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Effects of oxytocin on aggressive responding in healthy adult males

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Abstract

This study investigated the acute effects of oxytocin (OT) on human aggression using a well-established laboratory measure of state (reactive) aggression to test the hypothesis that OT would decrease the frequency of aggressive responding. In a within-subject design, 17 healthy male volunteers received placebo or 24 international units of intranasal OT. Aggression was measured via the Point Subtraction Aggression Paradigm at 30 min prior and 30, 60 and 90 min post-dose. Acute OT did not produce a significant main effect on aggressive behavior. OT attenuated the expected rise in diastolic blood pressure from morning to early afternoon observed under placebo, providing a possible indicator of biological activity. Examination of individual differences showed that aggressive responding following OT dosing (but not placebo) was positively correlated with psychometric measures of interpersonal manipulation and anger (Pearson's r = 0.57), indicating that higher scores on these antisocial personality traits were related to increased aggressive behavior following OT administration. These preliminary results stand in contrast to previous work on the prosocial effects of OT and highlight the need for further understanding of individual differences in aggression following OT administration. Such individual differences may have implications for the therapeutic use of OT in individuals with psychiatric disorders and dysfunctional social behavior.

Keywords

Aggression; Psychopathic traits; Oxytocin; human

Introduction

Aggression represents a class of antisocial behavior that is prevalent in several psychiatric disorders (Lane et al., 2011; Alcorn III et al., 2013; Beck and Heinz, 2013; Dack et al.,

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2013; Latalova et al., 2013; Coccaro et al., 2014). In maladaptive and persistent forms (e.g., violent crime, child abuse), aggression places a heavy burden on medical and public health systems. Accumulating evidence supports the therapeutic potential of oxytocin (OT) in enhancing prosocial behavior and socio-emotional processing. In humans, several studies have established that OT administration increases cooperation, trust, and generosity following acute administration (Kosfeld et al., 2005; Zak et al., 2007; Rilling et al., 2012). Notably, each of these studies utilized a dose of 24 international units (IU), delivered intranasally. Most human studies have employed between-group designs and examined 24 IU as the active dose (Bakermans-Kranenburg and van IJzendoorn, 2013; Bethlehem, et al., 2013). Collectively, the data suggest OT administration enhances prosocial behaviors. Therefore, we examined the possibility that it could reduce antisocial behaviors such as aggression. This hypothesis has rarely been tested directly.

To our knowledge, only two previous human studies have examined the acute effects of OT on experimentally-induced aggression. Campbell and Hausmann (2013) found an interaction effect in female subjects responding on the Point Subtraction Aggression Paradigm (PSAP), such that OT (vs. placebo) moderated reactive aggression in women with high state anxiety but not low state anxiety. Using a within-subject design in the PSAP, Alcorn III et al. (2015) investigated the effect of intranasal placebo, 12, 24, and 48 international units (IU) of OT in six adult males with combined antisocial personality disorder (ASPD) and substance use disorder (SUD). No orderly effects on aggressive behavior measured by the PSAP were observed, under OT dose. Alcorn III et al. (2015) investigated behavior at the individual-subject level, which revealed substantial dose-related variability in aggression (both increases and decreases) across particpants, despite very stable monetary-earning (non-social) response patterns. Owing to the extreme, atypical life histories of aggressive and impulsive behavior in the participants enrolled by Alcorn III et al. (2015), it was unclear if the observed variability was unique to this clinical population or a feature of OT effects on aggression under laboratory conditions.

The current within-subjects preliminary study was undertaken to determine the effects of acute OT administration on aggressive responding in healthy male participants without a history of psychiatric disorders and persistent aggression. Following Alcorn III et al. (2015), we also focused on potentially relevant personality factors that might be associated with individual differences in the effects of OT; specifically, the antisocial personality traits of anger and interpersonal manipulation. These traits were selected for two reasons: (i) they are consistent with the clinical profile of ASPD and SUD subjects (Ruiz et al., 2008; Burt, 2012; Alcorn III et al., 2013) and (ii) individuals with higher levels of interpersonal manipulation and poor anger regulation demonstrate higher levels of aggression and violent behavior (Buss and Perry, 1992; Nouvion et al., 2007; Alia-Klien et al., 2009; Vaillancourt and Sunderani, 2011).

We hypothesized that acute OT administration would decrease aggressive responding on the PSAP. Based on previous studies (Alcorn III et al., 2013, 2015), we also examined the relationship between the personality traits (interpersonal manipulation and anger) and changes in aggression following OT dosing.

