Detailed Protocol
Effect of Intranasal Oxytocin on Social Cognition

I. Background and Significance

Oxytocin is a nine amino acid neuropeptide, which is produced in the paraventricular and supraoptic nuclei of the hypothalamus. It is then secreted into the peripheral circulation via the posterior pituitary gland or released into the central nervous system to act on receptors widely distributed throughout the brain. Today, synthetic oxytocin (marketed as Pitocin® and Syntocinon®) is commonly administered intravenously to induce or augment labor in pregnant women.

Traditionally, oxytocin has been examined for its role in childbirth, lactation, and maternal attachment behavior. Given recent advances in delivering oxytocin via nasal administration, oxytocin has seen an exponential growth of research examining its effects on social cognition and behavior. For example, animal research has shown that intranasal administration of oxytocin to pairs of rats increases the duration of physical contact with each other (Witt, Winslow, & Insel, 1992), whereas administration of an oxytocin-receptor antagonist in male rats is associated with reduced social exploration of a con-specific male rat (Lukas et al., 2011). In human populations, studies have shown that oxytocin increases trust during a money transfer game (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005), improves memory for positive social information (Guastella, Mitchell, & Mathews, 2008), and attenuates amygdala reactivity to emotional stimuli (Domes et al., 2007).

These findings have major treatment implications for psychiatric disorders in which social cognitive deficits are prominent, such as autism, schizophrenia, and social anxiety disorder. Indeed, early evidence indicates that intranasal oxytocin may have therapeutic potential in these psychiatric populations. Studies have shown that oxytocin improves emotion recognition ability in autistic youth (Guastella et al., 2010), and patients with schizophrenia (Averbeck, Bobin, Evans, & Shergill, 2011). A recent meta-analysis found that intranasal oxytocin may enhance the recognition of facial expressions of emotion (van Ijzendoorn & Bakermans-Kranenburg, 2012). Furthermore, several experiments have now investigated the effect of intranasal oxytocin in patients with social anxiety disorder (SAD). One study examined the impact of administering oxytocin as an adjunct to exposure therapy for SAD and found that patients treated with oxytocin showed a positive effect in increasing positive evaluations of appearance and speech performance (Guastella, Howard, Dadds, Mitchell, & Carson, 2009). Another study demonstrated that OT modulates amygdala reactivity in patients with generalized SAD (Labuschagne et al., 2010), which may reflect an important mechanism of treatment. These studies are consistent with previous research in healthy individuals, which show that oxytocin may have therapeutic potential given its anxiolytic and pro-social effects.

Although the use of intranasal oxytocin has direct implications for the treatment of body dysmorphic disorder (BDD), no studies have yet investigated the effects of oxytocin in

this population. BDD is a highly distressing and debilitating psychiatric disorder that is characterized by an excessive preoccupation with appearance concerns about a perceived physical flaw (American Psychiatric Association, 2013). It is associated with significant functional impairment and poor quality of life (Phillips, Menard, Fay, & Pagano, 2005). Although research has tested some pharmacologic and psychological treatments for these disorders, evidence suggests that there is still considerable room for improvement, as most patients across clinical trials only improve by 30-50% in symptom severity (Veale et al., 1996; Wilhelm, Phillips, Fama, Greenberg, & Steketee, 2011).

Given that oxytocin is involved in the regulation of a variety of dimensions of social cognition and behavior, including emotion recognition and social information processing, there are direct implications regarding its role in the development of such deficits among individuals BDD in particular. Individuals with BDD display deficits in social cognition, as they are convinced that their appearance is flawed, and that people may be staring and laughing at their physical flaws. Experiments have shown that BDD is associated with selective attentional biases to imagined flaws in one's own face and to corresponding regions in unfamiliar others' faces (e.g., Grocholewski, Kleim, & Heinrichs, 2012). Moreover, research has shown that individuals with BDD incorrectly interpret faces showing neutral emotional expressions as contemptuous and angry (Buhlmann, Etcoff, & Wilhelm, 2006). Despite these obvious problems with regard to social cognition, no studies have yet examined the effect of oxytocin in BDD. The current study therefore aims to investigate the effect of oxytocin administration on modifying core social cognitive impairments associated with BDD.This study has major public health significance, given the prevalence of OC spectrum disorders and the need to investigate more parsimonious treatments.

II. Specific Aims

Primary Aim 1: To examine differential effects of oxytocin on social cognitive deficits during an emotion recognition task and trust game by diagnosis.

Hypothesis 1a: Individuals with BDD will exhibit poor performance on the emotion recognition task and trust game, compared to healthy controls.

Hypothesis 1b: The effects of oxytocin vs. placebo on the emotion recognition task and trust game will be greater for individuals with BDD than for healthy controls.

Secondary Aim 2: To examine the effect of oxytocin on cognitive biases (attentional and interpretive biases) associated with BDD.

Hypothesis 2a: Individuals with BDD (compared to healthy controls) will exhibit the following cognitive biases: attentional bias (difficulty disengaging from threat cues, as measured by a spatial cueing paradigm), and negative interpretive bias (as measured by an interpretation questionnaire).

Hypothesis 2b: For individuals with BDD (compared to healthy controls), oxytocin will attenuate these biases compared to placebo.

Exploratory Aim: To examine whether symptom severity, social anxiety, mood, attachment style, and rejection sensitivity moderate the effects of oxytocin.

