared to typically developing (TD) children. Other research has failed to replicate this finding, instead attributing this phenomenon to group differences in attention paid to yawn stimuli. A third possibility is that only a subgroup of children with ASD exhibits the impaired contagious yawn response, and that it can be identified biologically. Here we quantified blood concentrations of the "social" neuropeptide oxytocin (OXT) and evaluated yawning behavior and attention rates during a laboratory task in children with ASD ($N = 34$) and TD children ($N = 30$) aged 6–12 years. No group difference in contagious yawning behavior was found. However, a blood OXT concentration × group (ASD vs. TD) interaction positively predicted contagious yawning behavior ($F_{1,50} = 7.4987$; $P = 0.0085$). Specifically, blood OXT concentration was positively related to contagious yawning behavior in children with ASD, but not in TD children. This finding was not due to delayed perception of yawn stimuli and was observed whether attention paid to test stimuli and clinical symptom severity were included in the analysis or not. These findings suggest that only a biologically defined subset of children with ASD exhibits reduced empathy, as measured by the impaired contagious yawn response, and that prior conflicting reports of this behavioral phenomenon may be attributable, at least in part, to variable mean OXT concentrations across different ASD study cohorts.
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Lay Summary: People with autism may contagiously yawn (i.e., yawn in response to another's yawn) less often than people without autism. We find that people with autism who have lower levels of blood oxytocin (OXT), a hormone involved in social behavior and empathy, show decreased contagious yawning, but those who have higher blood OXT levels do not differ in contagious yawning from controls. This suggests that decreased contagious yawning may only occur in a biologically defined subset of people with autism.

Keywords: autism; contagion; empathy; oxytocin; social functioning; yawning

Introduction

Autism spectrum disorder (ASD) is characterized by core social impairments (e.g., reduced nonverbal social communication behaviors, lack of perspective taking, and deficits in social–emotional reciprocity) [American Psychiatric Association, 2013]. Individuals with ASD may also exhibit a reduced capacity for empathy, as defined and reviewed by Bons et al. [2013], including impairments in facial mimicry and emotion recognition. The contagious yawn response (i.e., yawning in response to the perception of another individual's yawn) has been found to be positively associated with performance on self-face recognition and theory of mind stories [Platek, Critton, Myers, & Gallup Jr., 2003]. Additionally, viewing yawns was found to increase activity in the mirror neuron system [Haker, Kawohl, Herwig, & Rössler, 2013]. As a result, contagious yawning has been used in research studies as a proxy measure of empathy [Senju et al., 2007].

Some studies have found contagious yawning to be reduced in children with ASD compared to typically developing (TD) children [Giganti & Esposito Ziello, 2009; Senju et al., 2007]. However, not all studies have replicated the impaired contagious yawn response finding in children with ASD. Several such studies have attributed the existence of this phenomenon instead to group differences in attention paid to yawn stimuli during task performance [Senju et al., 2009; Usui et al., 2013]. Another possibility, however, is that the impaired contagious yawn response exists, but only in a subset of children with ASD. This might be particularly true if individual differences in the biology that regulates social functioning drive contagious yawning behavior

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in children with ASD, thereby contributing to phenotypically heterogenous study cohorts and inconsistent study outcomes.

Although the neurochemical underpinnings of contagious yawning are unknown, a promising biological candidate is the neuropeptide oxytocin (OXT). In animal models, both OXT administration and activation of oxytocinergic neurons have been found to induce yawning [Eguibar, Cortes, Isidro, & Ugarte, 2015; Kita, Yoshida, & Nishino, 2006]. Moreover, OXT promotes prosocial functioning in mammals [Anacker & Beery, 2013] and administration of OXT enhances empathy in humans [Hurlemann et al., 2010]. Blood OXT concentration has also been found to predict cerebrospinal fluid OXT concentration in the same individuals [Carson et al., 2015], suggesting that blood OXT concentration may be a useful surrogate measure of brain OXT activity. For example, a previous study found low circulating blood concentrations of OXT to be associated with diminished theory of mind ability, a cognitive form of empathy, in human children [Parker et al., 2014]. The goal of the present study therefore was to test whether children with and without ASD differ in contagious yawning behavior, while concomitantly testing whether blood OXT concentration and attention paid to yawn stimuli during task performance impact this behavioral phenomenon.