Methods

All experimental procedures were reviewed and approved by the UTHSC-Houston Institutional Review Board. Informed consent was obtained from all participants prior to study participation.

Participants

Participants were recruited from a community sample by local newspaper advertisements. Potential participants (18-50 years of age) were first screened though an initial phone interview to obtain information about recreational drug use, psychiatric, and medical history. Potentially eligible participants were scheduled for more extensive in-person screening. Prior to study participation all participants underwent a physical exam to screen for exclusionary medical conditions (e.g. HIV, seizures, cardiovascular, kidney or endocrine diseases, diabetes, hypertension, and history of head trauma or loss of consciousness > 20 minutes) and current use of all prescription medication. Female participants were excluded from this experiment for two reasons, (i) the neuropeptide OT increases levels of luteinizing hormone (Evans et al., 2003) which could potentially affect the regularly occurring menstrual cycles of female participants and (ii) currently there are no data about interactions of OT administration with oral contraceptives (i.e. birth control), introducing the possibility of behavioral and physiological side effects. All participants were interviewed by a trained mental health professional using the Structured Clinical Interview for the DSM-IV (SCID) to assess for diagnosis of Axis I Disorders (First et al., 1996) and Axis II Disorders (Personality Disorders; First et al., 1997). The SCID-I and SCID-II were used to ensure that all potential participants did not meet DSM-IV criteria for any psychiatric disorders. All qualified participants were male, had no medical complications, and had no history of DSM-IV Axis I and/or DSM-IV Axis II personality disorder. The enrolled participants had a mean age of 32 (SD = ± 9.2) with a mean 13.6 years of education (SD = ± 2.1). Across the participants, 53% identified as African-American, 17.6% identified as Caucasian, and 29.4% identified as Hispanic.

Extraneous drug use was monitored by daily urine samples and expired alcohol breath samples prior to beginning participation. Urine samples were screened for extraneous drug use via the Enzyme Multiple Immunoassay Technique Drug Abuse Urine Assay (Innovacon; San Diego, CA). Expired breath samples were used for detecting alcohol consumption, prior to participation, and were analyzed using an Alcosensor III. Psychoactive medication was prohibited during study participation and caffeine consumption was prohibited on test days after entering the laboratory. No participant was positive for extraneous drug use or expired a positive BAC.

Procedure

Participants completed a minimum of four study days (one day in which they were dosed with OT, one day in which they were dosed placebo, and two days on which they were not dosed). In order to reduce variability in aggressive response patterns across doses (e.g., Alcorn et al., 2015), stability criteria were required on separate non-dosing days prior to the

administration of OT **and** placebo (coefficient of variation < 0.25 with no monotonic upward or downward trends).

Participants came to the lab 2 - 4 days a week, from 08:00 h to approximately 13:00 pmh each study day. Participants completed four sessions of the Point Subtraction Aggression Paradigm (PSAP; Cherek, 1992) each study day. On study days in which participants were dosed with OT or placebo, the first session was scheduled to occur at 08:30 h, 30 min before dose administration. The remaining three PSAP sessions were scheduled to occur at 30 min, 90 min, and 150 min post-dose. Each PSAP session lasted 25 min. The PSAP is a well-established and validated laboratory measure of human state aggression, the utility and experimental procedures of twhich have been documented across many studies, with demonstrated sensitivity to acute drug effects (Allen et al., 1997; Cherek et al., 1997, 2003; Bjork et al., 1999; Cherek and Lane, 1999; Lane and Cherek, 2000;).

Drug Administration

Dose order was counterbalanced across all participants. Prior to drug administration, all participants were trained on the dosing procedures using 1.5 ml of saline to ensure accurate administration and comfort with the administration procedure. Participants were administered an intranasal dose (24 international units, IU) of synthetic OT (Syntocinon, nasal spray: Novartis®) or placebo by research personnel. The dose level of 24 IU was selected for two reasons: (1) this dose was within the range of doses (12 IU, 24 IU, and 48 IU) that were previously tested on human aggressive behavior (Alcorn III et al., 2015), and (2) 24 IU is the most commonly used OT dose in human studies (reviewed in Bakermans-Kranenburg & van IJzendoorn, 2013; Shahrestani et al., 2013). The drug administration apparatus was a 3cc (3 ml) needleless-syringe attached to a nasal atomizer for intranasal administration. One spray was 4 IU, and each 4 IU of spray is equivalent to 0.1 ml. Thus, 24 IU of OT is equivalent to 0.6 ml of nasal spray fluid. For drug preparation, OT doses were brought to their corresponding volume (ml) in a 3cc needleless-syringe, and then each syringe was brought to a full volume of 1.5 cc by adding saline. This approach was used to blind participants to dose contents. The placebo dose contained only saline, and was also administered at a total volume of 1.5 ml (0.75 ml per nostril). Each dose (24 IU OT) and placebo were administered at a total volume of 1.5 ml intranasal (≈ 0.75 ml per nostril) under the supervision of research personnel. All administrations were completed within 8 min. All participants inhaled the total volume of 1.5 ml within this time frame.