III. Subject Selection

Inclusion Criteria for BDD Groups:

1. Treatment-seeking adult males and females ≥ 18 years of age
2. Meets DSM-IV criteria for principal BDD as determined by Structured Clinical Interview for DSM-IV (SCID) diagnostic interview
3. For females only: must be using low-dose hormonal contraceptives, as defined by <50 mcg daily dose of ethinyl estradiol. Female participants will bring medication labeling to the screening visit so study staff may verify acceptable drug composition.

Exclusion Criteria for BDD Groups:

1. Current diagnosis of schizophrenia, psychotic disorder, bipolar disorder, substance abuse or substance dependence. All other Axis I comorbidities will be permitted to foster the accrual of a clinically relevant sample.
2. Significant nasal pathology (e.g., atrophic rhinitis, history of hypophysectomy, recurrent nosebleeds)
3. Smokers who smoke ≥ 15 cigarettes daily
4. Serious medical illnesses (including untreated thyroid disease, diabetes, cardiovascular disease, and seizures, as assessed by medical history). Individuals who are taking levothyroxine or who report a history of thyroid disease will be given a blood test to determine thyroid hormone levels and eligibility for the study.
5. Active homicidal or suicidal ideation
6. Steroid or hormone use (except low-dose contraceptives for females, which is allowed)
7. For females only: positive urine pregnancy test and use of high dose contraceptives (low dose contraceptives will be allowed due to stability of hormone levels during active phase)

Inclusion Criteria for Control Participants:

1. Adult males and females ≥ 18 years of age
2. No current DSM-IV Axis I diagnosis, as determined by SCID
3. For females only: must be using low-dose hormonal contraceptives, as defined by <50 mcg daily dose of ethinyl estradiol. Female participants will bring medication labeling to the screening visit so study staff may verify acceptable drug composition.

Exclusion Criteria for Control Participants:

1. Current diagnosis of any DSM-IV Axis I disorder
2. Significant nasal pathology (e.g., atrophic rhinitis, history of hypophysectomy, recurrent nosebleeds)

3. Smokers who smoke ≥ 15 cigarettes daily
4. Serious medical illnesses (including untreated thyroid disease, diabetes, cardiovascular disease, and seizures, as assessed by medical history). Individuals who are taking levothyroxine or who report a history of thyroid disease will be given a blood test to determine thyroid hormone levels and eligibility for the study.
5. Active homicidal or suicidal ideation
6. Steroid or hormone use (except low-dose contraceptives for females, which is allowed)
7. For females only: positive urine pregnancy test and use of high dose contraceptives (low dose contraceptives will be allowed due to stability of hormone levels during active phase)

Source of Subjects and Recruitment Methods:
We will enroll a maximum of 50 participants to obtain a sample of 40 participants (20 BDD, and 20 healthy volunteers) in the study. Potential participants will be recruited to the MGH OCD and Related Disorders Program through flyers and general clinic advertisements in the General Recruitment Protocol (Protocol #2009P-002227), and databases of research volunteers, such as the Volunteer Research Registry (Protocol #2010P-002496). These referrals are presented in a weekly meeting to the clinicians. In the intake phone call, the coordinator asks the patient if he/she is willing to hear about a research study. If the patient meets initial eligibility criteria (e.g., has BDD) and agrees to be informed about a research study, then our research assistant will call the patient to conduct a BDD-specific phone screen, which has already been approved through the General Recruitment Protocol (Protocol # 2009P-002227). Given our high number of referrals, we do not anticipate any problems recruiting 20 participants with BDD for the current project. In the unlikely event that we have difficulty recruiting, we can collaborate with our colleagues in the Center for Anxiety and Traumatic Stress Disorders Program and Eating Disorders Clinic and Research Program, which receive a number of referrals for BDD. We will never identify potential participants through medical records, and we will never contact potential participants without their permission to be contacted. If a medical colleague identifies one of his or her patients as potentially appropriate for this study, we will request that the colleague encourage the patient to contact a member of the study staff directly. Alternatively, the colleague may ask the patient to give permission to be contacted over the phone by a member of the study staff. Additionally, the OCD and Related Disorders Program has funds available to pay for advertisements if necessary. Our clinic has had recruitment success by posting flyers at mental health private practices, primary care offices, and on the MBTA. Healthy volunteers will be recruited through approved online advertisements through Craigslist and the Partners Clinical Trials website. Healthy subjects will be matched by age and sex, such that group means for age and the number of females will not be significantly different between all 3 study groups.