Materials and Methods

Participants, Recruitment, Diagnosis, and Eligibility Criteria

This research was approved by the Stanford University School of Medicine Institutional Review Board. All participants' parents provided informed consent prior to initiation of study procedures. Assent was also obtained from participants when the child was deemed intellectually capable of understanding the study. Participants were $N = 64$ children ($N = 34$ ASD; $N = 30$ TD) aged 6–12 years. Children with ASD were primarily recruited through the Stanford Autism and Developmental Disorders Research Registry, flyers posted in the Stanford University Autism and Developmental Disorders Clinic, and special events. The ASD participants were drawn from two distinct study cohorts undergoing identical "baseline" testing procedures prior to their randomization in subsequent studies [Parker et al., 2017, 2019]. Unrelated TD children were recruited through advertisements posted online and hardcopy in the surrounding community.

A comprehensive diagnostic evaluation was performed on children with ASD to confirm the accuracy of their existing diagnosis based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) [American Psychiatric Association, 2000] or DSM-5 [American Psychiatric Association, 2013] criteria. This diagnosis was confirmed using research diagnostic methods (i.e., the Autism Diagnostic Instrument-Revised and the Autism Diagnostic Observation Schedule) [Gotham, Risi, Pickles, & Lord, 2007; Lord, Rutter, & Le Couteur, 1994], administered by assessors trained by a research-reliable clinician (J.M.P.).

Participants with ASD were included if they had a full-scale intelligence quotient (IQ) of 50 or above. TD participants were included if they had a full-scale IQ in the normal range. Cognitive functioning was determined using the Stanford Binet Scales of Intelligence, 5th Edition [Roid, 2003]. Social symptom severity was determined for all participants using the Social Responsiveness Scale, 2nd Edition [Constantino et al., 2003]. Children with ASD were not included if they had evidence of a genetic, metabolic, or infectious etiology for their ASD on the basis of medical history, neurologic history, and available laboratory testing for inborn errors of metabolism, and chromosomal analysis. Exclusion criteria additionally included a DSM-IV-TR or DSM-5 diagnosis of a severe mental disorder (e.g., schizophrenia; bipolar disorder).

ASD participants taking medications were included if their medications were stable for at least 4 weeks before blood collection. TD children were required to be free of neurological and psychiatric disorders in the present or past on the basis of medical history and have no sibling diagnosed with ASD.

Blood Sample Collection and OXT Quantification

Venous blood was drawn from the child's antecubital region by a pediatric phlebotomist. Whole blood was collected into ethylenediaminetetraacetic acid-treated vacutainer tubes and immediately placed on wet ice. Samples were promptly centrifuged (1,600*g* at 4°C for 15 min) and the plasma fraction aliquoted and flash-frozen on dry ice. All samples were stored at −80°C until quantification. A researcher blinded to experimental group extracted the plasma samples and then quantified OXT concentrations using a commercially available enzyme immunoassay kit (Enzo Life Sciences, Inc., Farmingdale, NY) as described in detail elsewhere [Carson et al., 2015; Parker et al., 2014]. Intra- and inter-assay coefficients of variation were 7.26% and 14.62%, respectively.

Contagious Yawn Laboratory Task

Participants were video-recorded as they were administered a laboratory task on a computer monitor. This task was previously designed and validated to elicit contagious yawning [Haker & Rössler, 2009]. Data were extracted from 16 stimulus trials (eight trials of an actor yawning; eight trials of an actor exhibiting a neutral expression); each trial lasted 15 sec in duration. Trial duration and number were chosen based on potential to elicit contagious behavior and hold the attention of a pediatric population. Video stimuli were recorded with eight volunteers (four men, four women, aged 27–58 years). Yawn stimuli consisted of one or two