Behavioral measures

The dependent measure of aggression in the PSAP was the aggressive response rate (aggressive responses per minute). Aggressive responding was maintained on an FR10 schedule of responding. Aggressive responding was elicited by provocation, which occurred probabilistically on average every 125 sec ± 20% and resulted in an ostensive loss of $0.15 from the participant's counter. These monetary loses (subtractions) were attributed to the fictitious individual paired with the participant. Participants were told that the other (fictitious) individual kept the money subtracted from the subject's counter. The participant was informed that money he subtracts from the fictitious individual's counter is not added to his own. Thus, the aggressive option was not maintained by monetary gain. The dependent

measure of motor-coordination (positive control) was the monetary response rate (monetary responses per second). Monetary responding was maintained on an FR100 (100 presses) schedule of responding, in which the participant gained $0.15 cents for each completed FR100. These two response options (aggressive and monetary responding) are measured in different response rate units, because monetary responding occurs more frequently than aggressive responding during PSAP sessions (Lane and Cherek, 2000; Cherek et al., 2006).

On days in which participants were given a **dose of OT (24 IU) or placebo**, aggressive response rates were measured at baseline (pre-dose) and at each subsequent post-dose session occurring 30 min, 90 min, 150 min post-dose (post-dose sessions 1, 2, 3, respectively). Behavioral data from each post-dose session were normalized to the baseline (pre-dose) session, and were thus calculated as a percent of the baseline pre-dose response rate: [(post-dose session response rate / pre-dose session response rate) *100].

Physiological measures

Blood pressure (BP) data were collected to provide confirmation of active OT. The participant's BP was measured using a sphygmomanometer (BpTru Vital Signs Monitor, Coquitlam, Canada) after each of the four PSAP sessions. BP data were collected to examine changes in autonomic nervous system activity after OT dosing, which can provide physiological confirmation of an active dose (Petersson et al., 1996). All BP data were transformed into a difference score (Δ score) of post-dose minus pre-dose.

Psychometric measures

The Self-Report Psychopathy Scale III (SRP-III; Paulhus et al., 2010; Mahmut et al., 2011) is a self-report measure of the clinical construct of psychopathy. The SRP-III consists of 64-items on a 5-point Likert-rating scale ranging from "Disagree Strongly" to "Agree Strongly". The SPR-III provides a total score in addition to four subscale scores measuring interpersonal manipulation, callous affect, erratic lifestyle, and criminal tendencies. The subscale of interpersonal manipulation was used for correlational analysis based on Vaillancourt and Sunderani (2011)s. The mean (raw) score on the interpersonal manipulation sub-scale was 11 (SD = ± 3).

The Buss-Perry Aggression Questionnaire (BPAQ; Buss and Perry, 1992) is a self-report measure of trait aggression consisting of 29-items on a 5-point Likert-rating scale ranging from "Not like me at all" to "A lot like me". The BPAQ provides a total score in addition four sub-scale scores measuring physical aggression, verbal aggression, anger, and hostility. The subscale of anger was used for correlational analysis based on Alia-Klien et al. (2009). The mean (raw) score on the anger sub-scale was 35.8 (SD = ± 7.4).

Data Analysis

All statistical tests were conducted using the statistical program STATA version 11.1. A two-way Repeated Measures Analysis of Variance (RM ANOVA) tested for main effects of dose and session, and the interaction of dose by session. The two within-subjects factors were dose (Placebo vs OT) and session (post-dose sessions 1-3). Statistical significance was set at $p < 0.05$. The following dependent variables were analyzed in the RM ANOVA

model: aggressive response rates (percent of pre-dose), monetary response rates (percent of pre-dose), and Δ scores from all cardiovascular data. Dose and session were coded in as factors. To correct for violations against sphericity, p-values were corrected using Huynh-Feldt epsilon correction. These corrected values were used to evaluate statistical significance. All ANOVA results are reported with the corrected p-values. If statistically significant results were found, follow-up post-hoc tests using Tukey's Honest Square Difference (HSD; Tukey, 1949) with statistical significance set at $p < 0.05$.