IV. Subject Enrollment

Methods of Enrollment:

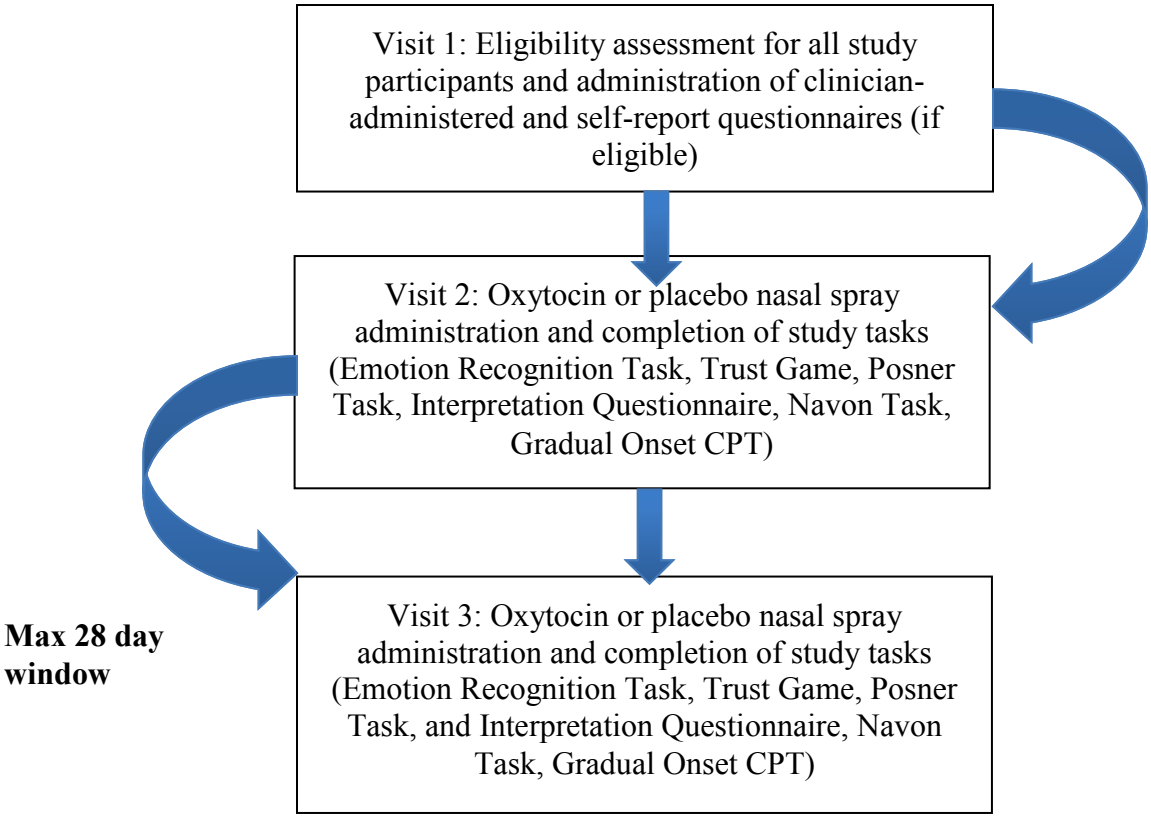
Potential participants who are eligible for the study after the phone screening procedure (described above) will be invited to the MGH OCD and Related Disorders Program for an initial evaluation to determine their eligibility for the study. After the consenting process, an advanced doctoral student or doctoral level member of the study staff will provide a diagnostic assessment using the SCID-I/P, as well as thoroughly assess each inclusion and exclusion criteria using direct questioning. Females will provide a urine pregnancy test to ensure that they are not pregnant. Females will also confirm the formulation of their contraception at the time of their screening visit. Any participant taking psychotropic medications will be allowed to participate in the study, and will be asked to keep taking their medication as usual during the study. If an enrolled BDD or healthy participant has already completed a SCID and the same clinician-administered and self-report questionnaires within the past six months as part of a different study within the OCD and Related Disorders Program, they will be able to consent to give us permission to access data from their previous screening assessment.

Procedures for Obtaining Informed Consent:
An advanced doctoral student or a doctoral level member of the study staff will obtain written informed consent, and will thoroughly review the consent form with the potential participant. If an advanced doctoral student obtains consent, a licensed physician investigator will be available to speak with the subject during the consent process. Subjects who are consented by advanced doctoral students will be offered the option of speaking with a physician Investigator during the consent process and this will be recorded in research records. During the consenting process, potential participants will be apprised of the voluntary nature of their participation in the study and that they can withdraw at any point in the study without penalty. Specifically, we will reassure all potential participants that refusal to participate will in no way influence their care or affiliation with the Clinics at the Massachusetts General Hospital or any other Harvard Medical School affiliated hospital. Potential participants will be informed that the study will examine how oxytocin impacts their performance on different social cognitive tasks, but they will not be informed as to the exact study hypotheses (e.g., how oxytocin's effects on social and cognitive functioning may relate to their BDD symptoms). It will be necessary to use incomplete disclosure at the outset of the study to ensure maximum internal validity of study results. Potential participants will also be given as much time as needed to consider participation, and will be given an opportunity to ask questions about the study prior to signing the consent form. We will obtain written informed signed consent through the use of a PHRC approved written consent from all participants before they enter into the study and start study procedures. After signing the consent form, participants will be given a copy of the consent, and the original copy will be filed in a locked file separate from study data in a research office.

Treatment Assignment Procedures:
Given the cross-over design, all participants will receive an oxytocin and placebo nasal spray at two separate visits. The MGH Research Pharmacy will randomize the order of nasal sprays that will be given to participants, and will thus be un-blinded of assigned drug condition for participants' study visits. All other study staff, as well as participants themselves, will be blind to drug condition.