yawns, with a brief pause before and after each yawn. The two conditions (yawning, neutral) were presented sequentially, with stimulus order kept consistent for all participants. Between each stimulus trial, participants were asked to answer two distractor questions on a five-step scale: how comfortable they felt viewing the stimulus, and how likeable they found the person in the stimulus trial. Two independent coders (M.G.M. and S.M.R.), blinded to experimental group, coded the frequency and duration of all yawn events for every participant across the 16 trials using Observer XT software (Noldus Information Technology Inc., Leesburg, VA). Yawns were considered contagious if they occurred during a yawn trial. Yawns were characterized by the presence of the stereotyped motor pattern of gaping of the mouth accompanied by a long inspiration followed by a shorter expiration [Usui et al., 2013]. Participants were coded as having paid attention to a stimulus if they viewed the screen for more than 50% of each stimulus presentation. In this manner, attention was scored as a 0 or 1 for each trial and then averaged over all 8 "yawn" trials. Inter-rater reliability (Cohen's kappa (κ) > 0.85) was established between the two coders for all measures prior to the initiation of coding, and confirmed periodically thereafter. Any coding disagreements were resolved by a third independent coder, whose interpretation was considered final.

Statistical Analyses

Data were managed in REDCap and analyzed as a weighted-least-squares (WLS) linear model in JMP 13 Pro for Windows (SAS Institute Inc., NC). For each participant, contagious yawn rates were calculated as the number of yawns observed per eight trials of yawn stimuli. Noncontagious (control) yawn rates were similarly calculated for neutral stimulus trials. The proportion of the eight yawn stimulus trials attended to by each participant was calculated and used as a weighting factor. This approach treats attention as a predictable source of error, but not as a predictor of yawn rate itself [Neter, Kutner, Nachstsheim, & Wasserman, 1996]. Later, to test whether attention did affect yawn rate in a predictable manner, the attention rate variable was removed as a weighting factor, and included as a predictor variable, and all tests were repeated. We also confirmed that social symptom severity was not mediating this effect. Full-scale IQ, ethnicity, sex, blood collection time, and yawn rate (from the neutral trials) were included as blocking (control) factors. Group was nested within study cohort to test for the effect of ASD while also accounting for any difference between the two ASD study cohorts. To test for OXT-dependent effects, blood OXT concentration and its interaction with group nested within cohort were included. To test for possible carryover effects between yawn and neutral stimulus trials, we performed the same analysis, but "swapped" the roles of the neutral and yawn stimulus trials (i.e., the WLS model now predicted noncontagious yawn rate, weighted by attention rate during the neutral stimulus trials, and included contagious yawn rate during the yawn stimulus trials as a blocking (control) factor). Y-variables were square root transformed to meet the assumptions of WLS, which were confirmed post hoc [Grafen & Hails, 2002]. Significant interactions were tested by Bonferroni-corrected post hoc contrasts. Separately, as a follow-up analysis, exploratory factor analysis (using varimax rotation) was performed on attention rate, contagious yawn rate, full-scale IQ score, and blood OXT concentration in children with ASD.

Results

Participant Characteristics

Demographic and clinical characteristics are summarized in Table 1. Two variables (full-scale IQ score and blood collection time) significantly differed between the ASD and TD groups. To eliminate the possibility that these confounding effects could generate false positive or false negative results [Grafen & Hails, 2002], we adopted the standard epidemiological approach to this problem and included these variables in the statistical models as blocking (control) factors.

Blood OXT Concentration and Contagious Yawn Rate

Children with ASD did not significantly differ from TD children in either blood OXT concentration ($F_{1,62}$ = 2.0582; P = 0.1564) or contagious yawning behavior ($F_{1,50}$ = 1.0936; P = 0.3007). However, contagious yawning rate was predicted by a significant interaction between blood OXT concentration and group (ASD vs. TD) ($F_{1,50}$ = 7.4987; P = 0.0085), whereby children with ASD showed progressively lower mean contagious yawns as blood OXT concentration decreased, while TD children showed no significant

Table 1. Participant Characteristics

Group	ASD	Control
N	34	30
Female	6	9
Male	28	21
Caucasian	19	22
Asian	4	3
Other	11	5
Age	9.26 ± 0.37	8.80 ± 0.40
Full-scale IQ*	81.74 ± 3.73	117.37 ± 3.97
Blood collection time*	14:11 pm ± 18 min	12:55 pm ± 19 min
Blood OXT concentration (pg/mL)	8.62 ± 0.92	10.54 ± 0.98

