THE EFFECTS OF INTRANASAL OXYTOCIN ON SOCIAL COGNITIVE FUNCTIONING IN ADOLESCENTS WITH BORDERLINE PERSONALITY DISORDER COMPARED TO A SAMPLE OF NON-CLINICAL ADOLESCENTS

A Dissertation

Presented to

The Faculty of the Department of Psychology

University of Houston

In Partial Fulfillment

Of the Requirements for the Degree of

Doctor of Philosophy

By

Carolyn Ha

May, 2016

THE EFFECTS OF INTRANASAL OXYTOCIN ON SOCIAL COGNITIVE FUNCTIONING IN ADOLESCENTS WITH BORDERLINE PERSONALITY DISORDER COMPARED TO A SAMPLE OF NON-CLINICAL ADOLESCENTS

An Abstract of a Dissertation

Presented to

The Faculty of the Department of Psychology

University of Houston

In Partial Fulfillment

Of the Requirements for the Degree of

Doctor of Philosophy

By

Carolyn Ha

May, 2016

THE EFFECTS OF INTRANASAL OXYTOCIN ON SOCIAL COGNITIVE FUNCTIONING IN ADOLESCENTS WITH BORDERLINE PERSONALITY DISORDER COMPARED TO A SAMPLE OF NON-CLINICAL ADOLESCENTS

Borderline Personality Disorder (BPD) is a severe psychiatric disorder where interpersonal dysfunction is central as a result of impairments in social cognitive abilities, specifically in mentalizing. A neuropeptide model of BPD has been proposed, suggesting that the oxytocin system is dysregulated, which contributes to the onset of interpersonal symptoms of the disorder (Stanley & Siever, 2010). To further understand the social-cognitive mechanisms involved BPD in adolescents, the current study investigated the effects of intranasal oxytocin on in-vivo mentalization in a sample of BPD patients in comparison to a group of non-clinical adolescents (ages 12-17) using a double-blind, randomized, and placebo-controlled experimental design. A secondary aim was to investigate whether trait-based mentalization moderated the effects of oxytocin and in-vivo mentalizing in adolescents, regardless of BPD status.

In an age- and gender- matched sample of 40 adolescents (BPD/non-clinical = 20/20), no significant effects were found for condition (oxytocin and placebo) or group (BPD and non-clinical) on overall in-vivo mentalizing or hypermentalizing. However, trait-based mentalizing was found to be a significant moderator for the relation between oxytocin and in-vivo mentalizing. Adolescents with high trait-based mentalizing displayed higher overall in-vivo mentalization after delivery of oxytocin in comparison to placebo. In contrast, adolescents with low trait-based mentalizing displayed lower overall in-vivo mentalization after oxytocin delivery compared to placebo. Trait-based mentalizing was also found to be a significant moderator on oxytocin and hypermentalizing. Adolescents with high trait-based mentalizing scored lower on hypermentalizing after receiving oxytocin in comparison to placebo, while adolescents with low

trait-based mentalizing scored higher on hypermentalizing after oxytocin delivery in comparison to placebo.

These findings are an important extension of the oxytocin research in BPD, which have only been investigated in adults thus far with several studies demonstrating the differential effects of intranasal oxytocin on social cognition. Indeed, in the current study, differential effects of oxytocin on social cognition were found for adolescents, with trait-based mentalizing moderating the relation between oxytocin and in-vivo mentalization. Adolescents with high trait-based mentalizing scored higher on in-vivo mentalization after receiving oxytocin in comparison to adolescents with low trait-based mentalizing, who scored lower on in-vivo mentalization after oxytocin delivery. Therefore, important moderators including individual characteristics such as trait-based mentalizing, age, gender, and other factors need to be considered in future evaluations of intranasal oxytocin as a potential intervention for adolescents diagnosed with BPD.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

THE EFFECTS OF INTRANASAL OXYTOCIN ON SOCIAL COGNITIVE FUNCTIONING IN ADOLESCENTS WITH BORDERLINE PERSONALITY DISORDER COMPARED TO A SAMPLE OF NON-CLINICAL ADOLESCENTS

Adolescence is a developmental stage with substantial changes occurring in various domains of functioning, including physical characteristics, social behaviors, and neural networks (Spear, 2000; Paus, et al., 2008). Consequently, adolescence is also a time period of peak onset for psychiatric disorders (National Comorbidity Survey Replication study; Kessler, et al., 2005). In fact, about 50% of Americans will meet criteria for a psychiatric disorder in their lifetime with the first onset occurring in childhood or adolescence (Kessler, et al., 2005). Given the prevalence of psychiatric disorders and its early onset in adolescence, an emphasis should be placed on the identification and treatment of adolescent psychopathology.

One aspect of psychopathology that has potential important public health consequences but receives relatively little research attention is personality disorders in youth. Prevalence studies have demonstrated that personality disorders are a relatively common form of psychopathology in the general population, with an estimated one out of ten adults in the United States suffering from a personality disorder (Lenzenweger, et al., 2007). Although 1.4% of adults in the general population were found to have Borderline Personality Disorder (BPD), the disorder is common in clinical populations, with an estimated 10% of adult psychiatric outpatients and 20% of inpatients having a diagnosis of BPD (Swartz, Blazer, George, & Winfield, 1990; Widiger & Weissman, 1991). BPD is characterized by deficits in multiple areas of functioning including cognitive, affective, and behavioral domains. The DSM-IV-TR requires that five out of nine clinical symptoms are present for a full diagnosis of BPD including fears of abandonment, identity disturbance, inappropriate and intense anger, suicidal ideation and

gestures, impulsivity, feelings of emptiness, emotional instability, transient-stress related paranoid thoughts, and unstable interpersonal relationships (APA, 2000).

Adolescent BPD

There is evidence for a diagnosis of Borderline Personality Disorder in adolescence (Chang, Sharp, & Ha, 2011; Chanen, Jovev, & Jackson, 2007; Miller, Muehlenkamp, & Jacobson, 2008; Sharp, Ha, Michonski, Venta, & Carbonne, 2012; Sharp, Pane, Ha, Venta, Patel, et al., 2011; Sharp & Romero, 2007). In clinical settings, BPD has been reported to affect 11% of outpatients (Chanen, et al., 2004) and 43% to 49% of inpatients (Grilo, et al, 1998; Levy, et al., 1999). Historically, diagnosing adolescents with BPD has faced some controversy due to concerns over the negative consequences of stigmatizing youth with a lifelong disorder (Hinshaw & Cicchetti, 2000). Another challenge to diagnosing adolescents was due to difficulty in determining whether BPD symptoms in youth are unique to the disorder rather than common of typical adolescent development. Nevertheless, increasing evidence has emerged concerning the reliability and stability of the diagnosis in this age group (Sharp et al., 2011; Sharp et al., 2012), with support for early disturbances in genes and environment contributing to BPD symptoms in adulthood (Carlson, Egeland, & Srouge, 2009; Bornovalova, Hicks, Iacono, & McGuie, 2009). Further, similarities between adult and adolescent BPD exist in symptomatology (McManus, Lerner, Robbins, & Barbour, 1984), diagnostic criteria, interview based measures, co-morbidity with antisocial behavior, the stability of the diagnosis, and in environmental risk factors (Sharp & Romero, 2007). In particular, work from our research lab has also shown that BPD can be diagnosed with good reliability and validity in adolescence (Sharp, Ha, Michonski, et al., 2012; Chang et al., 2011; Sharp, Mosko, Chang, & Ha, 2010; Michonski et al., 2012). Given the significant impact on psychosocial functioning that adolescents with BPD experience (Chanen, et

al, 2007; Miller, et al., 2008), and the poor prognosis associated with the disorder (Winograd, et al., 2008), it's important to investigate the mechanisms involved in the emergence of the disorder.

Social-cognitive model of BPD

A core characteristic of BPD involves impaired functioning in the interpersonal domain. Many etiological models have been proposed to explain the interpersonal impairments in BPD, including both biological and environmental factors. Fonagy and colleagues (1991, 2006, 2007, 2008, 2009) have theorized that problems BPD patients experience in interpersonal functioning are a result of impairment in social cognitive abilities, specifically, in theory of mind (ToM) or mentalization. The term mentalizing has gained popularity in both neuroscience and developmental literature and has been used interchangeably with ToM (Morton, 1989; Frith, 1992). Mentalizing involves an individual's capacity to understand and interpret mental states in terms of self and others (Fonagy, et al., 1991; Fonagy & Sharp, 2008; Sharp, 2006). In other words, it is the person's capacity to think about and reflect on his/her own mental states and formulate interpretations about their own and others' behavior based on mental state understanding.

Mentalization can be conceptualized as having three dimensions including: 1) implicit or explicit encoding of information 2) in relation to self or other, and 3) in cognitive or affective aspects (Choi-Kain & Gunderson, 2008). These dimensions demonstrate the multidimensional nature of mentalization. Furthermore, mentalization is related to, but can be distinguished from constructs of mindfulness, psychological mindedness, empathy, and affect consciousness (Choi-Kain & Gunderson, 2008). The capacity to mentalize develops during infancy and childhood from early attachment experiences (Fonagy, et al., 1991; see Figure 1 adapted from Fonagy &

Luyten, 2009). While it is not the aim of this study to test the different aspects of this model, we present the model here as a conceptual framework for the role of hypermentalizing in the development of BPD in youth. This model provides an overview of the context-specific nature of mentalization impairments, therefore, it is important to assess for both trait-based and in-vivo mentalizing.

Figure 1

In adolescents, evidence has emerged in support of a link between mentalization impairment in youth and emerging BPD traits (Sharp, Pane, Ha, et al., 2011; Sharp, Ha, Carbone, et al., 2013) as assessed by an in-vivo mentalization task. Prior work in our lab showed that patients with emerging BPD demonstrate a style of social cognitive reasoning characterized by hypermentalizing (or over-interpretation of social cues), and this was mediated by poor emotion regulation strategies (Sharp, et al., 2011). More recently, work in our lab demonstrated that certain aspects of mentalizing are differentially associated with BPD (Sharp, et al., 2013). Given the heterogeneity and multi-dimensionality of the mentalization construct, it is important to assess for both explicit and implicit forms of mentalization. Trait-based mentalizing will tap into explicit mentalization capacity, while in-vivo mentalizing will assess implicit mentalization capacity during real-time social interaction.

Oxytocin in BPD

A link between mentalization impairment and dysfunction of the oxytocin system in adults with BPD has been established. Stanley and Siever (2010) have proposed a neuropeptide model of BPD suggesting that dysfunction of oxytocin impairs mentalization, which plays an important role in the onset of interpersonal symptoms of the disorder (i.e. unstable interpersonal relationships).

Oxytocin is a neuropeptide consisting of nine amino acids and is produced in the hypothalamus region of the brain, serving as both a hormone and neurotransmitter/ neuromodulator (MacDonald & MacDonald, 2010). It is integral in promoting positive social interactions (Hurlemann, et al., 2010; Uvnas-Moberg, 1998; Winslow & Insel, 2004; Zak, et al., 2005), improving social cognition (Domes, et al., 2007b), and emotion recognition (Domes, et. al., 2007a; Guastella, et al., 2010), and has been demonstrated to reduce stress in social interactions, which increases trust (Heinrich, et al., 2003). Oxytocin has often been referred to as the "prosocial neuropeptide" for its positive effects in improving social cognition, or more specifically mentalization (Domes, et al., 2007b), in both healthy adults and adults with autism spectrum disorders.