V. Study Procedures

Overview of Study Procedure:
The study will consist of 3 study visits in total. The first visit will involve the diagnostic assessment and medical screen to determine eligibility for the study, in addition to the administration of clinician-administered and self-report questionnaires. This visit will take approximately 2.5 hours to complete. If participants are eligible, they will be asked to return to the clinic for two additional study visits, which will be identical in procedure and take approximately 2 hours each to complete. Female participants must complete Visits 2 and 3 during the active phase of their contraceptive medication (e.g. not during their menses); female subjects using multiphasic contraceptives must be on the same dose of ethinyl estradiol for both Visit 2 and 3. Participants will be instructed to avoid alcohol, caffeine, and nicotine for 24 hours prior to Visits 2 and 3. These visits will involve the administration of both an oxytocin and placebo nasal spray, in randomized order, and the completion of various social cognition tasks. They will be separated by a one-week washout period (**maximum 28 day** window period). The study design and procedures are represented in the following schematic:

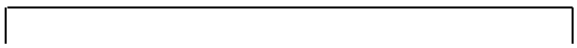


Diagnostic Assessment and Medical Screen:
After obtaining informed consent, participants will be administered the Structured Clinical Interview for DSM-IV (SCID-I/P; First, Spitzer, Gibbon, & Williams, 2002) to determine diagnostic eligibility. The SCID allows the investigator to assess all diagnostic inclusion and exclusion criteria. Participants who are recruited for the healthy control

group will be given the SCID-I/P to confirm the absence of Axis I psychopathology. Participants who meet the diagnostic inclusion and exclusion criteria will be given a medical screen consisting of a history and physical examination (H&P) by a study nurse or physician to determine the participant's eligibility and safety for the study. In addition, a urine pregnancy test will be given to females during this visit, as well as at the beginning of Visits 2 and 3 to ensure continued eligibility.

Investigational Agent (dose, method, schedule of administration, dose modifications):

Oxytocin (OT) is a nine-amino-acid peptide, or nonapeptide, which is produced in the paraventricular and supraoptic nuclei of the hypothalamus and projected to many brain regions, particularly within the limbic system. The empirical formula of OT is $C_{43}H_{66}N_{12}O_{12}S_2$ (molecular weight 1007.19). The structural formula of OT is as follows:



H-Cys-Tyr-Ile-Glu (NH2)- Asp(NH2)-Cys-Pro-Leu-Gly-NH2
1 2 3 4 5 6 7 8 9

Synthetic oxytocin (e.g., Syntocinon® or Pitocin®) is typically administered intravenously in neonatal settings to induce labor. It is widely distributed throughout the extracellular fluid and causes uterine response almost immediately. Its removal from the blood is facilitated by the kidney and liver, and has a plasma half-life of approximately 1 to 6 minutes (per Pitocin package insert). Intranasal delivery of oxytocin enables actions within the brain and produces pro-social behavioral effects in humans.

The oxytocin and placebo nasal sprays to be used in the current investigation will be the commercially available product known as Syntocinon®, which is widely used in studies investigating intranasal oxytocin but is currently not available in the U.S. Therefore, the nasal sprays will be provided by Pharmaworld in Switzerland (http://www.pharmaworld.com), and manufactured by Novartis. The nasal sprays will consist of 24 IU of oxytocin (with 4 IU per puff), and will be dispensed in 5 ml metered-dose nasal spray bottles. Oxytocin nasal sprays will be shipped in boxes with identical placebo nasal sprays (containing all of the same ingredients as the oxytocin sprays but without the active oxytocin ingredient), and will require cooling at 2-8ºC during shipping. The MGH Research Pharmacy will provide drug accountability and storage services. Upon arrival at MGH, the MGH Research Pharmacy will ensure that the labels on the bottles are identical in order to protect the blind. Per Syntocinon® package insert, the product should be stored in a refrigerator between 2-8ºC. Nasal sprays for each participant will be ordered by a written prescription to the MGH Research Pharmacy by the study physician or nurse practitioner on a patient-by-patient basis.

Oxytocin and Placebo Administration:
Oxytocin and placebo administration will occur at Visit 2 and Visit 3. 24 international units (IU) of oxytocin and placebo will be administered in a double-blind manner to subjects. This represents the most commonly used dosage in studies involving

intranasal administration of oxytocin (MacDonald et al., 2011). The nasal sprays (Syntocinon® nasal spray, 40 IU/ml) will be purchased from Pharmaworld and manufactured by Novartis in Switzerland under an Investigational New Drug (IND) application from the Food and Drug Administration. The principal investigator, Angela Fang, Ph.D., and study physician, Elizabeth A. Lawson, M.D., both have experience obtaining an IND for intranasal oxytocin, and are familiar with the sponsor-investigator responsibilities associated with maintaining the IND. As the physician on the IND, Dr. Lawson will provide medical oversight regarding reported adverse events, as well as risk coverage for subjects enrolled in the study. Subjects will follow a standardized protocol for self-administering the metered dose nasal sprays (see attached administration protocol) with three sprays per nostril (4 IU oxytocin per spray). A study nurse at the MGH Clinical Research Center, who will be blind to the subject's assigned drug condition, will be present for drug administration. Only the MGH Research Pharmacy will be un-blinded to drug condition during the study, as they will be responsible for treatment assignment at each study visit.

Clinician-Administered Measures:
Structured Clinical Interview for DSM-IV-TR (SCID; First, Spitzer, Gibbon, & Williams, 2002): The SCID is a clinician-administered, semi-structured interview that assesses current Axis I disorders. Given that the SCID has not yet been updated to reflect DSM-5 diagnostic criteria, we will assess diagnoses based on DSM-IV criteria. The SCID will be administered during the screening visit to diagnose participants, characterize the sample, and screen for other eligibility criteria.