Likelihood ratio tests were used to test whether the distribution of individuals in the two experimental groups differed by sex and ethnicity; no significant effects were found. For age, IQ, blood collection time, and blood oxytocin (OXT) concentration, differences between groups were tested with a simple one-way general linear model (*P < 0.05). The values are reported as mean ± standard error.

relationship between these two variables. Thus, children with ASD exhibited fewer contagious yawns than TD children at lower blood OXT concentrations, but did not differ behaviorally from TD children at higher blood OXT concentrations (Fig. 1).

Mean contagious yawn rate had no significant relationship with IQ ($F_{1,50}$ = 1.1485, P = 0.28901). We also ran this analysis including SRS total score to rule out the possibility that the blood OXT and contagious yawning relationship was mediated by clinical symptom severity. The relationship between blood OXT concentration and contagious yawning rate remained significant when SRS total score was included in the model ($F_{1,49}$ = 7.971; P = 0.0069), and the SRS total score did not predict contagious yawning rate ($F_{1,49}$ = 0.633; P = 0.4300). To ensure that our finding was not the result of a delay in the perception of yawn stimuli, we next tested for carry-over effects between yawn and neutral stimulus trials. Children with ASD did not significantly differ from TD children in yawning rates during neutral stimulus trials ($F_{1,50}$ = 0.0180; P = 0.8939), nor was there a blood OXT concentration by group interaction in this model (ASD vs. TD) ($F_{1,50}$ = 1.0988; P = 0.2997).

We next removed attention rate as a weighting factor and included it as a predictor in the model. Attention rate did not account for yawn rate ($F_{1,51}$ = 1.3111; P = 0.2575) and the relationships described above did not change. When we repeated the analyses without attention as either a weighting factor or a predictor, the relationships described above did not change. Finally, our exploratory factor analysis yielded two factors. Factor 1 loaded attention rate and full-scale IQ score, whereas Factor 2 loaded contagious yawning rate and blood OXT concentration (Table 2). Thus, this analysis further supported the observed relationship between blood OXT concentration and contagious yawning behavior.

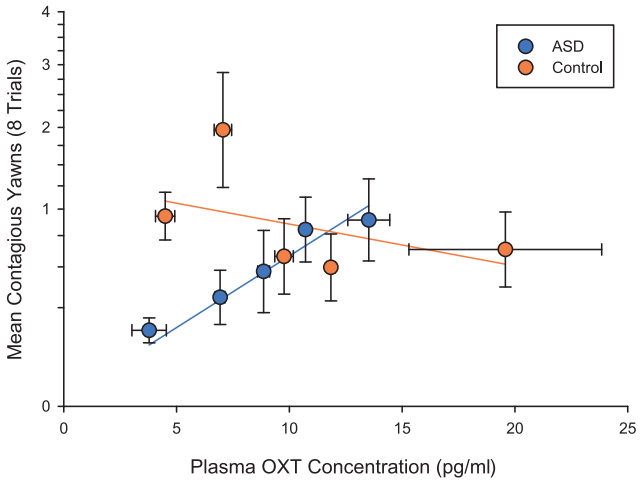

Figure 1. Blood oxytocin (OXT) concentration predicts contagious yawning behavior in children with autism spectrum disorder (ASD) but not in typically developing (TD) children. Least squares lines are plotted corrected for the following blocking (control) factors: full-scale IQ, ethnicity, sex, blood collection time, yawning rates during neutral stimulus trials, and attention rate during stimulus presentation. Data are plotted as a mean ± standard error for each OXT concentration quintile within the ASD and TD groups for ease of visualization. Yawning rates were square root transformed prior to analysis. Study data were collected from two ASD cohorts (which did not differ), and the mean response is shown here.