To explore the association between aggressive responding under OT and personality traits of interpersonal manipulation (SRP-III) and anger (BPAQ), both psychometric scores were independently standardized to have a mean of 0 and a standard deviation of 1. The standardized scores (z-scores) of interpersonal manipulation and anger were then added together to create a composite score, as the composite was expected to provide a better profile of phenotypic heterogeneity than individual subscales (Crawford, 2003). Correlational analysis exploring the association between aggressive responding (mean of the three post-dose session change scores) and the combined personality trait score was conducted with pair-wise comparisons using Pearson's correlation coefficient.

One participant dropped out prior to receiving the placebo dose and completing the psychometric data. For this participant, the missing score was imputed by using the placebo sample mean of the normalized aggressive response rate and the normalized cardiovascular data to provide non-biased but balanced cells for statistical analysis. Psychometric scores were similarly imputed using the sample mean.

Results

Behavioral and cardiovascular data

For normalized (percent of pre-dose) aggressive response rates, the main effects of dose ($F(1,16) = 0.78$, N) and session ($F(2, 32) = 1.51$, NS), and the dose by session interaction ($F(2,32) = 1.65$, NS) were all nonsignificant.

For normalized (percent of pre-dose) monetary response, the main effects of dose ($F(1,16) = 0.95$, NS) and session ($F(2, 32) = 2.47$, $p = 0.10$), and the dose by session interaction ($F(2,32) = 0.02$, NS) were all nonsignificant.

For Systolic BP data (Δ scores), the main effects of dose ($F(1,16) = 2.75$, NS) and session ($F(2, 32) = 1.64$, NS), and the dose by session interaction ($F(2,32) = 1.76$, NS) were all nonsignificant.

For Diastolic BP data (Δ scores), a statistically significant main effect of dose was observed **($F(1,16) = 6.73$, $p = 0.01$);** The main effect of session ($F(2, 32) = 0.83$, NS) and the dose by session interaction ($F(2,32) = 1.02$, $p = 0.37$) were nonsignificant. Post-hoc analysis using Tukey's HSD revealed that diastolic BP was significantly lower ($p < .05$) following the OT dose vs. placebo. Diastolic BP data (Δ scores) for OT and Placebo across all post-dose sessions are presented in Figure 1.

Measures of central tendency and variance for normalized (percent of pre-dose) aggressive response rates and monetary response rates, and cardiovascular data (Δ scores) are presented in **Table 1**. Statistics of all raw PSAP and physiological data are presented in Table 2. Importantly, baseline (pre-dose) values of PSAP and blood pressure data were similar, indicating that the observed effects on BP (and non-effects in PSAP) were not the result of differential pre-dose values between placebo and OT.

Behavioral data and personality traits

There was a statistically significant positive correlation between mean aggressive response rates under OT (percent of pre-dose; averaged across all post-dose sessions) and the composite psychometric scores ($r(16) = 0.57$, $p = 0.01$). The correlation without the imputed scores was $r = 0.48$, $p < .05$ A scatterplot of mean aggressive response rates (percent of pre-dose) and the composite psychometric scores is presented in Figure 2. To examine the possibility that this correlation was spurious, we examined the correlation between the composite psychometric scores and (1) baseline (pre-OT dose) aggressive responding, and (2) aggressive responding without the imputed data points missing from one subject. The correlation with the baseline pre-OT dose session was $r = -0.34$, NS, indicating that the observed correlation with post-OT dose responding was not facilitated by the baseline (pre-dose) level of aggressive responding. . This association was specific to the OT administration; there was not a significant correlation between mean aggressive response rates (percent of pre-dose) under Placebo and the composite psychometric scores ($r(16) = -0.12$, NS) and there was no significant correlation between mean monetary response rates (percent of pre-dose) under OT and composite psychometric scores ($r(16) = 0.16$, NS).

Discussion

This study utilized the PSAP to measure the acute effects of oxytocin (OT) on the frequency of aggressive behavior in humans. The PSAP has an established utility in behavioral pharmacology, e.g., demonstrating decreases in aggressive behavior following administration of serotonergic compounds (Cherek and Lane, 1999; 2001; Cherek et al., 2002) and increases in aggressive responding following testosterone administration (Kouri et al., 1995; Carré et al., 2009; 2010). On the basis of multiple studies suggesting that acute OT increases the likelihood of prosocial behaviors such as cooperation and trust, we reasoned that OT would decrease operationally-defined human aggression, a class of behavior that can be considered antisocial.