Demographics and Eligibility Form: This clinician-administered measure will be developed specifically for the purposes of this study to assess demographic information, and to document other inclusion and exclusion criteria (e.g., medical illnesses, nasal pathology, suicidal/homicidal ideation, cigarette use, concurrent medications, steroid use, pregnancy test results).

Yale-Brown Obsessive-Compulsive Scale modified for BDD (BDD-YBOCS; Phillips, Hollander, Rasmussen, & Aronowitz, 1997): The BDD-YBOCS is a 12-item clinician-administered severity rating scale for BDD. It will be administered during the screening visit. (BDD participants only)

Brown Assessment of Beliefs Scale (BABS; Eisen et al., 1998): The BABS is a 7-item clinician-administered scale to assess degree of insight and conviction of beliefs. It will be administered during the screening visit to assess degree of delusionality. (BDD participants only)

Self-Report Questionnaires:
Body Dysmorphic Disorder Symptom Scale (BDD-SS; Wilhelm, unpublished): The BDD-SS revised is a self-report measure that assesses severity of specific BDD symptom domains. The scale organizes symptoms into conceptually similar clusters, such as checking and comparing, fixing and correcting, weight and shape concerns, skin picking

and hair pulling, avoiding and hiding, seeking cosmetic surgery, and beliefs about appearance.

Liebowitz Social Anxiety Scale- Self-Report (LSAS; Liebowitz, 1987): The LSAS is a 24-item measure that assesses fear and avoidance of social situations in the past week. It is widely used in treatment studies for SAD. The LSAS has been validated in clinical samples and has high internal consistency (α = .82-.92) (Heimberg et al., 1999).

Brief Fear of Negative Evaluation Scale (BFNE; Leary, 1983): The BFNE is an abbreviated 12-item self-report questionnaire adapted from the original Fear of Negative Evaluation Scale (Watson & Friend, 1969), which measures apprehension about others' evaluations, expectation for negative evaluation, avoidance of evaluative situations, and distress associated with negative evaluation.

Interpersonal Sensitivity Measure (IPSM; Boyce & Parker, 1989): The original IPSM is a 36-item self-report measure to assess sensitivity to rejection. It has been demonstrated to have good internal consistency (Boyce & Parker, 1989; Harb, Heimberg, Fresco, Schneier, & Liebowitz, 2002).

Experience in Close Relationships Inventory (ECR; Brennan et al., 1998): The ECR is a 36-item self-report questionnaire that measures attachment anxiety and avoidance in adults. It yields two subscales reflecting attachment anxiety (anxiety about being rejected or abandoned) and attachment avoidance (discomfort with closeness and intimacy).

Depression Anxiety Stress Scale-21 (DASS; Lovibond & Lovibond, 1995): The DASS is a shortened, 21-item version of the original DASS self-report questionnaire designed to measure dimensional aspects of depression, anxiety, and stress.

Positive and Negative Affect Scales (PANAS; Watson, Clark, & Tellegen, 1988): The PANAS is a 20-item self-report measure of positive and negative affect.

Mini-Markers Scale (MM; Saucier, 1994): The Mini-Markers Scale is a 40-item self-report measure of the five factor model personality factors: extraversion, agreeableness, conscientiousness, emotional stability, and openness. It asks participants to rate how accurately each item describes themselves on a 1-9 point Likert scale ranging from "extremely inaccurate" to "extremely accurate."

Adverse Events Form: This self-report form will be administered at Visits 2 and 3 after nasal spray administration to assess for any adverse events. Participants will be asked to report on a symptom checklist whether they experienced a negative reaction to the oxytocin and placebo nasal sprays. If participants endorse 'yes' on any item, a study clinician or nurse will follow up and ask them whether the symptom resolves by the end of the study visit.

Assessment of Blind Form: This questionnaire will be given at Visits 2 and 3 after nasal spray administration to assess for participants' expectancies regarding the drug they received. Participants will be asked which nasal spray they believe they received (oxytocin or placebo), to rate their degree of certainty, and to describe their reasons why.

Tasks:

The following tasks will be administered at each study visit approximately 45 minutes after drug administration. The order of tasks will be the same within each participant in the study between Visit 2 and Visit 3 in order to minimize variance for the within-subject analysis and isolate the effect of the drug. However, the order of tasks will be counterbalanced between participants in the study, to account for possible carry-over effects.

Emotion Recognition Task (ERT; Buhlmann, Etcoff, & Wilhelm, 2006): In this task, subjects will view 24 facial photographs (Ekman & Friesen, 1975), each expressing a different emotion (anger, disgust, neutral, surprise). The photographs will be drawn from the new facial affect collection (http://www.paulekman.com/). In this computerized, self-administered task, each emotion will be presented 6 times, and each facial photograph will be followed by either a *self-referent* scenario ("Imagine this bank teller is looking in *your* direction") or *other-referent* scenario ("Imagine this bank teller is looking in *your friend's* direction"). Participants will identify the emotion for each scenario. Total scores for correctly identifying the emotion range from 0-24 for each questionnaire (self- vs. other-referent), whereas for each emotion subcategory, scores range from 0-6. Moreover, for each scenario, participants will rate whether the other person's emotional expression was caused by the participant (self-attributional, score=0) or by the situation or some other factor (other-attributional, score=1). Total scores for attribution range from 0-24 for each questionnaire (self- vs. other-referent), with higher scores reflecting other-referent attribution.