Several studies have been published on the effects of intranasal oxytocin on social cognition, trust, and prosocial behavior (Bartz, Zaki, Bolger, & Ochsner, 2011b, Guastella & MacLeod, 2012). However, the findings remain mixed, with some studies reporting positive effects of oxytocin in improving social cognition, emotion recognition, and trust, while other studies have reported contradictory effects for oxytocin on social cognition, depending on social context and individual traits (Bartz, Zaki, Bolger, et al., 2010a; Bartz, Simeon, Hamilton, et al., 2011a; Bartz, et al., 2011b; Bakermans-Kranenburg & van IJzendoorn, 2013). Currently, only a handful of studies have investigated the effects of intranasal oxytocin in adults with BPD assessing for trust behavior, cooperation, and social perception (Bartz, et al., 2011a; Amad, Thomas, & Perez-Rodriguez, 2015). These studies have reported a differential response to intranasal oxytocin in adults with BPD, with some BPD subjects demonstrating an increase in trust as a result of oxytocin delivery, while a subgroup of anxiously attached BPD subjects showed less trusting behaviors and lower cooperation (Bartz et al., 2011a), emphasizing the

importance of individual differences and situational factors involved in the disorder (Bartz, et al., 2011a; Bartz, et al., 2011b; Amad et al., 2015).

Studies of intranasal oxytocin and social cognition has primarily been conducted with adult males, as oxytocin has a differential response in females with phase of menstrual cycle and sex hormones including estrogen which interact with oxytocin (Salonia, Nappi, Pontillo, et al., 2005). Oxytocin research in youth is limited and primarily focused on youth with autism spectrum disorders (Guastella, et al., 2010; Gordon, Vander Wyk, Bennett, et al., 2013; Dadds, MacDonald, Cauchi, et al., 2014). Findings revealed that in comparison to placebo, youth who received intranasal oxytocin improved in social-cognitive (mentalization) performance.

It appears that research examining the effects of intranasal oxytocin has typically demonstrated an improvement on mentalization performance, yet there is an emerging contradictory finding that in some individuals with BPD, the oxytocin system may be dysregulated (Bartz, et al., 2011a; Stanley & Siever, 2010). Given the integral role of mentalization in interpersonal functioning, it is necessary to evaluate the effects of intranasal oxytocin as a potential treatment for adolescents with impairments in this domain, particularly in individuals with BPD who struggle with maintaining healthy social relationships.

Current Study

The present study was designed to evaluate the effects of intranasal oxytocin on in-vivo mentalization capacity in adolescents with and without BPD. On the one hand, adolescent patients with BPD may demonstrate improvement in in-vivo mentalization after administration of intranasal oxytocin or, alternatively, their oxytocin system may be dysregulated, which would be demonstrated by no effect of oxytocin on mentalization performance. In the latter case, it is possible that such effects are only apparent in the presence of trait-based mentalizing capacity.

The primary aim of this proposed study is to investigate the effect of oxytocin vs. placebo on overall (1) mentalization capacity and (2) hypermentalizing in adolescents with BPD compared to a non-clinical sample of healthy adolescents. There will be a main effect of condition such that both BPD patients and healthy controls will show (1) improved overall mentalization and (2) reduction in hypermentalizing after oxytocin delivery. There will be a main effect of group so that BPD patients demonstrate (1) significantly lower overall mentalizing capacity and (2) higher hypermentalizing compared to healthy controls. There will be no interaction effect for group x condition for either overall mentalizing capacity or hypermentalizing. Therefore, both BPD patients and healthy controls will be affected by oxytocin delivery at the same magnitude.

A secondary aim of this proposed study is to determine whether trait-based mentalizing capacity moderates the relation between oxytocin and in-vivo mentalizing. All adolescents (n = 120), regardless of BPD status, will complete a trait-based mentalizing measure (Sharp, et al., 2009; Ha, Sharp, Ensink, Fonagy & Cirino, 2013) prior to administration of intranasal oxytocin. The difference between mean levels of mentalizing on the in-vivo mentalization task for the placebo and oxytocin groups will be larger for those with high trait-based mentalizing capacity. Therefore, trait-based mentalizing will moderate the relation between oxytocin and in-vivo mentalizing.

Method

Participants

Adolescent inpatients with BPD were recruited from The Menninger Clinic, Adolescent Treatment Program (ATP), which is an inpatient specialty treatment program for adolescents with a wide range of psychiatric illnesses. The unit offers comprehensive assessment and

treatment for patients from 12-17 years of age. Adolescents typically stayed in the program from a range of 3-6 weeks and on average, the unit census has been approximately 100 admissions per year (Sharp, Williams, Ha, et al., 2009). Prior studies have shown that approximately 30% of adolescents meet criteria for BPD (Sharp, et al., 2012; Sharp, et al., 2009). This clinical site served as recruitment site for adolescents with BPD.

Non-clinical adolescents were recruited from the community through local advertisements placed on Craigslist, flyers placed in local youth organizations, and on campus, by word of mouth, and through public and private high schools in the community. Inclusion criteria for both BPD patients and non-clinical adolescents included participants ages 12-17, and English proficiency (based on WRAT-3 in community sample and as a requirement for admission to the psychiatric hospital). Proficiency in English was required to maintain consistency in the experimental task and assessment instructions. Additionally, due to the unknown effects of oxytocin on pregnancy, female adolescents were required to have a negative pregnancy result to meet inclusion criteria. For the BPD group, only patients who met criteria for a full diagnosis of BPD on the CI-BPD were invited to participate in the study.

Exclusions for non-clinical adolescents included any current psychiatric problems as determined by parent-report during the telephone screen and by adolescent self-report on a measure of psychopathology (YSR). Further, non-clinical adolescents were excluded if they met criteria for BPD on the CI-BPD. In the BPD group, additional exclusions were made for adolescents with a diagnosis of schizophrenia or Autism Spectrum Disorder (ASD), as determined by clinician diagnoses.

Measures

Demographics. A demographic questionnaire was completed by parents, gathering information on their adolescent's age, gender, ethnic/racial background, education level, parental marital status, household income, and parental education level.

Language. Reading level was assessed for in non-clinical adolescents using the reading subtest of the Wide Range Achievement Test, 3rd edition (WRAT-3; Wilkinson, 1993). Inpatient adolescents were screened for English proficiency by the hospital at admission. Prior research on the adolescent unit (Ha, et al., 2013) has reported high average IQ (M = 106.88, SD = 13.84) which is typical for the adolescents admitted to this hospital.

Psychopathology. Psychopathology was examined using the Youth Self-report (YSR; Achenbach & Rescorla, 2001), which is a standardized and well normed self-report measure assessing for a broad range of psychopathology in youths ages 6 to 18. It consists of 112 problem items, where adolescents are asked to rate items on a 3-point scale with '0' for not true, '1' for somewhat or sometimes true, or '2 for very or often true. Eight syndrome scales make up the two broader scales for Internalizing and Externalizing problems. Anxious/depressed, withdrawn/depressed, and somatic complaints subscales encompass the Internalizing problem scale, and rule-breaking and aggressive behavior subscales comprise the Externalizing problem scale. A Total Problem scale is derived from summing all subscales including anxious/depressed, withdrawn/depressed, somatic complaints, social, thought, attention problems, aggressive and rule-breaking behaviors. Good psychometric properties have been reported for this self-report measure (Achenbach & Rescorla, 2001). Additionally, eight DSM-oriented scales are provided on the YSR and have been found to significantly relate to DSM-IV psychiatric diagnoses (Achenbach & Rescorla, 2001; Kasius, Ferdinand, Berg, & Verhulst, 1997). Clinically elevated scores on these scales suggest a consideration for a DSM diagnosis.

For analyses, we used T-scores for the DSM-oriented scales of Affective, Anxiety, Somatic, Attention Deficit Hyper Active Disorder (ADHD), Oppositional Defiant Disorder (ODD), Conduct Problems (CP), Obsessive Compulsive Problems (OCP), and Posttraumatic Stress (PTS) on the YSR. All adolescents (BPD and non-clinical) completed this measure.

Borderline Personality Disorder. Patients and non-clinical adolescents completed a semi-structured interview called the Childhood Interview for DSM-IV Borderline Personality Disorder (CI-BPD; Zanarini, 2003). In this interview, 5 out of 9 symptoms must be met for a diagnosis of BPD. The interview was conducted by trained research staff and clinical psychology doctoral students.

Trait-based Mentalizing. All adolescents completed a self-report measure of mentalization using the Reflective Function Questionnaire for Youth (RFQY; Sharp, et al., 2009; Ha, et al., 2013) prior to oxytocin administration to assess for trait-based mentalizing capacity. Preliminary findings support the validity of the RFQY for assessing mentalization capacity in adolescents (Ha, et al., 2013).

The RFQY consists of 46 items with a 6-point Likert scale ranging from "strongly disagree" to "strongly agree". Two scales are computed based on scoring procedure (scale A and B), with 23 items on each scale. Scale has a mid-point scoring, where the midpoint of the scale indicated an optimal RF score. Items on this scale were scored so that extreme values on this scale ("strongly disagree" or "strongly agree") were assigned a (2), and items at the mid-point of the scale ("disagree somewhat" or "agree somewhat") were scored as (6). Responses of "agree" or "disagree" received a score of (4). An example of a scale A item is: "I always know what I feel". Scale B also consists of 23 items. These items are designed in a linear scoring on the Likert scale, with the response "strongly agree" yielding the highest RF (6) and the response "strongly

disagree" has the lowest value of (1). An example of a scale B item is: "In an argument, I keep the other person's point of view in mind". Eight items on scale B are reverse-scored with the response "strongly agree" indicating poor RF. An example of a reverse-scored item is: "I find it difficult to see other people's point of view". The average scores from scales A and B are then summed for a total score of RF. See Ha et al., 2013 for details on the scoring of the measure. In this study, a dichotomous variable was formed for high and low trait-based mentalizing using a median split.

In-vivo Mentalization. After oxytocin administration, in-vivo mentalization outcome was assessed using the Movie for the Assessment of Social Cognition (MASC; Dziobek, et al., 2006). This task is a realistic, in-vivo assessment of mentalizing which has been demonstrated to be an ecologically valid social cognitive assessment tool (Preißler, et al., 2010) and has been shown to be sensitive in discriminating patients with BPD from patients without the disorder (Sharp, et al., 2011; Sharp, et al., 2013). There are four scales of mentalization derived from the MASC including an overall mentalization capacity scale, and scales to assess for errors in mentalization including hypermentalizing, no mentalizing, and undermentalizing. As described in our prior research (Sharp, et al., 2011), hypermentalizing describes an over-interpretation of mental states, no mentalizing is a complete lack of mentalization which includes responses that do not consist of a mental state interpretation of behavior, and undermentalizing is when the individual may refer to a mental state attribution, but fails to use it appropriately. The MASC has also demonstrated dysfunction in mentalization capacity in several adult patient populations ranging from Autism Spectrum Disorder (Dziobek, et al, 2006), bipolar disorder (Montag, et al., 2009), Narcissistic Personality Disorder (Ritter, Dziobek, Preißler, et al., 2011) and BPD (Preißler, et

al., 2010). In this study, we examined the overall total mentalization score and the hypermentalizing score.