Contrary to our hypothesis, we observed no statistically significant main effect of OT on aggressive responding. There was a broad range of changes in aggressive responding on the PSAP under OT, including both increases and decreases, suggesting that individual differences played a role in moderating the effects. Similar effects were not observed for responding on the monetary option – response rates were highly stable across conditions, and there were no meaningful correlations between OT dosing and monetary responding. This outcome is consistent with one we observed previously in individuals with combined substance use disorder and antisocial personality disorder (Alcorn III et al., 2013), and provides further support for the conclusion that individual differences in OT effects were

specific to aggression rather than non-specific effects on overall response rates (e.g., motor stimulation or sedation). More extensive work is needed to determine factors that mediate (or moderate) individual differences in response to OT. Alternatively, it is possible that features of the PSAP under the repeated testing protocol interact with acute OT in a manner that produces sufficient between-subject variability to obscure possible systematic effects. A study design that examined the role of personality factors in a moderation- or mediation-based design (which would require a much larger sample size) could address this question more directly. It should be emphasized that our logic was based on the following idea: a compound that increases prosocial behaviors might be incompatible with (and therefore decrease) an antisocial behavior such as aggression. However, these two classes of behavior may also be orthogonal rather than inversely correlated, in which case OT could engender prosocial actions while having no effect on aggression. Further research would be necessary to test this possibility, and would need to examine OT-related changes in both prosocial and aggressive behavior in a repeated-measures within-subjects fashion.

OT significantly modulated diastolic BP changes. Specifically, the known rise in BP from the early AM to the afternoon (Kaplan & Victor, 2010) – which was observed under placebo (see Tables 1 and 2) – was attenuated following administration of OT. Very few human studies have provided biological verification of OT activity following intranasal administration. Even the least invasive method of verification requires repeated plasma sampling, which can be invasive to data collection in studies of laboratory behavior. Thus, while the modest sample size leaves this finding preliminary, the results imply that OT was biologically active, as previous work has also reported decreases in BP following OT administration (Petersson et al., 1996).

The primary finding of interest was a positive correlation between the combined personality traits of interpersonal manipulation + anger and aggressive responding following OT dosing, but not following placebo. This result is contrary to our prediction that individuals with highest levels of antisocial traits would show the greatest reductions. This logic was based on the documented pro-social effects of OT in other social interaction paradigms such as the ultimatum game (Zak et al., 2007). The current findings suggest that these antisocial personality traits (interpersonal manipulation and anger) might moderate the effects of OT on aggression. Importantly, DeClerck et al. (2014) recently reported that effects of OT on social interaction in the prisoner’s dilemma task were dependent on prior interaction with the paired partner, such that with prior contact OT enhanced cooperation, whereas without contact OT increased competition (i.e. self-interested behavior). The present outcomes are generally consonant with DeClerck et al. (2014). Participants in the PSAP never meet the ostensible “other” player, the task context only provides options of self-interest (monetary earning) or aggression (monetary subtraction), and OT enhanced aggression in those with greater antisocial traits.

Limitations of this preliminary study relate to the limited dose range, small sample size, and male-only participants -- the latter precluding information regarding gender effects. An additional limitation is the generalizability of the positive correlation to populations with psychiatric disorders characterized by impulsive aggression. Additional research with these populations will be needed. Additionally, the personality traits (anger and interpersonal

manipulation) were selected based on a statistical profile of ASPD+SUD individuals in Alcorn III et al. (2013), as well as previous studies in populations with psychiatric disorders (Alia-Klein et al., 2009; Vaillancourt and Sunderani, 2011). However, this particular combination of personality traits does not have validated utility in distinguishing clinically relevant groups, limiting generalizability.

Collectively, the results of this preliminary study (i) extend the data on acute OT effects in relation to moderating social behavior, (ii) elucidate sources of individual differences related to aggressive behavior in the context of the OT; and (iii) tentatively suggest that OT may not be an efficacious therapeutic for managing impulsive aggression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Literature Cited

Alcorn JL III, Gowin JL, Green CE, Swann AC, Moeller FG, Lane SD. Aggression, impulsivity, and psychopathic traits in combined antisocial personality disorder and substance use disorder. J Neuropsychiatry Clin Neurosci. 2013; 25(3):229–232. Summer. [PubMed: 24026715]

Alcorn JL III, Rathnayaka N, Swann AC, Moeller FG, Lane SD. Intranasal Oxytocin on Aggressive Responding in Antisocial Personality Disorder. The Psychol Rec. 2015 in press.