Interpretation Questionnaire (Buhlmann et al., 2002; 2006): This questionnaire consists of 33 ambiguous scenarios (11 BDD-related, 11 social, and 11 general scenarios), with each scenario involving a short description followed by three possible thoughts. Participants will be asked to rate the likelihood of each thought coming to mind on a scale from 0 (very unlikely) to 4 (very likely).

Posner Task (Posner, 1980; Posner, Snyder, & Davidson, 1980): The Posner Task is a spatial cueing paradigm that measures attentional engagement toward and disengagement from certain visual cues. The stimuli for this task will be modified to include a set of disgust, happy, and neutral faces. The task will consist of 360 trials. During each trial, the participant will see a fixation cross. On each trial, a face (disgust, happy, or neutral) will appear within either the top or bottom half of the screen (the other half of the screen will remain blank) and then disappear. Then, a probe (the letter "E" or "F") will appear in the top or bottom half of the screen. The participant will be instructed to identify the letter as quickly and accurately as possible by clicking the left or right mouse button (left for "E", right for "F"). Upon responding, the next trial will commence.

For valid trials, the probe will appear in the position previously occupied by the face stimulus, whereas for invalid trials, the probe will appear in the empty half of the screen. Response latencies for valid and invalid trials will reflect the participant's attentional engagement towards threat and disengagement from threat, respectively, and will be used to calculate attentional bias scores for threat cues.

Trust Game: The participant will be told that he will be playing the Trust Game with another player in a different room, and that both players will be allocated a sum of 10 game dollars to start the game. The participant will be told that he will take the role of Player 1. The instructions for the game will be as follows: Player 1 will have the opportunity to transfer all, some, or none of his 10 game dollars to Player 2, the sum given by Player 1 will be tripled, and Player 2 will have to choose to return some, all, or none of his game dollars to Player 1. The role of Player 2 will be played by a member of the study staff. The participant will play the Trust Game twice. The amount of money given by the participant is recorded and represents a measure of "trust". Three game dollars will equal $1. The subject will be paid the value of this amount in dollars.

Social Perception Tasks: Testmybrain.org: Data for the following tests will be collected through testmybrain.org (approved under Harvard FAS IRB protocol F15795). Before starting the tests, the experimenter will be asked to enter a randomly generated ID code for the participant. The participant will then complete the measures described below. No uniquely identifying information will be collected and stored on testmybrain.org for the participant. Instead, ID codes will be kept along with identifying participant information on password-protected computers accessible only by approved research staff. At the end of the study, participant codes that are retained in TestMyBrain databases will be destroyed along with any other study-specific information or information linking a particular testing session with the external research study. **Data stripped of both participant and study-specific information will then be included in the large data repository that TestMyBrain uses to understand and interpret test scores of other participants and may also be submitted to a publicly available data repository for the benefit of the broader academic and research community.** Publicly available datasets will not include any information that can be used to identify the participant, the study, the researcher, or the institution where the data was collected. **Testmybrain.org will not be used for any purpose in our study other than collection and storage of data, and there is no other involvement of this website.**

Navon Task: The Navon Task is a measure of attention and inhibition, which will be used to examine how oxytocin affects global and local processing of non-social stimuli. Participants will be asked to view big letters that are made up of smaller letters (e.g., an H that is made up of little S's). They will be asked to judge the letter being depicted by the overall letter shape or the smaller letter shape, as quickly as possible.

Gradual Onset Continuous Performance Test: This task is a measure of cognitive control and responsive inhibition. Participants will be asked to attend to images that gradually transition from one image to the next. They will be asked to press a button when they see a new street image (most images), and not to press a button when they

see a mountain image (occurs much less frequently). This task will allow us to examine how oxytocin affects inhibitory control.

VI. Biostatistical Analysis

Prior to analysis, all major variables will be screened for inconsistent or abnormal values, and continuous measures assessed for skewness and outliers. Variable distributions will be examined and transformations made when distributions are skewed or otherwise violate analytic assumptions. Linear regression models will be used, and in all models, the effect of diagnosis will be based not on the global (type III) effect, but on the specific pair-wise comparison of interest: BDD vs. Healthy Controls. Analyses will be conducted using SAS v9.4 (SAS Institute, Cary, NC), and all models will employ a two-sided alpha=0.05 to determine significance.

Aim 1 Analyses:
The primary outcomes will be the Emotion Recognition Task total score and the Trust Game "back transfer" amount. Two sets of outcome scores will be obtained for each subject - one during placebo and the other during oxytocin administration. To test Hypothesis 1a, we will regress placebo outcome scores against diagnosis. To test Hypothesis 1b, we will regress oxytocin outcome scores against diagnosis, and will control for the placebo outcome score. If we find significant differences in oxytocin Emotion Recognition Task total score by diagnosis, we will further examine the 3 Emotion Recognition Task valence categories (positive, negative, neutral) as exploratory outcomes.