Procedures

This study was approved by the ethical institutional (IRB) boards at respective sites (Baylor College of Medicine and the Committee for Protection of Human Subjects at the University of Houston). A protocol was developed to monitor for possible adverse events, and no adverse events were reported during the study. All adolescents and their parents were provided with informed consent and assent, and participants were reimbursed in gift cards to a general store.

Inpatient adolescents with BPD and non-clinical adolescents recruited from the community were randomized to either oxytocin or placebo sprays. Both the experimenter and participant were blind as to which spray the adolescent received. Non-clinical adolescents recruited through the community were first screened over the telephone for clinical symptoms of BPD using the derived cut-off score 7 on the MSI. Any non-clinical adolescent who scored below cut-off on the MSI was invited to schedule an appointment for study participation. At this appointment, adolescents and parents were provided with informed consent and assent, and study procedures were explained. The diagnostic assessment consisted of parents completing a demographic questionnaire, and adolescents completing the reading subtest of the WRAT-3 and the CI-BPD in a private room. Youth completed the RFQY for assessment of trait-based mentalizing prior to oxytocin administration. The assessments took approximately 2 hours for non-clinical adolescents.

Inpatient adolescents were screened for exclusions including a diagnosis of schizophrenia, or language exclusions as determined by clinicians at the ATP. During the

patient's stay on the unit, s/he received diagnostic interviews including the CI-BPD as a part of a broader research study. In addition, a self-report assessment of trait-based mentalizing (RFQY) was administered to all adolescents prior to receiving oxytocin. All assessments were conducted in private with adolescents by trained research staff or clinical psychology doctoral students. Only patients who met full criteria for BPD as determined by the CI-BPD were invited for participation in the oxytocin phase of the study.

Intranasal Oxytocin vs. Placebo Administration (BPD patients and non-clinical controls). Using a between-subject randomized, double-blind, placebo-controlled design, the effects of intranasal oxytocin on adolescent mentalization capacity was assessed. Each adolescent was randomly assigned either the active (oxytocin) or inactive (placebo) nasal spray just prior to conducting the in-vivo mentalization task. All subjects and research staff responsible for observing the administration were blinded to the identity of the oxytocin or placebo sprays.

Oxytocin and placebo spray preparation and storage. Oxytocin spray (Syntocinon-Spray, Novartis) was purchased from the International Pharmacy (Waisenhausplatz 21, CH- 3011 Bern, Switzerland) and shipped by FedEx directly to the Investigational Compounding Pharmacy. Placebo sprays were prepared to exactly match the components of the oxytocin spray, minus the active drug ingredient. The investigational pharmacy repackaged the Syntocinon into nasal spray containers that were identical to placebo, labelled with the study ID code (A or B), and shipped the sprays to each respective site. The pharmacy also maintained the record of randomization, and ensured that the order of administration of active drug vs. placebo was balanced across groups (BPD vs non-clinical controls). As the study was double-blinded, experimenters and study participants were not informed of the drug identity until study completion. The sprays were

stored in a locked refrigerator at each site (The Menninger Clinic & University of Houston), and a daily log of maximum and minimum refrigerator temperatures was maintained.

Drug Administration. Adolescents from both groups were invited to a private room at their respective sites, to self-administer a dose of either oxytocin (3 puffs per nostril [4 IU per puff] = 24 IU total) or a placebo spray which contained only the inactive ingredients of the oxytocin solution. Trained research staff were present to ensure that the spray was administered correctly with the correct dose. Single puffs were administered to alternate nostrils with a 30 second pause between doses. Both experimenters and subjects were blind to the treatment adolescents received. A stopwatch was started at the moment the subject began intranasal administration, so that the outcome assessment (MASC) was started exactly 45 minutes after spray administration. Previous studies of intranasal oxytocin have used a 45-minute delay time (Guastella, et al., 2010; Domes, et al., 2007b) for both adults and adolescents. It is important to note that no adverse side effects have been reported following the administration of the proposed single dose (24 IU) of intranasal oxytocin in any of the previously published studies in both adults and youth (MacDonald, et al., 2011), and participants are generally unable to consciously distinguish active drug from placebo.

Data Analytic Strategy

This study had a 2 x 2 between-subjects design, with in-vivo mentalization capacity as outcome in both (1) overall mentalizing capacity and (2) hypermentalizing. The between-group independent variables consisted of group (BPD vs non-clinical adolescents), and drug condition (oxytocin vs. placebo). In addition, trait-based mentalizing (high vs low RF) was included as a moderator for addressing the secondary aim.

Preliminary analyses were conducted to examine the distribution of variables, and to identify extreme values and outliers. Means and standard deviation were analyzed on performance in outcome measure of in-vivo mentalization (MASC) using both overall mentalization and hypermentalization scores for both groups. Descriptive statistics including means and standard deviation were also examined for trait-based mentalizing (RFQY) in both groups (patients and controls).

Between-groups Factorial Design. The analysis strategy for both Aims 1 and 2 consisted of generalized linear models. Aim 1 involved a 2x2 between-group ANOVA where main-effects and interaction effects were investigated for both total mentalization capacity and hypermentalization separately. For Aim 2, a 2 X 2 ANOVA design was carried out in which the independent variable is oxytocin status (oxytocin v. placebo), the moderator is trait-based mentalizing capacity (assigned categorically based on the median split), and the dependent variable is level of in-vivo mentalizing during the MASC (total scores and hypermentalizing).

Results

Preliminary Analyses

The final dataset consisted of 40 age and gender-matched BPD (n = 20) with non-clinical adolescents (n = 20). All participants were randomly assigned to receive to nasal spray conditions (oxytocin/placebo). In this sample, 10 BPD patients received an oxytocin spray and 10 received placebo. In the non-clinical group, 10 adolescents received oxytocin and 10 received a placebo spray. The average age for the overall sample was 15.03 years (SD = 1.48). Females comprised of 78% of the sample (n = 31).

Normality assumptions were checked for all dependent variables (MASC) using the Shapiro-Wilk statistic for group (BPD v non-clinical) by condition (oxytocin v. placebo). Table 1 displays normality tests for all MASC scales. Non-normality was observed in the BPD group in

the placebo condition for hypermentalizing, and in the non-clinical group for total mentalizing in the oxytocin condition.

Table 1

Descriptive Analyses

Descriptive statistics for main study outcome variables were examined separately for each condition (oxytocin v. placebo), and results are displayed in Table 2. Correlations were conducted to examine associations between trait-based mentalizing (RFQY), in-vivo mentalizing (MASC total), and hypermentalizing, separately for oxytocin and placebo conditions. No significant associations were found for RFQY with in-vivo mentalizing or hypermentalizing in placebo or oxytocin conditions. As expected, in-vivo mentalizing was significantly and negatively correlated with hypermentalizing in both placebo and oxytocin conditions. Adolescents with higher scores on in-vivo mentalizing, scored lower on hypermentalizing.

Table 2

Differences between BPD and non-clinical adolescents were investigated for CI-BPD, YSR DSM-oriented variables (affective, anxiety, somatic, ADHD, ODD, CD, OCP, PTS), and for trait-based mentalizing (RFQY). A one-way multivariate analysis of variance (MANOVA) was performed to test the hypothesis that there would be significant mean differences between adolescents with BPD and non-clinical adolescents on several psychopathology variables. Results of the MANOVA revealed a statistically significant effect, Pillais' Trace = .961, $F(10, 27) = 66.86$, $p < .001$. Given the significance of the overall test, the univariate main effects were examined and displayed in Table 3. As expected, adolescents with BPD scored significantly higher on psychopathology than non-clinical adolescents. While BPD adolescents received lower mean scores (Table 3) on the trait-based mentalizing measure (RFQY), both groups did not differ

significantly on trait-based mentalizing although there was a trend in the expected direction (p = .055).

Table 3

Effect of Nasal Spray Condition (Oxytocin v Placebo) and group (BPD v non-clinical) on in-vivo mentalization (MASC)

The first aim in this study was to investigate the effect of oxytocin on overall mentalization capacity and hypermentalizing in adolescents with BPD compared to non-clinical adolescents. It was expected that there would be a main effect of condition such that both BPD patients and non-clinical adolescents demonstrate improved overall mentalization and a reduction in hypermentalizing after receiving oxytocin. It was also hypothesized that there would be a main effect of group so that BPD patients demonstrate significantly lower overall mentalizing capacity and higher hypermentalizing compared to non-clinical adolescents. Further, it was proposed that there would be no significant interaction effect for group x condition for either overall mentalization or hypermentalizing, so that both BPD patients and healthy controls would be affected by oxytocin delivery at the same magnitude.

First, a 2x2 between-group ANOVA was conducted to examine the effects of nasal spray condition (oxytocin v placebo) on in-vivo mentalization (total MASC) for adolescents with BPD and non-clinical adolescents. The independent variables in this study are nasal spray condition (oxytocin v placebo) and group (BPD v non-clinical). The dependent variable is overall in-vivo mentalization (total MASC). Higher scores on total MASC indicates higher overall in-vivo mentalization ability. All means and standard deviations for group (BPD and non-clinical) and condition (oxytocin and placebo) are displayed in Table 4.

Table 4

ANOVA statistics for main and interaction effects on in-vivo mentalization are presented in Table 5. There was no significant interaction between nasal spray condition (Oxytocin v placebo) and group (BPD v non-clinical), as predicted (see Figure 2). However, contrary to our hypotheses, no significant main effects were found for condition or group on overall in-vivo mentalization (total MASC). Inspection of the group means revealed that BPD patients and non-clinical adolescents scored similarly on the MASC under the oxytocin condition (see table 4). In the placebo condition, group means for BPD patients were higher than non-clinical controls on overall in-vivo mentalization.

Table 5

Figure 2

Next, a 2x2 between-group ANOVA was conducted to examine the effects of nasal spray condition (oxytocin v placebo) on hypermentalizing for adolescents with BPD and non-clinical adolescents. The independent variables in this analysis are nasal spray condition (oxytocin v placebo) and group (BPD v non-clinical). The dependent variable was hypermentalizing. Higher scores on hypermentalizing indicates greater use of hypermentalizing strategies.

Table 6

Table 6 displays main effects and interaction effects for the 2x2 ANOVA. As hypothesized, there was no significant interaction between nasal spray condition (Oxytocin v placebo) and group (BPD v non-clinical). These effects are displayed visually in Figure 3. No significant main effects were found for condition or group on hypermentalizing (Table 6). When examining group means (Table 4), BPD patients who received oxytocin scored lower on hypermentalizing, compared to BPD patients who received placebo. Similarly, adolescents in the

non-clinical group who received oxytocin scored lower on hypermentalizing in comparison to non-clinical adolescents who received placebo.

Figure 3

Effect of Nasal Spray Condition (Oxytocin v Placebo) and trait-based mentalizing (RFQY) on overall in-vivo mentalizing (Total MASC and Hypermentalzing)

A secondary aim of this study was to investigate whether trait-based mentalizing capacity moderates the relation between oxytocin and in-vivo mentalizing. It was hypothesized that regardless of BPD status, the difference between mean levels of mentalizing on the in-vivo mentalizing task for placebo and oxytocin conditions would be larger for adolescents with high trait-based mentalizing capacity as measured by the RFQY. A dichotomous variable was formed using the median split score for the RFQY (8.78), with adolescents receiving scores of 8.78 or higher coded as high RF, and those who scored less than 8.78 were coded as low RF. Trait-based mentalizing was examined as a moderator for the relation between oxytocin and overall mentalization using total MASC scores, then separately for hypermentalizing scores.