Discussion

Previous research on contagious yawning behavior in children with ASD has produced equivocal results. Some studies have reported an impaired contagious yawn response in children with ASD versus TD children [Giganti & Esposito Ziello, 2009; Senju et al., 2007], whereas other studies have failed to replicate this finding [Senju et al., 2009; Usui et al., 2013], instead attributing its existence to group differences in attention paid to yawn stimuli. The present study sought to address this discrepancy by testing whether a subset of children with ASD had this impairment and if it could be biologically identified. This was indeed the case, as children with ASD at lower blood OXT concentrations exhibited an impaired contagious yawn response but those at higher blood OXT concentrations were behaviorally similar to TD children. Importantly, this finding was observed whether attention paid to test stimuli was included in the statistical model or not, and attention never predicted yawn rate. The conclusion that attention is not a significant driver of yawn rates was further supported by our exploratory factor analysis showing that attention rate and IQ score significantly loaded onto one factor, whereas blood OXT concentration and contagious yawning rate significantly loaded onto another.

We found no evidence that children with ASD showed delayed perception of yawn stimuli, as they did not differ from TD children in yawning rates during neutral stimulus trials. We likewise found no relationship between SRS total score and contagious yawning in children with ASD, and the relationship between blood OXT concentration and contagious yawning held whether or not SRS total score was included in the model. These findings suggest that an impaired contagious yawn response is not due to social perceptual delays or greater clinical symptom severity, but

Table 2. Factor Analysis of the Study's Key Variables

Variable	Factor 1	Factor 2
Attention rate	**0.641333***	−0.126702
Contagious yawn rate	−0.118476	**0.411994***
Full-scale IQ score	**0.794016***	0.202913
Blood OXT concentration	0.327778	**0.751497***

Exploratory factor analysis was performed on four variables in children with autism spectrum disorder (ASD).

*Statistically significant (i.e., P < 0.05) with a loading factor ≥0.341 for N = 34.

rather, that individuals with low OXT concentrations may constitute an ASD "subgroup" characterized by empathy-related impairments in facial mimicry and reflexive behavior copying [Massen & Gallup, 2017]. Additional research including pharmacological manipulation of the OXT system is now required to more fully test this hypothesis.

Interestingly, the relationship between blood OXT concentration and contagious yawning behavior was specific to children with ASD. Exactly why TD children did not show this relationship is unknown, but it is not due to "ceiling" effects in their contagious yawning behavior. One possible explanation for this finding is that in individuals whose social functioning is unaffected, higher OXT concentrations may enhance social awareness of contagious yawning, and thus lead to its suppression [Gallup & Church, 2015]. Our participants completed the contagious yawning task in a room containing both a webcam and a researcher; the presence of each of these individually has been shown to decrease contagious yawning behavior in TD individuals [Gallup, Church, Miller, Risko, & Kingstone, 2016].

This study had several limitations. First, our sample was male biased, in keeping with ASD's population prevalence [Christensen, 2016], but nevertheless not powered to discern potential sex differences in the relationship between blood OXT concentrations and contagious yawning behavior. Second, this study related blood OXT concentrations to a brain-mediated social behavior. Whether or not peripheral OXT concentrations are a robust indicator of brain-related OXT activity remains to be determined, but at least some research suggests that this may be the case [Carson et al., 2015]. Third, although all of our study participants underwent identical experimental procedures, it should be noted that participants nevertheless were drawn from several distinct study populations. Fourth, our ASD participants were not medication-free. Although their medications were stable (i.e., for at least 4 weeks) before blood collection, it is possible that blood OXT concentrations and/or the contagious yawn response were influenced by their medication status. Finally, this study manually coded attention as a binary measure per stimulus trial. Follow-up research could benefit from measuring attention with a more precise technology (e.g., eye tracking).

In closing, despite potential limitations, the present study provides the first evidence that blood OXT concentration is positively associated with contagious yawning behavior in children with ASD. This study also identified a subset of children with ASD with lower blood OXT concentrations who exhibit an impaired contagious yawn response compared to TD children. These collective findings suggest that a biologically defined subset of children with ASD may exhibit reduced empathy, as measured by an impaired contagious yawn response, and that discrepant reports of this behavioral phenomenon in the literature may be attributable, at least in part, to variable mean OXT concentrations across ASD study cohorts.

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