Aim 2 Analyses:
Secondary outcomes include the Posner Task difference score for disengagement response latencies between disgust vs. neutral faces, and the Interpretation Questionnaire total score. Mirroring the analyses for the primary aim, we will test Hypothesis 2a by regressing the placebo secondary outcome scores against diagnosis, and will test Hypothesis 2b by regressing the oxytocin secondary outcome scores against diagnosis, controlling for the placebo secondary outcome scores.

Exploratory Analyses:
Exploratory moderators include the BDD-YBOCS total score, YBOCS total score, LSAS total score, BFNE total score, ECR Anxiety subscale mean, ECR Avoidance subscale mean, and IPSM total score. To test the moderation effects, we will enter each moderator (one at a time) into each of the aforementioned linear regression models along with a covariate representing the interaction between the moderator and diagnosis (the term of interest). We will examine moderation of each pair-wise comparison separately.

For all analyses, we will include concomitant medication use as a covariate, in order to control for the effect of concomitant medications on study results. We will also compare participants who are taking psychotropic medications from participants who are not, on

demographic and clinical variables, to ensure there are no systematic differences between these groups.

Power and Sample Size:
Given the novelty of our approach, no background data on the effects of oxytocin in BDD exist to inform the power calculation. Therefore, the proposed sample size of 40 participants (20 per group) was chosen based on feasibility. With 20 participants per group and a two-sided alpha=0.05, for our primary pair-wise comparison (BDD vs. healthy controls) of the mean within-subject difference (oxytocin vs. placebo) in Emotion Recognition Task total score and Trust Game "back transfer" amount, we will have 81% power to detect a moderate effect size of f=0.23.

VII. Risks and Discomforts

Oxytocin-Related Risks and Side Effects:
Between 1990 and 2010, there have been 38 controlled studies involving intranasal delivery of oxytocin (MacDonald et al., 2011). A total of 1,529 participants have received intranasal oxytocin or placebo, and nine studies have included participants (N=182) who had a developmental, medical, or mental health disorder. The dosage of oxytocin has typically been a single dose ranging from 20 international units (IU) to 40 IU. Out of the 1,529 participants who have received intranasal oxytocin or placebo, 279 (18%) reported mild side-effects (MacDonald et al., 2011). The most common side-effect was a feeling of calmness, but this did not differ between those who received oxytocin or placebo. A recent review of studies using intranasal oxytocin supported the short-term use of oxytocin, demonstrating that oxytocin produced minimal side-effects, no detectable differences in side-effects between oxytocin or placebo recipients, no subjective changes in recipients, and is equally safe to use with vulnerable populations as with healthy adults (MacDonald et al., 2011). The proposed study intends to use a single 24 IU dose of intranasal oxytocin, which has been the most commonly used dose in previous trials (25 out of 38 studies).

Potential risks associated with intranasal oxytocin include headaches, nausea, and allergic dermatitis (≥ 1/10,000, <1/1,000), and uterine contractions (< 1/10,000), per Novartis Basic Prescribing Information for Syntocinon®. Additional sources of discomfort may include lightheadedness, nasal irritation, or dry mouth/throat, although these appear to be mild (MacDonald et al., 2011). Participants with any serious adverse events will be immediately withdrawn from the study. The half-life of oxytocin is approximately three minutes when administered intravenously, therefore, it will not remain in the system for very long.

Regarding the use of TestMyBrain.org, the following steps will minimize risk to subjects:

(1) Identifying Information: TestMyBrain does not collect any uniquely identifying information about the participant, including birth date or IP addresses. A participant will only be linked to his/her data through the participant codes generated by the external researcher and the participant will not be identifiable based solely on information in TestMyBrain databases.

(2) Data Transfer between Client (Browser) and Server: TestMyBrain uses SSL (secure sockets layers) encryption to protect any information that is being transferred between a browser and server and all study-specific links will use secure communications protocols incorporating SSL (https).

(3) Database and Web Hosting: All data is stored through TestMyBrain.org in custom MySQL databases provided by the host and managed by TestMyBrain investigators. TestMyBrain is currently hosted through Rackspace, which offers added customer support and security benefits http://www.rackspace.com/. Their comprehensive privacy policy insures that they will not have access to any of the data that goes through TestMyBrain without permission or unless required by law: http://www.rackspace.com/information/legal/privacystatement. Rackspace offers an automatic backup system with nightly updates.

(4) Monitoring and Quality Assurance: TestMyBrain.org has been in operation since 2008, with numerous collaborations resulting in a dozen peer-reviewed papers and over 900,000 participants. No complaints or incidents have been reported that would indicate a privacy, security, or personal risk to participants.

(5) Protection from Malicious Attack: The TestMyBrain system is implemented as a virtual Linux host, so the primary danger from malware is malicious SQL injection attacks. To guard against this, all entered data are sanitized before being included in any SQL updates.

(6) Transmission of Data: Participant test data and codes will be transmitted directly from the TestMyBrain.org database to the external researcher using either secure http file transfer or secure SQL connection protocol.

(7) Storage of Data: Once the study is complete and all data have been downloaded from TestMyBrain.org databases, participant codes that are retained in TestMyBrain databases will be destroyed along with any other study-specific information or information linking a particular testing session with the external research study.