In these analyses, 11 adolescents with low RF received an oxytocin spray and 8 received placebo. In the high RF group, 8 adolescents received oxytocin and 11 received a placebo spray. A 2x2 ANOVA with nasal spray condition (oxytocin v placebo) and the dichotomized trait-based mentalizing score (high RF v low RF) were entered as the independent variables for this analysis. The dependent variable was overall in-vivo mentalizing using total MASC scores. As predicted, the results revealed a significant interaction effect for nasal spray condition (oxytocin v placebo) with trait-based mentalizing (high RF v low RF) on overall in-vivo mentalizing (see Table 7).

Table 7

After receiving oxytocin, adolescents with high trait-based mentalizing scores demonstrated higher overall mentalization scores compared to adolescents who received placebo, while adolescents with low trait-based mentalizing scores demonstrated lower overall mentalization scores after receiving oxytocin compared to the placebo condition (Figure 4). This indicates that oxytocin has an effect on increasing overall in-vivo mentalization for adolescents with high trait-based mentalizing capacity, and not for adolescents with low trait-based mentalizing abilities. Instead, in adolescents with low trait-based mentalizing capacity, oxytocin has the opposite effect, decreasing overall in-vivo mentalizing abilities. Examination of group means (Table 8) revealed higher mean scores on overall mentalization for adolescents with high trait-based mentalizing who received an oxytocin spray compared to placebo. In contrast, mean overall in-vivo mentalization scores for adolescents with low trait-based mentalizing were lower for adolescents who received an oxytocin spray compared to placebo.

Table 8

Figure 4

Next, the effect of oxytocin and trait-based mentalizing on hypermentalizing was examined. A 2x2 ANOVA was conducted with nasal spray condition (oxytocin v placebo) and the dichotomized trait-based mentalizing score (high RF v low RF) entered as the independent variables for this analysis. The dependent variable was hypermentalizing score. As predicted, findings revealed a significant interaction effect for nasal spray condition (oxytocin v placebo) with trait-based mentalizing (high RF v low RF) on hypermentalizing (see Table 9).

Table 9

After receiving oxytocin, adolescents with high trait-based mentalizing scores demonstrated lower hypermentalizing scores compared to adolescents who received placebo,

while adolescents with low trait-based mentalizing scores demonstrated higher hypermentalizing scores after receiving oxytocin compared to the placebo condition (Figure 5).

Figure 5

These findings demonstrated that adolescents with high trait-based mentalizing who received oxytocin displayed lower hypermentalizing scores, while adolescents with low trait-based mentalizing showed increased hypermentalizing scores after receiving oxytocin compared with adolescents in the placebo condition. Examination of group means revealed lower mean scores on hypermentalizing for adolescents with high trait-based mentalizing who received an oxytocin spray compared to placebo (Table 8). In contrast, mean hypermentalizing scores for adolescents with low trait-based mentalizing were higher for adolescents who received an oxytocin spray compared to placebo.

Discussion

The present study was designed to evaluate the effects of intranasal oxytocin on in-vivo mentalization capacity (overall mentalization and hypermentalizing) in adolescents with BPD compared to a non-clinical control group of adolescents. Overall, findings in an age and gender matched sample did not support the main prediction that adolescents (BPD and non-clinical) would demonstrate improved overall mentalization after oxytocin delivery. Non-clinical adolescents displayed increases in overall mentalization in the oxytocin condition, but BPD patients showed a reduction in overall mentalizing in the oxytocin condition, suggesting a potential interaction effect, although these findings were not significant. Similarly, hypermentalizing was not affected by oxytocin delivery for BPD patients or non-clinical controls. While these findings were not significant, both groups exhibited reductions in hypermentalizing in the oxytocin condition compared to placebo. There may be several reasons

for the lack of significant findings in both BPD and non-clinical groups in relation to oxytocin and overall mentalization abilities. Effects of oxytocin in the adult literature has been mixed, with some studies reporting no effect or negative effects in healthy, non-clinical participants as well as in psychiatric samples (Bakermans-Kranenburg & van IJzendoorn, 2013), with the most robust findings in support of oxytocin improving social cognition in individuals with Autism Spectrum Disorder, showing the largest combined effect size (Bakermans-Kranenburg & van IJzendoorn, 2013). Oxytocin has also been shown to have differential effects depending on context and individual characteristics (Guastella & MacLeod, 2012; Van IJzendoorn, & Bakermans-Kranenburg, 2012; Micolajcak, et al., 2010; Bakermans-Kranenburg & van IJzendoorn, 2013; Amad et al., 2015). Therefore, null findings in our primary hypothesis may be explained by other moderators.

The secondary aim of this study was to determine whether trait-based mentalizing moderated the relation between oxytocin and in-vivo mentalizing (overall mentalizing and hypermentalizing), regardless of BPD status. As predicted, a significant interaction was found between trait-based mentalizing and oxytocin, on in-vivo mentalization. Adolescents high on trait-based mentalizing displayed higher overall mentalization scores after oxytocin delivery in comparison placebo. In contrast, adolescents with low trait-based mentalizing scored lower on overall mentalizing after receiving oxytocin than compared to placebo. Regarding hypermentalizing, a significant interaction was also found between trait-based mentalizing and oxytocin. Adolescents with high trait-based mentalizing scored lower on hypermentalizing after receiving oxytocin, while adolescents with low trait-based mentalization scored higher on hypermentalizing compared to adolescents who received placebo. Overall, the results showed that oxytocin was effective in increasing overall mentalization and reducing hypermentalizing

for adolescents with high trait-based mentalizing, but the effects in adolescents with low trait-based mentalizing were paradoxical, with oxytocin reducing overall mentalization and increasing use of hypermentalizing. While these findings diverge from prior studies which have reported oxytocin improving social cognition in adults and adolescents (Domes, et al., 2007b; Guastella et al., 2010; Guastella & MacLeod, 2012), they are in line with emerging oxytocin research reporting on the context-specific nature of oxytocin (Bartz et al., 2010a; Bartz et al., 2010b; Bartz et al. 2011a, Bartz et al., 2011b). In particular, Bartz and colleagues (2011a) found that a subgroup of BPD subjects (anxiously attached) demonstrated less trusting behaviors and lower cooperation after oxytocin delivery. Further, another study found attachment anxiety as a moderator in the relation between oxytocin and perceptions of maternal care and closeness in adults, with less anxiously attached adults recalling their mother as more caring during childhood after oxytocin delivery, while adults who were more anxiously attached perceived their mother as less caring in childhood after oxytocin delivery (Bartz, et al., 2010b).

Research on the effects of oxytocin in adults with BPD is only emerging, and the findings are mixed, with some clinical trials demonstrating a positive effect of oxytocin in improving emotional responses and reducing hypersensitivity to social threats, and others finding a negative effect for oxytocin in trust behaviors (Amad, et al., 2015). Findings from the present study are in partial support of Bartz and colleagues' (2011b) "interactionist model of the social effects of oxytocin", which proposed that the effects of oxytocin are dependent on context and individual characteristics. Therefore, increasing oxytocin may not improve mentalization abilities in all adolescents, particularly for BPD patients who have low-trait based mentalizing abilities. Adolescents with BPD have been shown to have significantly poorer explicit mentalizing abilities as assessed with the RFQY, in comparison to other adolescent inpatients (Ha, et al.,

2013), which suggests that administration of intranasal oxytocin to BPD patients, particularly with low-trait based mentalizing abilities would be contraindicated and only reduce overall mentalizing abilities or increase use of poor mentalizing strategies such as hypermentalizing. While results from the present study cannot specifically address the interactionist model in regards to the effects of intranasal oxytocin in adolescents with BPD, as there was no main effect for group or condition, our findings revealed an interaction effect for trait-based mentalizing in influencing response to oxytocin in adolescents, supporting the notion that individual characteristics can lead to differential oxytocin effects.

Several limitations to this study should be taken into consideration. First, the final sample size was smaller than what was proposed a-priori, due to difficulty with recruitment of non-clinical controls. Indeed, the expected relation between trait-based mentalizing and in-vivo mentalizing in the placebo condition was not supported in the sample due to the small sample size. Prior research has reported significant relations between mentalization assessed by the RFQY with mentalization assessed by the MASC in adolescents (Ha, et al., 2013). Therefore, we expected significant positive correlations for RFQY with MASC total, and negative correlations for RFQY with hypermentalizing. Instead, the relation between RFQY and MASC were not significant and the correlations were in an opposite direction than expected. These relations, although non-significant, may also have influenced the moderation analyses when using a median-split RFQY score to determine high and low trait-based mentalizing groups. In the placebo condition, adolescents with high trait-based mentalizing received low scores on in-vivo mentalization and high scores on hypermentalizing, which was unexpected. Adolescents in the low trait-based mentalizing group also appeared to have unexpected scores in the placebo condition, demonstrating high scores on in-vivo mentalizing and low scores on

hypermentalizing. This may a result of unequal sample sizes for high and low trait-based mentalizing groups in the placebo condition, with 8 adolescents in the low trait-based mentalizing group and 11 adolescents in the high trait-based mentalizing group. Other considerations for splitting high and low trait-based mentalizing should be considered, such as creating groups which are +/- 1 SD around the mean. Nevertheless, prior studies investigating effects of intranasal oxytocin in adolescents with autism spectrum disorder have reported significant effects (Guastella, et al., 2010) with small sample sizes (n = 16).

Another limitation to the current study was that patient and non-clinical controls may have differed in cognitive abilities. While IQ differences was not explored statistically, due to limitations in systematically collecting this information from the patient group, the patient sample on average had higher cognitive functioning and therefore scored higher on mentalizing abilities. Further, the patient group was comprised of primarily of Caucasian adolescents (95%), while the non-clinical group was more ethnically diverse (40% Caucasian, 45% Black or African American, 10% Hispanic, 5% Multiracial). Consequently, these findings may not generalize in patient populations with more diverse ethnicity and cognitive abilities.

Findings from the current study should also be interpreted with caution as we did not examine the potential effects of menstrual cycle phase or the effects of females taking oral contraceptives as a potential moderator in the relation between oxytocin and in-vivo mentalization. In the current, study we had a limited number of female adolescents reporting use of oral contraceptives (n = 3), and only collected limited information on whether adolescents were currently on their menstrual cycle (n = 8). Given that the phase of menstrual cycles and sex hormones including estrogen are known to interact with oxytocin (Salonia, Nappi, Pontillo, et al., 2005; Skuse, & Gallagher, 2009), future studies should consider more thorough assessments of

menstrual cycle phase, as well as use of oral contraceptives as oxytocin has a differential response in females due to these factors.

Further, the current study was not an intervention study, therefore we employed a between-subject randomized, double-blind, placebo-controlled design, instead of a randomized, double-blind, placebo-controlled, cross-over design, where every adolescent would randomly receive both placebo and oxytocin conditions. A cross-over design would reduce between-group variability in participants because participants would function as their own control, and fewer subjects would be required to attain the same level of power. However, the current study does make use of an age- and gender-matched sample, controlling for the effects of these potential covariates.