Alia-Klein N, Goldstein RZ, Tomasi D, Woicik PA, Moeller SJ, Williams B, Craig IW, et al. Neural mechanisms of anger regulation as a function of genetic risk for violence. Emotion. Jun; 2009 9(3): 385–96. [PubMed: 19485616]

Allen TJ, Moeller FG, Rhoades HM, Cherek DR. Subjects with a history of drug dependence are more aggressive than subjects with no drug use history. Drug Alcohol Depend. 1997; 6(46(1-2)):95–103. [PubMed: 9246557]

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th. Author; Washington, DC: 2000.

Bakermans-Kranenburg MJ, van IJzendoorn MH. Sniffing around oxytocin: review and meta-analyses of trials in healthy and clinical groups with implications for pharmacotherapy. Trans Psychiatry. 2013; 3:e258.

Beck A, Heinz A. Alcohol-related aggression-social and neurobiological factors. Dtsch Arztebl Int. Oct; 2013 110(42):711–5. [PubMed: 24223671]

Bethlehem RA, van Honk J, Auyeung B, Baron-Cohen S. Oxytocin, brain physiology, and functional connectivity: A review of intranasal oxytocin fMRI studies. Psychoneuroendocrinology. Jul; 2013 38(7):962–74. [PubMed: 23159011]

Bjork JM, Doughtery DM, Moeller FG, Swann AC. Differential behavioral effects of plasma tryptophan depletion and loading in aggressive and nonaggressive men. Neuropsychopharmacology. Apr; 2000 22(4):357–69. [PubMed: 10700655]

Burt SA. How do we optimally conceptualize the heterogeneity within antisocial behavior? An argument for aggressive versus non-aggressive behavioral dimensions. Clin Psychol Rev. Jun; 2012 32(4):263–279. [PubMed: 22459789]

Buss AH, Perry M. The aggression questionnaire. J Personality Soc Psychol. 1992; 63:452–459.

Campbell A, Hausmann M. Effects of oxytocin on women's aggression depend on state anxiety. Aggress Behav. Jul-Aug;2013 39(4):316–22. [PubMed: 23553462]

Carré JM, Putnam SK, McCormick CM. Testosterone responses to competition predict future aggressive behaviour at a cost to reward in men. Psychoneuroendocrinology. May; 2009 34(4): 561–70. [PubMed: 19054624]

Carré JM, Gilchrist JD, Morrissey MD, McCormick CM. Motivational and situational factors and the relationship between testosterone dynamics and human aggression during competition. Biol Psychol. May; 2010 84(2):346–53. [PubMed: 20381580]

Cherek, DR. Point-subtraction aggression paradigm. University of Texas, Houston: 1992.

Cherek DR, Lane SD. Effects of d,l-fenfluramine on aggressive and impulsive responding in adult males with a history of conduct disorder. Psychopharmacology. Oct; 1999 146(4):473–481. [PubMed: 10550498]

Cherek DR, Lane SD. Acute effects of D-fenfluramine on simultaneous measures of aggressive escape and impulsive responses of adult males with and without a history of conduct disorder. Psychopharmacology (Berl). Sep; 2001 157(3):221–7. [PubMed: 11605076]

Cherek DR, Moeller FG, Schnapp W, Dougherty DM. Studies of violent and non-violent male parolees I. Laboratory and psychometric measurements of aggression. Biol Psychiatry. 1997; 41:514–522. [PubMed: 9046983]

Cherek DR, Lane SD, Pietras CJ, Steinberg JL. Effects of chronic paroxetine administration on measures of aggressive and impulsive responses of adult males with a history of conduct disorder. 2002

Cherek, DR.; Pietras, CJ.; Lane, SD. Laboratory Measures: Point Subtraction Aggression Paradigm (PSAP). In: Coccaro, E., editor. Aggression: Assessment and Treatment. Marcel Dekker; New York: 2003. p. 215-228.

Cherek, DR.; Tcheremissine, OV.; Lane, SD. Psychopharmacology of aggression. In: Nelson, RJ., editor. Biology of Aggression. Oxford University Press; Oxford, UK: 2006. p. 424-446.

Coccaro EF, Lee R, McCloskey MS. Validity of the new A1 and A2 criteria for DSM-5 intermittent explosive disorder. Compr Psychiatry. Feb; 2014 55(2):260–7. [PubMed: 24321204]

Crawford, JR. Psychometric foundations of neuropsychological assessment. In: Goldstein, LH.; McNeil, J., editors. Clinical Neuropsychology: A Practical Guide to Assessment and Management for Clinicians. Wiley; Chichester: 2003.