Other Risks:
Information obtained from participants will be treated confidentially. There may be some discomfort associated with nasal spray administration. Nurses at the MGH Clinical Research Center are highly skilled in educating patients about nasal spray use and sensitive to expressions of discomfort. There may also be mild discomfort associated with responding to questions during the diagnostic assessment and answering multiple questionnaires about negative symptoms. Participants will be told that they can refuse to answer any questions that they do not want to answer, and that they can withdraw participation at any point without penalty. Participants with an emergent need for immediate psychiatric care will be referred to the Acute Psychiatry Service at MGH.

VIII. Potential Benefits

Potential Benefits to Participating Individuals:

There are no immediate benefits to the individual for participating in this study. Participants with BDD may receive feedback regarding their symptoms. In the case that participants need referrals for psychiatric treatment, we will facilitate those referrals to MGH or other appropriate facilities. Participants will be provided compensation for their time, in a pro-rated hourly amount of $15/hour, with a maximum of $100, plus any additional earnings from the Trust Game (up to $20), by the end of the study visit for completing all study procedures. In addition, participants will be compensated for parking and public transportation costs such that participants are not responsible for any costs associated with participating in the study.

Potential Benefits to Society:
Data gathered from this study may benefit other individuals with BDD in the future. To date, no studies have examined the oxytocin system in BDD. Given the mounting evidence for oxytocin's role in social and cognitive deficits in autism spectrum disorders, schizophrenia, and other disorders, it is clear that the effects of oxytocin have transdiagnostic implications. Our findings may show that a single administration of intranasal oxytocin may alter social cognitive processes thought to maintain BDD. More importantly, if study aims are achieved, we may learn how to improve treatments for BDD, and identify individuals who would be responsive to oxytocin. Thus, the current study represents a translational approach to investigating potential pathophysiological mechanisms underlying BDD, and will advance knowledge regarding the potential of a promising novel therapeutic agent for BDD.

IX. Monitoring and Quality Assurance

Data and Safety Monitoring Plan:
The study will be monitored for quality assurance and adherence to the protocol according to the following monitoring plan:

A Data Safety and Monitoring Board (DSMB) will be formed consisting of three members who are not associated with the study. The purpose of the DSMB is to: (1) review all adverse events, (2) assess the timeliness, completeness, and quality of the data collected, (3) assess the adherence to protocol requirements, especially measures taken to protect participant safety, and (4) assess the benefit/risk ratio of study procedures. The DSMB will meet once after 40 subjects have been enrolled, and will be provided with the following data prior to this meeting: (1) all adverse events reported, and (2) subject recruitment, enrollment, and dropout numbers. During the meeting, the board will review these data and have 30 days to generate a report, which reflects their opinion of whether the study should be permitted to continue and whether any changes need to be made. This report will then be submitted to the IRB. If any serious adverse events occur during the study, DSMB members will be apprised of them within 24 hours of the event and will be provided unblinded information with regard to the participants' treatment assignment and corresponding study visit. DSMB members will then provide suggestions for the progress of the study, as well as determine whether modifications to the protocol are needed.

Adverse Event Reporting Guidelines:

Definitions:

1. ***Adverse event*** means any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

2. ***Serious adverse event*** means any event temporally associated with the subject's participation in research that meets any of the following criteria:
   - results in death;
   - is life threatening (places the subject at immediate risk of death from the event as it occurred);
   - requires inpatient hospitalization or prolongation of existing hospitalization;
   - results in a persistent or significant disability/incapacity;
   - results in a congenital anomaly/birth defect; or
   - any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

3. ***Unanticipated problem involving risks to subjects or others*** means any incident, experience, information, outcome, or other problem that is *unexpected* and related to the research, and that indicates that the research places subjects or others at an increased risk of physical, psychological, economic, legal, or social harm than was previously known or recognized.

4. ***Unexpected*** means that the incident, experience, or outcome is unexpected (in terms of nature, severity or frequency) given the (a) research procedures that are described in the protocol- related documents, such as the IRB-approved research protocol and informed consent document and (b) the characteristics of the study population being studied.

5. ***Unexpected adverse event*** means any *adverse event* occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is not consistent with either: (1) the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-

approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or (2) the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

Reporting Requirements:
According to the PHRC adverse events reporting policy, PIs are required to report unanticipated problems that occur during the conduct of the study, after study completion, or after subject withdrawal or completion, to be submitted within 5 working days/7 calendar days of the date the PI first becomes aware of the problem. Specifically, reports of unanticipated problems involving risks to subjects or others are to be submitted through Insight/eIRB within 5 working days/7 calendar days of the date the PI first becomes aware of the problem.

Internal adverse events that are **unexpected** and **related/possibly related** to the research and **external** adverse events that are **serious, unexpected and related/possibly related** must be reported to the IRB within 5 working days/7 calendar days of the date the PI first becomes aware of them. Any less serious, expected (e.g., documented in the protocol), or unlikely related adverse events will be reported to the IRB as part of its yearly continuing review process.

Adverse events to be **expected** in the current study, based on Syntocinon® Basic Prescribing Information, previously published data, and from participants in the study to date, include:

- Headaches
- Nausea
- Allergic dermatitis
- Uterine contractions
- Lightheadedness
- Nasal irritation
- Dry mouth/throat
- Feeling of calmness or euphoria
- Anxiety or depression
- Feeling drowsy or sleepy
- Difficulty sitting still
- Trouble concentrating
- Tremors or shakiness

X. References

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