Finally, there are several potential moderators which were not investigated as a part of the current study, including a history of child maltreatment, family support, harsh parental discipline, and attachment (Bakermans-Kranenburg & van IJzendoorn, 2013). Research investigating intranasal oxytocin in healthy non-clinical adults have highlighted the context-and person-specific nature of oxytocin (Bakermans-Kranenburg & van IJzendoorn, 2013), with individual factors including quality of early caregiving experiences, harsh parental discipline in childhood, and positive family support, differentially affecting response to oxytocin (Riem, van IJzendoorn, Tops, et al., 2013; Bakermans-Kranenburg, van IJzendoorn, Tops, et al., 2012; Bakermans-Kranenburg & van IJzendoorn, 2013). Additionally, oxytocin has been shown to improve cooperation and trust only with in-group members, but when there's a perception of threat in out-group members, oxytocin has been shown to increase non-cooperation (De Dreu, Greer, Handgraaf, et al., 2010; Bakermans-Kranenburg & van IJzendoorn, 2013; Van IJzendoorn, & Bakermans-Kranenburg, 2012). Given that BPD is associated with early

maladaptive childhood experiences (Westin, Ludolph, Misle, et al., 1990; Venta, Kenkel-Mikelonis, & Sharp, 2012; Zanarini & Wedig, 2014), invalidating family environment (Linehan, 1993; Fruzetti, Shenk, & Hoffman, 2005; Stepp, Whalen, & Pederson, 2014), harsh parental discipline (Beziganian, Cohen, & Brook, 1993), and oversensitivity in detecting threat in social settings (Bertsch, et al., 2013); the null findings in our primary aim may be better explained by these moderators. While these are important moderators in the effects of oxytocin, they were not directly examined in this study because the focus of the current study was to investigate the effects of oxytocin on overall in-vivo mentalization. Future studies should investigate whether individual variables such as attachment, family support, or other variables as important moderators of oxytocin, as prior research in adults with BPD have found that a subgroup of BPD patients with anxious attachment styles displayed decreased trust and cooperation after receiving oxytocin (Bartz, et al., 2011).

Despite the limitations, the current study provides important contributions to the oxytocin literature in BPD by examining these effects in adolescents with BPD (in comparison to a non-clinical group), and investigating individual characteristics including trait-based mentalizing in moderating the effects of oxytocin. These findings are an important step toward understanding the underlying social and biological mechanisms involved in the interpersonal impairments associated with BPD. While the findings are preliminary and require replication, the null findings for an effect of oxytocin on overall mentalization and hypermentalizing may suggest that BPD patients have a dysregulated oxytocin system as proposed by Stanley and Siever (2010). Importantly, the present study found differential effects for oxytocin in adolescents with high and low trait-based mentalizing in regards to overall mentalization and hypermentalizing. A prior study in adults had reported that individuals with low baseline social-cognitive abilities

improved in empathic accuracy after receiving oxytocin, but there was no effect for individuals with high baseline social-cognitive skills (Bartz et al., 2010a). While our findings also found support for differential effects of oxytocin in adolescents with high and low trait-based mentalizing, the effects were in contrast to those reported in adults, where adolescents with lower trait-based mentalizing demonstrated negative effects on overall mentalization and hypermentalizing abilities after oxytocin delivery. This may reflect differences in assessing outcomes, with the adult study investigating empathic accuracy, which is a narrow aspect of social cognition compared to mentalization, which is multi-dimensional and a more complex form of social cognition.

The current study has several additional strengths, employing an age- and gender-matched sample, which limited the effects of confounds in the study. It is the first study to investigate the effects of oxytocin on mentalization in adolescents with BPD, in comparison to non-clinical adolescents. Both implicit and explicit mentalization were assessed in this study, which is important because mentalization is a multidimensional construct. Additionally, this study examined biases in mentalizing (hypermentalizing). Given that hypermentalizing has been proposed as a core impairment in BPD, it is important to evaluate as a potential area to intervene. In conclusion, the current study provides important preliminary steps toward understanding social and biological mechanisms which underpin the interpersonal impairments that are at the core of BPD, and also provides initial evidence toward the utility of intranasal oxytocin as an intervention for adolescent patients with BPD. In future clinical trials, trait-based mentalizing abilities should be assessed, as it is an important moderator in oxytocin.

Potential Clinical Utility for Oxytocin

Currently, the clinical utility for intranasal oxytocin in treatment of psychiatric disorders is undergoing investigation, primarily for individuals diagnosed with Autism Spectrum Disorder (ASD). Promising findings have emerged from clinical trials of intravenous or intranasal administration of oxytocin for individuals with ASD (Preti, Melis, Siddi, Vellante, Doneddu, et al., 2014). However, positive effects were primarily found for oxytocin increasing emotional recognition and eye gaze in individuals with ASD, while oxytocin administration appeared less effective in reducing repetitive behaviors (Preti, et al., 2014). Therefore, oxytocin may improve certain symptoms in ASD, but not alleviate all symptoms of the disorder. Additionally, frequency, dosage, and administration of oxytocin varied in these clinical trials, with duration of treatment lasting as long as 1-3 weeks, and up to 6-weeks. The potential for the use of oxytocin as a psychiatric drug is still unclear as the research in this field is only in its infancy, and it remains unknown what dosage, frequency, duration, or method of delivery is most effective for which disorder. Importantly, long-term outcomes for oxytocin use has not been investigated. Prior studies only evaluated immediate outcomes after six weeks of treatment or less (Petri, et al., 2014). Additionally, administration of oxytocin via intranasal routes can also create varying effects depending on individual differences in nasal cavity structure (Guastella et al., 2013). Safety issues must be better understood and addressed in the use of oxytocin as a viable treatment option, as oxytocin has been known to cause adverse effects. Careful screening methods to exclude patients with cardiovascular problems, neurological disorders including epilepsy, or excluding use during pregnancy would be essential (Preti, et al., 2014). Overall, the clinical trials emerging from intervention studies in individuals with ASD suggest a complex picture for the potential clinical utility of oxytocin, and it remains unknown what harmful effects

may result from chronic oxytocin use or what the effects are for chronic use in children and adolescents whose brains are still undergoing development.

As reviewed by Netherton and Schatte (2011), many clinical trials are in progress to investigate the effectiveness of oxytocin treatment in patients with schizophrenia, anxiety, autism, and in conjunction with cognitive behavioral therapy for individuals with drug dependence. However, these effects have been primarily examined in adults and have been limited to youths with autism spectrum disorders. Specifically related to individuals with BPD, few clinical trials exist in adults, and the initial findings are mixed, with some evidence of negative effects in this population (Amad, et al., 2015). It can be speculated that similar to individuals with ASD, oxytocin may have certain positive effects and potential negative effects in individuals with BPD. Therefore, thorough screening methods must be utilized as oxytocin may be effective for some individuals with BPD, but not all individuals with the disorder. Much more research is needed to elucidate the underlying mechanisms of oxytocin prior to consideration of its potential as a psychiatric drug or its potential for use in conjunction with evidence-based treatments for individuals with BPD, particularly in youth populations.

Table 1. Normality tests for MASC variables by group (BPD v non-clinical) and condition (OT v placebo).

	Placebo							
Variables	*BPD*				*Non-Clinical*			
	Skew	*Kurtosis*	*S-W*	*p*	*Skew*	*Kurtosis*	*S-W*	*p*
Total	-0.63	0.29	0.68	0.001*	-0.32	1.32	0.98	0.97
Hypermentalizing	1.71	3.40	0.78	0.004*	0.47	-1.00	0.88	0.13
	Oxytocin							
	BPD				*Non-Clinical*			
	Skew	*Kurtosis*	*S-W*	*p*	*Skew*	*Kurtosis*	*S-W*	*p*
Total	-0.45	-1.39	0.95	0.70	-1.94	4.45	0.83	0.04*
Hypermentalizing	1.33	2.33	0.87	0.11	1.18	1.49	0.91	0.28

**Abbreviations*: MASC = Movie for the Assessment of Social Cognition; BPD = Borderline Personality Disorder; S-W = Shapiro-Wilk

Table 2. Descriptive statistics for mentalization variables by condition.

	M	SD	1	2	3
Oxytocin					
1. Trait-based MZ (RFQY)	8.77	.726	--		
2. In-vivo MZ (MASC total)	33.30	4.33	.334	--	
3. Hypermentalzing	6.55	3.09	-.377	-.781**	--
Placebo					
1. Trait-based MZ (RFQY)	8.74	.719	--		
2. In-vivo MZ (MASC total)	33.4	5.26	-.180	--	
3. Hypermentalzing	7.55	5.04	.158	-.938**	--

**Notes*: MZ = mentalizing; RFQY = Reflective Function Questionnaire for Youth; MASC = Movie for the Assessment of Social Cognition.

Table 3. MANOVA summary for differences in psychopathology variables on groups (BPD vs non-clinical).

Measure	Group		Statistics	
	BPD (*n* = 20) *M (SD)*	Non-clinical (*n* =20) *M (SD)*	F (1, 38)	p
YSR Affective	74.80 (11.38)	54.50 (5.30)	53.76	<.001
YSR Anxiety	64.15 (8.91)	52.00 (3.06)	40.26	<.001
YSR Somatic	61.15 (9.12)	51.35 (3.00)	22.55	<.001
YSR ADHD	64.70 (9.56)	53.35 (4.49)	21.45	<.001
YSR ODD	61.95 (10.92)	53.05 (4.16)	9.37	.044
YSR CP	63.30 (9.51)	53.60 (4.66)	14.50	.001
YSR OCP	70.50 (12.83)	54.00 (5.15)	31.99	<.001
YSR PTS	71.45 (9.98)	52.75 (4.47)	60.25	<.001
CIBPD	13.90 (1.86)	0.90 (1.52)	567.17	<.001
RFQY	8.54 (0.79)	8.98 (.57)	3.93	.055

**Abbreviations*: YSR = Youth self-report; ADHD = Attention-deficit hyperactivity disorder; ODD = Oppositional Defiant Disorder; CP = Conduct Problems; OCP = Obsessive-compulsive problems; PTS = Post-traumatic Stress; CIBPD = Childhood Interview for DSM-IV Borderline Personality Disorder; RFQY = Reflective Function Questionnaire for Youth

Table 4. Means and standard deviations for In-vivo Mentalizing and Hypermentalizing by group (BPD and non-clinical) and condition (oxytocin and placebo).

Variables	**Groups**					
	Non-clinical			*BPD*		
Oxytocin	M	SD	n	M	SD	n
In-vivo MZ	33.50	5.04	10	33.10	3.76	10
Hypermz	6.10	2.81	10	7.00	4.67	10
Placebo						
In-vivo MZ	32.50	4.93	10	34.30	5.68	10
Hypermz	7.70	4.67	10	7.40	5.64	10

**Notes*: MZ = mentalizing, Hypermz = hypermentalizing, BPD = Borderline Personality Disorder

Table 5. ANOVA Summary for In-vivo Mentalizing for group (BPD vs non-clinical) by condition (oxytocin vs placebo).

Source	*SS*	*df*	*MS*	*F*	*p*	eta^2	Power
Condition	0.10	1	0.10	0.004	0.95	0.000	0.05
Group	4.90	1	4.90	0.204	0.65	0.006	0.07
Condition X Group	12.10	1	12.10	0.504	0.48	0.014	0.12
Error	864.00	36	24.00			0.981	
Total	881.10	39					

**Abbreviations*: BPD = Borderline Personality Disorder

Table 6. ANOVA Summary for Hypermentalizing for group (BPD vs non-clinical) by condition (oxytocin vs placebo).