Dack C, Ross J, Papadopoulos C, Stewart D, Bowers L. A review and meta-analysis of the patient factors associated with psychiatric in-patient aggression. Acta Psychiatr Scand. Apr; 2013 2013 127(4):255–68. [PubMed: 23289890]

Declerck CH, Boone C, Kiyonari T. The effect of oxytocin on cooperation in a prisoner's dilemma depends on the social context and a person's social value orientation. Soc Cogn Affect Neurosci. 2014; 9(6):802–809. [PubMed: 23588271]

Evans JJ, Reid RA, Wakeman SA, Croft LB, Benny PS. Evidence that oxytocin is a physiological component of LH regulation in non-pregnant women. Hum Reprod. Jul; 2003 18(7):1428–31. [PubMed: 12832367]

First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JB. Biometrics Research Department. New York State Psychiatric Institute; New York: 1996. Structured clinical interview for DSM-IV axis I disorders-patient edition.

First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JB.; Benjamin, L. Structured clinical interview for DSM-IV axis II personality disorders (SCID-II). Biometrics Research Institute, New York State Psychiatric Institute; New York: 1997.

Kaplan, NM.; Victor, RG. Kaplan's Clinical Hypertension. 10th. Lippincott, Williams, and Wilkins; Philadelphia, PA: 2010.

Kosfeld M, Neinrichs M, Zak PJ, Fischbacher U, Fehr E. Oxytocin increases trust in humans. Nature. 2005; 435:673–676. [PubMed: 15931222]

Kouri EM, Lukas SE, Pope HG Jr, Oliva PS. Increased aggressive responding in male volunteers following the administration of gradually increasing doses of testosterone cypionate. Drug Alcohol Depend. 1995; 40:73–79. [PubMed: 8746927]

Lane, SD.; Cherek, DR. Biological and behavioral investigation of aggression and impulsivity. The science, treatment and prevention of antisocial behavior: applications to the criminal justice system. In: Fishbein, DH., editor. Civic Research Institute; Kingston, NJ: 2000. p. 5.1-5.21.

Lane SD, Kjome KL, Moeller FG. Neuropsychiatry of aggression. Neurol Clin. Feb; 2011 29(1):49–64. vii. [PubMed: 21172570]

Latalova K, Prasko J, Kamaradova D, Sedlackova J, Ociskova M. Comorbidity bipolar disorder and personality disorders. Neuro Endocrinol. Lett;2013 34(1):1–8.

Mahmut MK, Menictas C, Stevenson RJ, Homewood J. Validating the factor structure of the Self-Report Psychopathy scale in a community sample. Psychol Assess. 2011; 23:670–768. [PubMed: 21517188]

Moeller FG, Dougherty DM, Rustin T, Swann AC, Allen TJ, Shah N, Cherek DR. Antisocial personality disorder and aggression in recently abstinent cocaine dependent subjects. Drug Alcohol Depend. Mar 14; 1997 44(2-3):175–82. [PubMed: 9088790]

Moeller FG, Dougherty DM, Lane SD, Steinberg JL, Cherek DR. Antisocial personality disorder and alcohol-induced aggression. Alcohol: Clin Exp Res. Dec; 1998 22(9):1898–902. [PubMed: 9884131]

Newman WJ. Psychopharmacologic management of aggression. Psychiatr Clin North Am. Dec; 2012 35(4):957–72. [PubMed: 23107573]

Nouvion SO, Cherek DR, Lane SD, Tcheremissine OV, Lieving LM. Human proactive aggression: Association with personality disorders and psychopathy. Aggress Behav. 2007; 33:552–562. [PubMed: 17654689]

Paulhus, DL.; Neuman, CF.; Hare, RD. Manual for the Self-Report Psychopathy Scale. Multi-Health Systems; Toronto: 2010.