Source	*SS*	*df*	*MS*	*F*	*p*	eta^2	Power
Condition	10.00	1	10.00	0.55	0.47	0.015	0.11
Group	0.90	1	0.90	0.05	0.83	0.001	0.06
Condition X Group	3.60	1	3.60	0.20	0.67	0.005	0.07
Error	659.40	36	18.32			0.978	
Total	673.90	39					

**Abbreviations*: BPD = Borderline Personality Disorder

Table 7. ANOVA Summary for Trait-based mentalizing with In-vivo Mentalizing by group (high vs low RF) and condition (oxytocin vs placebo).

Source	*SS*	*df*	*MS*	*F*	*p*	eta^2	Power
Condition	0.00	1	0.00	0.00	1.00	0.000	0.05
RF group	0.00	1	0.00	0.05	1.00	0.000	0.05
Condition X RF group	140.73	1	140.73	6.48	0.02	0.160	0.70
Error	738.11	34	21.71			0.840	
Total	878.84	37					

**Abbreviations*: RF = reflective function, as measured by the Reflective Function Questionnaire for Youth

Table 8. Means and standard deviations for In-vivo Mentalzing and Hypermentalizing by trait-based mentalizing (high and low RF) and condition (oxytocin and placebo).

Variables	**Groups**					
	Low RF			*High RF*		
Oxytocin	M	SD	n	M	SD	n
In-vivo MZ	31.73	4.86	11	35.63	2.62	8
Hypermz	7.73	3.52	11	4.75	1.39	8
Placebo						
In-vivo MZ	35.63	2.83	8	31.73	6.31	11
Hypermz	5.38	2.14	8	9.18	6.19	11

**Notes*: MZ = mentalizing, Hypermz = hypermentalizing, BPD = Borderline Personality Disorder; trait-based mentalizing was assessed using the Reflective Function Questionnaire for Youth.

Table 9. ANOVA Summary for Trait-based Mentalizing with Hypermentalizing by group (high vs low RF) and condition (oxytocin vs placebo).

Source	*SS*	*df*	*MS*	*F*	*p*	eta^2	Power
Condition	10.02	1	10.02	0.62	0.44	0.015	0.12
RF group	1.59	1	1.59	0.10	0.76	0.002	0.06
Condition X RF group	106.58	1	106.58	6.55	0.02	0.159	0.70
Error	553.19	34	16.27			0.824	
Total	672.97	37					

**Abbreviations*: RF = reflective function, as measured by the Reflective Function Questionnaire for Youth

Figure 1. A dynamic mentalization-based model of Borderline Personality Disorder (adapted from Fonagy & Luyten, 2009).

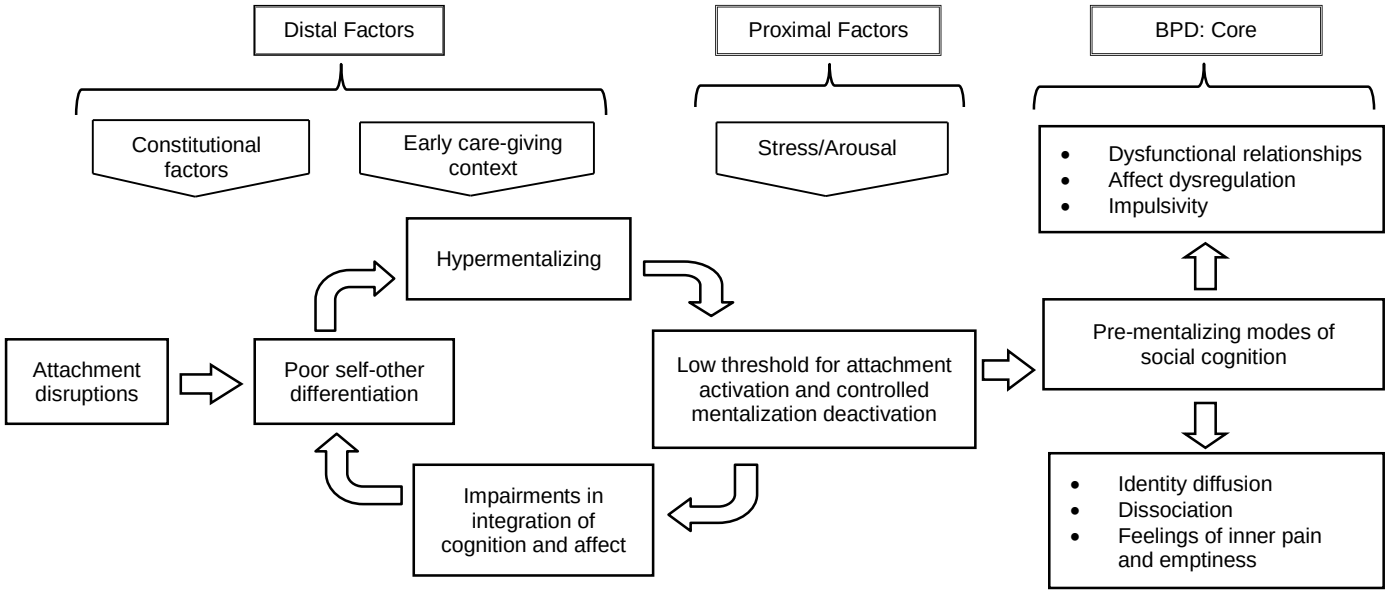
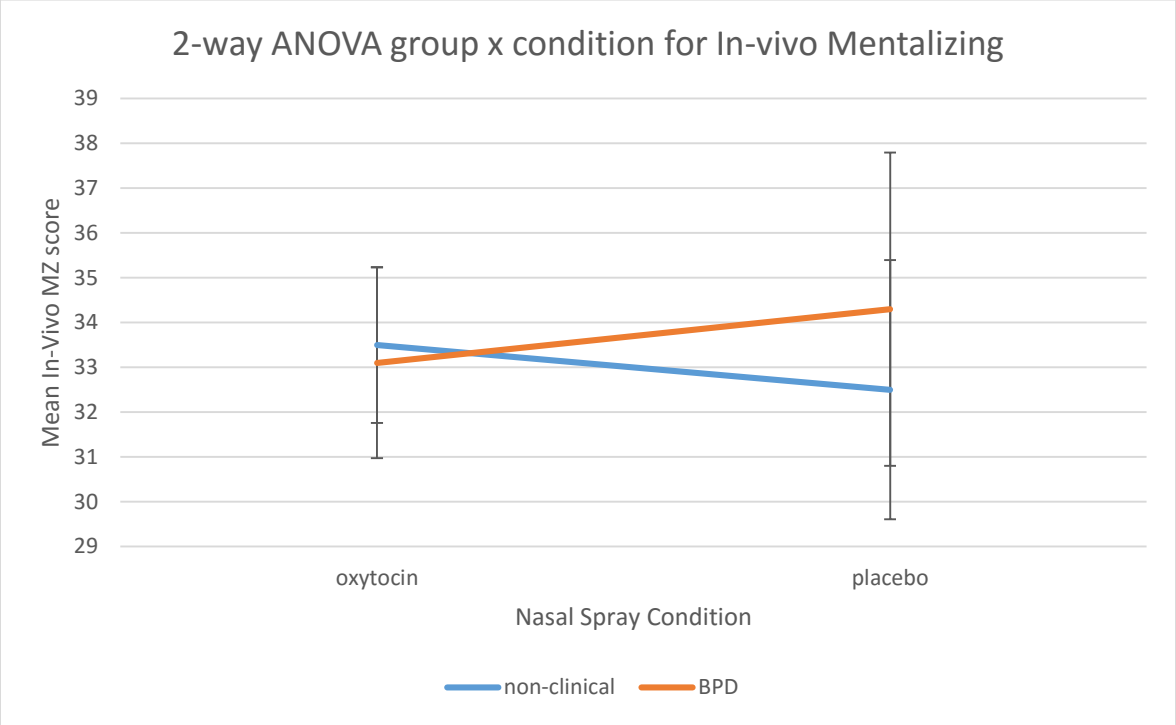
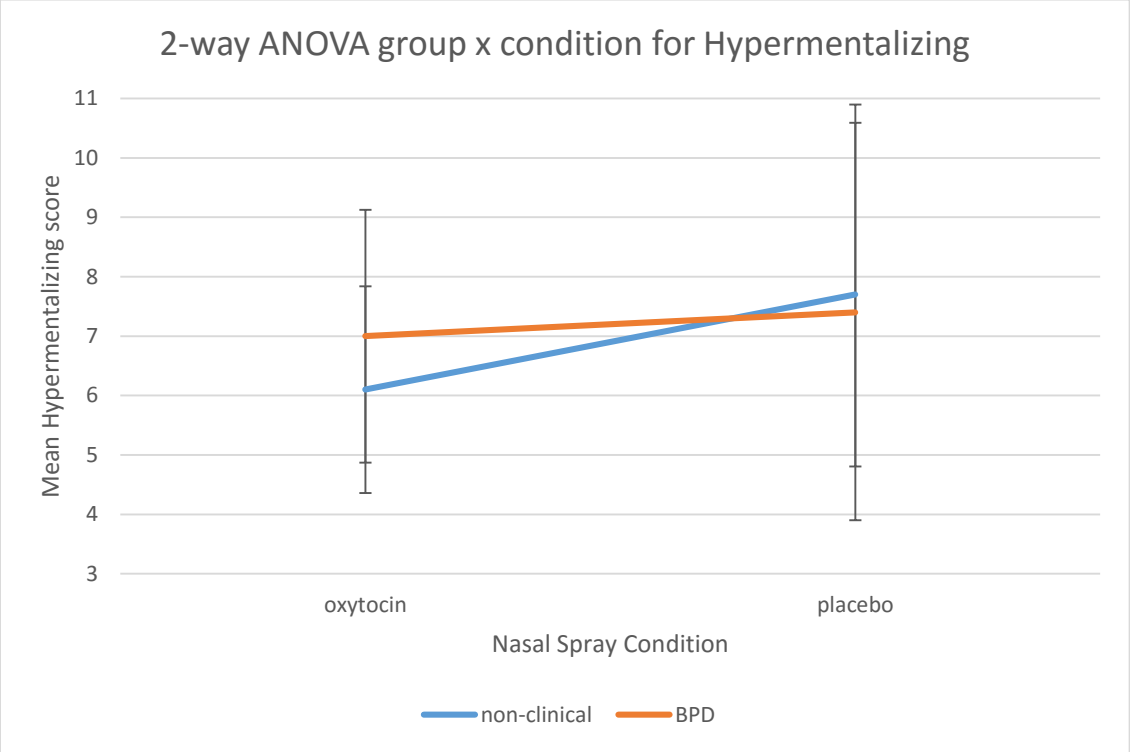


Figure 2. Group x condition effects on overall In-vivo Mentalization.



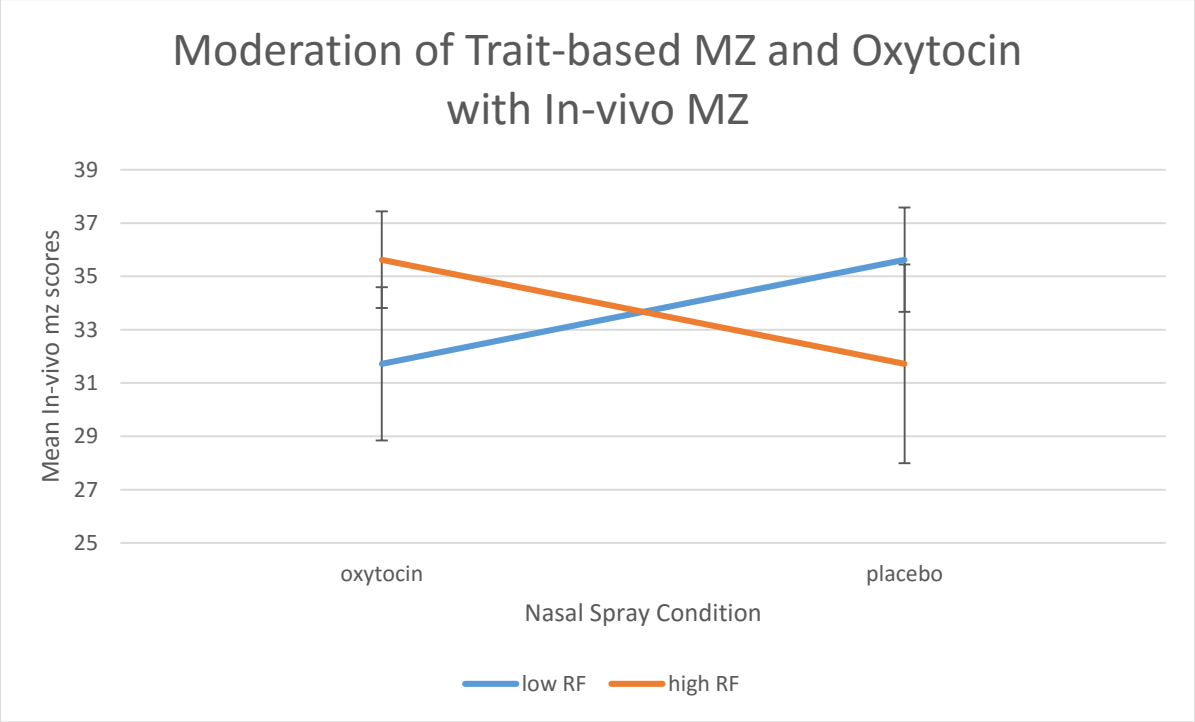
**Abbreviations*: BPD = Borderline Personality Disorder

Figure 3. Group x condition effects on Hypermentalizing.



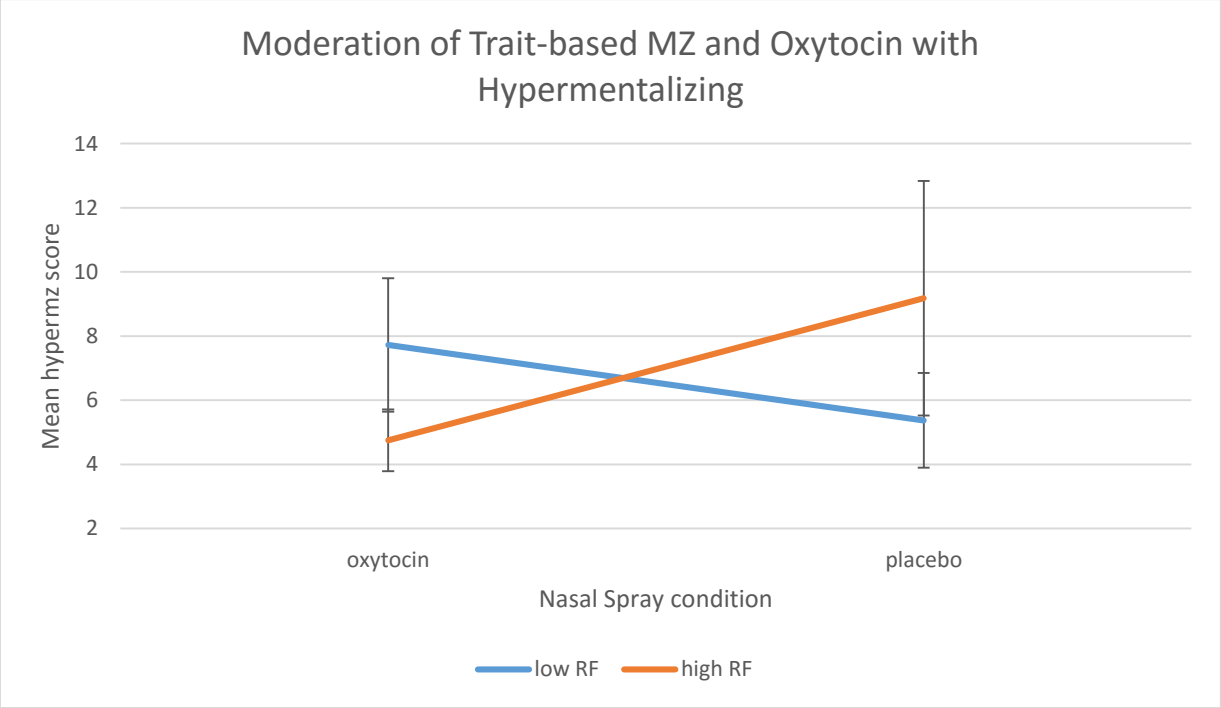
**Abbreviations*: BPD = Borderline Personality Disorder

Figure 4. Moderation of Trait-based Mentalizing and Nasal Spray Condition on overall In-vivo Mentalization.



*_Abbreviations_: MZ = mentalizing; RF = reflective function

Figure 5. Moderation of Trait-based Mentalizing and Nasal Spray Condition on Hypermentalizing.



**Abbreviations*: MZ = mentalizing; RF = reflective function

References

Achenbach, T. M., & Rescorla, L. (2001). ASEBA School-Age Forms & Profiles. *Aseba*.

Amad, A., Pierre, T., & Perez-Rodriguez, M.M. (2015). Borderline Personality Disorder and Oxytocin: Review of Clinical Trials and Future Directions. *Current Pharmacological Design*, 21(23), 3311-3316.

American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders*. 4th Ed. Text Revision. Washington, D.C: APA (DSM-IV-TR).

Bakermans-Kranenburg, M.J., & van IJzendoorn, M.H. (2013). Sniffing around oxytocin: review and meta-analyses of trials in healthy and clinical groups with implications for pharmacotherapy. *Translational Psychiatry*, 3, e258.

Bartz, J.A., Simeon, D., Hamilton, H., Kim, S., Crystal, S., Braun, A., et al. (2011a). Oxytocin can hinder trust and cooperation in borderline personality disorder. *Social Cognitive and Affective Neuroscience, 6(5)*, 556-563.

Bartz, J. A., Zaki, J., Bolger, N., Hollander, E., Ludwig, N. N., Kolevzon, A., & Ochsner, K. N. (2010a). Oxytocin selectively improves empathic accuracy. *Psychological Science*, 21(10), 1426-1428.

Bartz, J. A., Zaki, J., Ochsner, K. N., Bolger, N., Kolevzon, A., Ludwig, N., & Lydon, J. E. (2010b). Effects of oxytocin on recollections of maternal care and closeness. *PNAS Proceedings Of The National Academy Of Sciences Of The United States Of America*, 107(50), 21371-21375.

Bartz, J.A., Zaki, J., Bolger, N. & Ochsner, K.N. (2011b). Social effects of oxytocin in humans: context and person matter. *Trends in Cognitive Sciences, 15*, 301-309.

Bezirganian, S., Cohen, P., & Brook, J. (1993). The impact of mother-child interaction on the development of borderline personality disorder. *American Journal of Psychiatry. 150,* 1836–1842.

Bertsch, K., Gamer, M., Schmidt, B., Schmidinger, I., Walther, S., Kastel, T., et al., (2013). Oxytocin and reduction of social threat hypersensitivity in women with borderline personality disorder. *American Journal of Psychiatry,* 170, 1169-1177.

Bornovalova, M. A., Hicks, B. M., Iacono, W. G., & McGue, M. (2009). Stability, change, and heritability of borderline personality disorder traits from adolescence to adulthood: a longitudinal twin study. *Development and Psychopathology, 21*(4), 1335-1353.

Carlson, E. A., Egeland, B., & Sroufe, L. A. (2009). A prospective investigation of the development of borderline personality symptoms. *Development and Psychopathology, 21*(4), 1311-1334.

Chanen, A. M., Jackson, H. J., McGorry, P. D., Allot, K. A., Clarkson, V., & Yuen, H. P. (2004). Two-year stability of personality disorder in older adolescent outpatients. *Journal of Personality Disorders*, 18(6), 526−541.

Chanen, A.M., Jovev, M., & Jackson, H.J. (2007). Adaptive functioning and psychiatric symptoms in adolescents with borderline personality disorder. *Journal of Clinical Psychiatry,* 68, 297–306.

Chang, B., Sharp, C., & Ha, C. (2011). The criterion validity of the Borderline Personality Feature Scale for Children in an adolescent inpatient setting. *Journal of Personality Disorders, 25*(4), 492-503.

Choi-Kain, L. W., & Gunderson, J. G. (2008). Mentalization: Ontogeny, assessment, and application in the treatment of borderline personality disorder. *American Journal of Psychiatry, 165*(9), 1127-1135.

Dadds, M.R., MacDonald, E., Cauchi, A., Williams, K., Levy, F., & Brennan, J. (2014). Nasal oxytocin for social deficits in childhood autism: a randomized controlled trial. *Journal of Autism and Developmental Disorders*, 44(3), 521-531.

De Dreu, C.K.W., Greer, L.L., Handgraaf, M.J.J., Shalvi, S., Van Kleef, G.A., Baas, M., et al., (2010). The neuropeptide oxytocin regulates parochial altruism in intergroup conflict among humans. *Science*, 328, 1408—1411.

Domes, G., Heinrichs, M., Glascher, J., Buchel, C., Braus, D.F., & Herpertz, S.C. (2007a). Oxytocin attenuates amygdala responses to emotional faces regardless of valence. *Biological Psychiatry, 62*, 1187–1190.

Domes, G., Heinrichs, M., Michel, A., Berger, C., & Herpertz, S. (2007b). Oxytocin improves "mind-reading" in humans. *Biol. Psychiatry* 61,731–733.

Dziobek, I., Fleck, S., Kalbe, E., Rogers, K., Hassenstab, J., Brand, M., et al. (2006). Introducing MASC: A Movie for the Assessment of Social Cognition. *Journal of Autism and Developmental Disorders, 36*(5):623-36.

Fonagy, P. & Bateman, A. (2006). Mechanisms of change in mentalization-based treatment of BPD. *Journal of Clinical Psychology*, 62, 411-430.

Fonagy, P. & Bateman, A. (2007). Mentalizing and borderline personality disorder. *Journal of Mental Health, 16(1),* 83-101.

Fonagy, P. & Bateman, A. (2008). The development of Borderline Personality Disorder – A Mentalizing Model. *Journal of Personality Disorders, 22(1),* 4-21.

Fonagy, P. & Luyten, P. (2009). A developmental, mentalization-based approach to the understanding and treatment of borderline personality disorder. *Dev Psychopathol*, 21(4), 1355-1381.