Petersson M, Alster P, Lundeberg T, Uvnäs-Moberg K. Oxytocin causes a long-term decrease of blood pressure in female and male rats. Physiol Behav. 1996; 60:1311–1315. [PubMed: 8916187]

Rilling JK, DeMarco AC, Hackett PD, Thompson R, Ditzen B, Patel R, Pagnoni G. Effects of intranasal oxytocin and vasopressin on cooperative behavior and associated brain activity in men. Psychoneuroendocrinology. 2012; 37(4):447–461. [PubMed: 21840129]

Ruiz MA, Pincus AL, Schinka JA. Externalizing pathology and the five-factor model: a meta-analysis of personality traits associated with antisocial personality disorder, substance use disorder, and their co-occurrence. J Pers Disord. Aug; 2008 22(4):365–88. [PubMed: 18684050]

Shahrestani S, Kemp AH, Guastella AJ. The impact of a single administration of intranasal oxytocin on the recognition of basic emotions in humans: a meta-analysis. Neuropsychopharmacology. Sep; 2013 38(10):1929–36. [PubMed: 23575742]

Tukey J. Comparing Individual Means in the Analysis of Variance. Biometrics. Jun.1949 5(2):99–114. [PubMed: 18151955]

Valliancourt T, Sunderani S. Pscyhopathy and indirect aggression: the roles of cortisol, sex, and type of psychopathy. Brain Cogn. Nov; 2011 77(2):107–175.

Zak PJ, Stanton AA, Ahmadi S. Oxytocin increases generosity in humans. PLoS One. Nov 7.2007 2(11):e1128. [PubMed: 17987115]

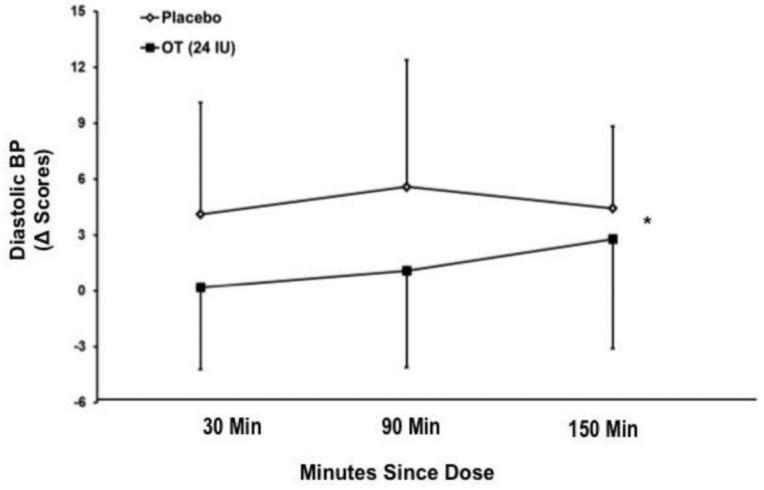

Figure 1. Diastolic BP (Δ scores) across three post-dose sessions for both doses

Presented are the Diastolic BP (Δ scores) over the course of three different post-dose time points (sessions) for both dose levels. All data are presented as mean (S.D.). * = $p<0.05$, main effect of dose. Minutes since dose: 30 Min, 90 Min, and 150 Min represent post-dose session 1, 2, and 3, respectively. All data are presented as mean (S.D.). IU = international unit.

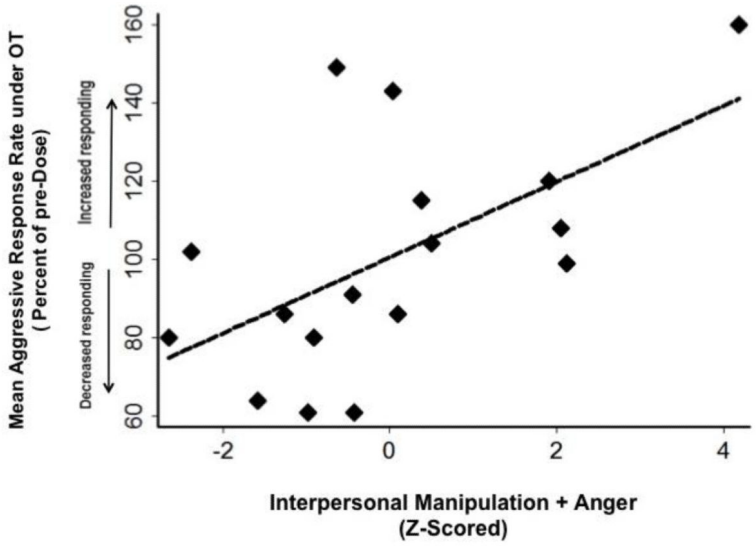

Figure 2. Scatterplot of aggressive response rates (percent of pre-dose) under OT dose and combined psychometric scores of Interpersonal Manipulation and Anger

Plotted are mean aggressive response rates under OT on the y-axis and combined subscales scores of Interpersonal Manipulation and Anger (Z-Scored) on the x-axis. Mean refers to the mean of all three post-dose sessions with aggressive responding from each post-dose session converted as a percent of the pre-dose.