Fonagy, P. & Sharp, C. (2008). *Treatment outcome of childhood psychological disturbance: The perspective of social cognition.* In Sharp, C., Fonagy, P., and Goodyer, I.M. (Eds.), Social cognition and Developmental Psychopathology, pp. 409-468. Oxford: Oxford University Press.

Fonagy, P., Steele, H., Moran, G., Steele, M., & Higgitt, A. (1991). The capacity for understanding mental states: The reflective self in parent and child and its significance for security of attachment. *Infant Mental Health Journal, 13*(3), 200–217.

Frith C.D. (1992). *The Cognitive Neuropsychology of Schizophrenia*. Hillsdale, NJ: Erlbaum.

Fruzzetti, A.E., Shenk, C., & Hoffman, P.D. (2005). Family interaction and the development of borderline personality disorder: A transactional model. *Development and Psychopathology*, 17(4), 1007 – 1030.

Gordon, I., Vandery Wyk, B., Bennett, R., Cordeaux, C., Lucas, M., Eilbott, J., et al. (2013). Oxytocin enhances brain function in children with autism. *Proceedings of the National Academy of Sciences*, 110(52), 20953-20958.

Grilo, C.M., McGlasha, T.H., Quinlan, D.M., Walker, M.L., Greenfield, D., & Edell, W.S. (1998). Frequency of personality disorders in two age cohorts of psychiatric inpatients. *American Journal of Psychiatry*, 155(1), 140-142.

Guastella, A.J., Einfeld, S.L., Gray, K.M., Rinehart, N.J., Tonge, B.J., Lambert, T.J., & Hickie, I.B., (2010). Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. *Biological Psychiatry* 67, 692—694.

Guastella, A.J., Hickie, I.B., McGuinness, M.M., Otis, M., Woods, E.A., Disinger, H.M., Chan, H.K., Chen, T.F., & Banati, R.B. (2013). Recommendations for the standardization of oxytocin nasal administration and guidelines for its reporting in human research. *Psychoneuroendocrinology*, 38, 612–625.

Guastella, A.J., & MacLeod, C. (2012). A critical review of the influence of oxytocin nasal spray on social cognition in humans: evidence and future directions. *Hormones and Behavior*, 61, 410–418.

Ha, C., Sharp, C., Ensink, K., Fonagy, P., & Cirino, P. (2013). The measurement of reflective function in adolescents with and without borderline traits. *Journal of Adolescence*, 36, 1215-1223.

Heinrichs, M., Baumgartner, T., Kirschbaum, C., & Ehlert, U. (2003): Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *Biological Psychiatry*, 54, 1389 –1398.

Hinshaw, S.P. & Cicchetti, D. (2000). Stigma and mental disorder: Conceptions of illness, public attitudes, personal disclosure, and social policy. *Development and Psychopathology*, 12(4), 555-598.

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

Kasius, M.C., Ferdinand, R.F., van den Berg, H., & Verhulst, F.C. (1997). Associations between different diagnostic approaches for child and adolescent psychopathology. *Journal of Child Psychology and Psychiatry*, 38 (6), 625-632.

Kessler, R.C., Bergulund, P., Demler, O., Jin, R., Merikangas, K.R., & Walters, E.E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, 62, 593-602.

Levy, K.N., Becker, D.F., Grilo, C.M., Mattanah, J., Garnet, K.E., et al., (1999). Concurrent and predictive validity of the personality disorder diagnosis in adolescent inpatients. *American Journal of Psychiatry, 156,* 1522-1528.

Lenzenweger, M.F., Lane, M.C., Loranger, A.W., & Kessler, R.C. (2007). DSM-IV personality disorders in the National Comorbidity Survey Replication. *Biological Psychiatry*, *62*(*6*), 553-564.

Linehan, M. M. (1993). *Cognitive–behavioral treatment of borderline personality disorders*. New York: Guilford.

MacDonald, E., Dadds, M.R., Brennan, J.L., Williams, K., Levy, F., Cauchi, A.J. (2011). A review of safety, side-effects and subjective reactions to intranasal oxytocin in human research. *Psychoneuroendocrinology*, 36(8), 1114-1126.

MacDonald, K., & MacDonald, T.M., (2010). The peptide that binds: a systematic review of oxytocin and its prosocial effects in humans. *Harvard Review of Psychiatry*, 18, 1—21.

McManus, M., Lerner, H., Robbins, D., & Barbour, C. (1984). Assessment of borderline symptomatology in hospitalized adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry*, *23*, 685–694.

Michonski, J.D.M., Sharp, C., Steinberg, L., & Zanarini, M. (2012). An Item Response Theory analysis of the borderline personality disorder criteria in a population-based sample of 11 to 12-year-old children. *Journal of Personality Disorders: Theory, research and treatment.*

Miller, A.L., Muehlenkamp, J.J., & Jacobson, C.M. (2008). Fact or fiction: Diagnosing borderline personality disorder in adolescents. *Clinical Psychology Review, 28*, 969-981.

Montag, C., Ehrlich, A., Neuhaus, K., et al. (2009). Theory of mind impairments in euthymic bipolar patients. *Journal of Affective Disorders, 123(1-3),* 264-269.

Morton, J. (1989) The origins of autism. *New Scientist,* 124, 44-47.

Netherton, E., & Schatte, D.S. (2011). Potential for oxytocin use in children and adolescents with mental illness. *Human Psychopharmacology: Clinical and Experimental*, *25(4-5)*, 271-281.

Paus, T., Keshavan, M., & Giedd, J.N. (2008). Why do many psychiatric disoders emerge during adolescence? *Nature Reviews Neuroscience,* 9(12), 947-957.

Preti, A., Melis, M., Siddi, S., Vellante, M., Doneddu, G., & Fadda, R. (2014). Oxytocin and autism: A systematic review of randomized controlled trials. *Journal Of Child And Adolescent Psychopharmacology*, 24(2), 54-68.

Preißler, S., Dziobek, I., Ritter, K., Heekeren, H.R. & Roepke, S. (2010). Social cognition in borderline personality disorder: Evidence for disturbed recognition of the emotions, thoughts, and intentions of others. *Frontiers in Behavioral Neuroscience,* 4, 1-8.

Riem, M., van IJzendoorn, M.H., Tops, M., Boksem, M., Rombouts, S., & Bakermans-Kranenburg, M.J. (2013). Oxytocin effects on complex brain networks are moderated by experiences of maternal love withdrawal, *European Neuropsychopharmacology*, 23(10), 1288-1295.

Ritter, K., Dziobek, I., Preißler, S., Rütter, A., Vater, A., Fydrichm, T. et al., (2011). Lack of empathy in patients with narcissistic personality disorder. *Psychiatry Research*, 187(1-2), 241-247.

Salonia, A., Nappi, R.E., Pontillo, M., Daverio, R., Smeraldi, A., Briganti, A., et. al., (2005). Menstrual cycle-related changes in plasma oxytocin are relevant to normal sexual function in healthy women. *Hormones and Behavior*, 47(2), 164-169.

Sharp, C. (2006). *Mentalizing problems in childhood disorders.* In J.G. Allen & P. Fonagy (Eds.), Handbook of mentalization-based treatments, pp. 201-212. Chichester: John Wiley & Sons.

Sharp, C., Ha, C., Carbone, C., Kim, S., Perry, K., Williams, L., & Fonagy, P. (2013). Mentalizing in adolescent inpatients with borderline traits: Treatment effects. *Journal of Personality Disorders.*

Sharp, C., Ha, C., Michonski, J., Venta, A., & Carbone, C. (2012). Borderline personality disorder in adolescents: Evidence in support of the CI-BPD in a sample of adolescent inpatients. *Comprehensive Psychiatry*.

Sharp, C., Mosko, O., Chang, B., & Ha, C. (2010). The cross-informant concordance and concurrent validity of the Borderline Personality Features Scale for Children in a sample of male youth. *Clinical Child Psychology and Psychiatry*.

Sharp, C. Pane, H., Ha, C., Venta, A., Patel, B., Sturek, J., & Fonagy, P. (2011). Theory of mind and emotion regulation difficulties in adolescents with borderline traits. *Journal of the American Academy of Child and Adolescent Psychiatry.*

Sharp, C., & Romero, C. (2007). Borderline personality disorder: a comparison between children and adults. *Bulletin of the Menninger Clinic, 71*(2), 85-114.

Sharp, C., Williams, L., Ha, C., Baumgardner, J., Michonski, J., Seals, R., et al. (2009). The development of a mentalization-based outcomes and research protocol for an adolescent in-patient unit. *The Bulletin of the Menninger Clinic, 73*(4), 311-338.

Spear, L.P. (2000). The adolescent brain and age-related behavioral manifestations. *Neuroscience and Biobehavioral Reviews, 24,* 417-463.

Stanley, B., & Siever, L. J. (2010). The interpersonal dimension of borderline personality disorder: Toward a neuropeptide model. *American Journal of Psychiatry, 167,* 24–39.

Stepp, S.D., Whalen, D.J., & Pederson, S.L. (2014). *The externalizing pathway to borderline personality disorder in youth.* In C. Sharp & J.L. Tackett (Eds.), Handbook of borderline personality disorder in children and adolescents, pp. 247-263. New York: Springer.

Swartz, M. S., Blazer, D., George, L., & Winfield, I. (1990). Estimating the prevalence of borderline personality disorder in the community. *Journal of Personality Disorders, 4,* 257–272.

Uvnas-Moberg, K. (1998). Oxytocin may mediate the benefits of positive social interaction and emotions. *Psychoneuroendocrinology* 23, 819–835.

Van IJzendoorn, M.H. & Bakermans-Kranenburg, M.J. (2012). A sniff of trust: Meta-analysis of the effects of intranasal oxytocin administration on face recognition, trust to in-group, and trust to out-group. *Psychoneuroendocriniology*, 37, 438-443.

Venta, A., Kenkel-Mikelonis, R., & Sharp, C. (2012). A preliminary study of the relation between trauma symptoms and emerging BPD in adolescent inpatients. *Bulletin of the Menninger Clinic*,76(2), 130-46.

Weston, D., Ludolph, P., Misle, B., Ruffins, S., & Block, J. (1990). Physical and sexual abuse in adolescent girls with borderline personality disorder. *American Journal of Orthopsychiatry*, 60, 55– 66.

Widiger, T. A., & Weissman, M. M. (1991). Epidemiology of borderline personality disorder. *Hospital and Community Psychiatry, 42*(10), 1015–1021.

Wilkinson, G. S. (1993). *The Wide Range Achievement Test administration manual.* Wilmington, DE: Wide Range.

Winograd, G., Cohen, P., Chen, H. (2008). Adolescent borderline symptoms in the community: prognosis for functioning over 20 years. *Journal of Child Psychology and Psychiatry,* 49 (9), 933-941.

Winslow, J. T., and Insel, T. R. (2004). Neuroendocrine basis of social recognition. *Curr. Opin. Neurobiol.* 14, 248–253.

Zak, P. J., Kurzban, R., and Matzner, W. T. (2005). Oxytocin is associated with human trustworthiness. *Horm. Behav.*48, 522–527.

Zanarini, M.C. (2003). *The Child Interview for DSM-IV Borderline Personality Disorder*. Belmont, MA: McLean Hospital.

Zanarini, M.C., & Wedig, M.M. (2014). *Childhood adversity and the development of borderline personality disorder.* In C. Sharp & J.L. Tackett (Eds.), Handbook of borderline personality disorder in children and adolescents, pp. 265-276. New York: Springer.