Title: **Effects of MDMA on responses to affective touch in individuals with a range of autistic traits** ("Effects of drugs on responses to brain and emotional processes" on the consent form)

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Detailed Protocol

Title: **Effects of MDMA on responses to affective touch in individuals with a range of autistic traits** ("Effects of drugs on responses to brain and emotional processes" on the consent form)

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Objectives: To study the effects of MDMA on responses to affective touch in individuals with a range of autistic traits

Background and Specific Aims:

Autism spectrum disorder (ASD) affects an estimated 2.47% of U.S. children and adolescents (Xu et al. 2018), leading to significant reduction in quality of life and millions of dollars in disability costs (Beuscher et al. 2014). Although medications have been used to treat individual symptoms of the disorder, there are no accepted pharmacological treatments for ASD. ASD is characterized by repetitive behaviors, communication difficulties and, importantly, social deficits. One manifestation of the social and communication deficits is a hypo-responsiveness to pleasantness of 'affective touch' (Voos et al. 2012, Kaiser et al. 2015, Cascio et al. 2012). Identifying the brain processes underlying reactivity to affective touch could provide an opportunity to elucidate the neural circuits involved in the disorder, and to develop effective new treatments.

Two classes of medication that have been proposed as potential treatments for ASD are those targeting the oxytocinergic and serotonergic systems. Several studies have examined the effects of oxytocin on ASD symptoms, but the findings have been mixed, perhaps because intranasal oxytocin does not readily enter the brain (Guastella and Hickie 2016). In one recent randomized controlled clinical trial in adults with ASD, intranasal oxytocin enhanced gaze fixation on socially relevant stimuli (Yamasue et al. 2018), and in another study plasma levels of oxytocin predicted responsiveness to treatment (Parker et al. 2017). Other studies have examined the effects of selective serotonin reuptake inhibitors (SSRIs) in the treatment of ASD but the results have been mostly unsuccessful (Autism Speaks 2009). Yet, recent evidence with rodents suggests that manipulating serotonin may enhance social behaviors. For example, in a preclinical model of ASD, direct activation of 5HT-1B neurons in the nucleus accumbens enhances social behavior (Walsh et al. 2018). Thus, there is suggestive evidence that both oxytocin and serotonin signaling may be important targets of medications for ASD, but neither system has yet led to effective treatments.

Our laboratory has conducted a series of behavioral studies with the psychostimulant drug ±3,4-methylenedioxymethamphetamine (MDMA), a drug that rapidly increases both oxytocinergic and serotonergic signaling. MDMA increases synaptic levels of serotonin, and increases plasma levels of oxytocin to a greater extent than intranasal administration of oxytocin itself (Kirkpatrick et al. 2014. Behaviorally, MDMA facilitates social behaviors, including those implicated in ASD, in both rodent models and healthy human volunteers (Kamilar-Britt and Bedi 2016), suggesting that it may have potential in the treatment of autism. Indeed, one recent study reported that MDMA reduces social anxiety in individuals with autistic traits (Danforth et al.

2018). To date, however, no controlled laboratory studies have investigated the neurobiological actions of MDMA in individuals with autistic traits, and little is known about how the drug affects behavioral indices of the social communication deficits, such as affective touch. We propose to address this gap in knowledge by testing the acute effects of MDMA, compared to placebo, on subjective, neural, and hormonal responses to affective touch in individuals with mild autistic-like traits.

Specific Aim 1: To determine the effects of MDMA on <u>subjective</u> responses to affective touch in individuals with a range of mild autistic-like traits
Our preliminary data suggest that MDMA enhances pleasantness ratings of affective touch in healthy adult volunteers (Bershad et al. 2019). Here we will extend this finding to individuals with symptoms of ASD. Adult volunteers with a range of mild autistic-like traits (N=45) as measured by the Autism Spectrum Quotient (ASQ) will attend two laboratory sessions during which they will be given placebo or 1.5mg/kg MDMA (oral). At the expected time of peak drug effect, they will complete behavioral tasks assessing responses to affective touch. We hypothesize that individuals with higher ASQ scores will rate the pleasantness of affective touch lower than those with low ASQ scores, and that MDMA will ameliorate this effect, increasing pleasantness ratings to levels similar to those of the low ASQ group without MDMA.

Specific Aim 2: To determine the effects of MDMA on <u>neural</u> responses to affective touch in individuals with a range of autistic traits.
fMRI studies indicate that individuals with autistic symptoms exhibit reduced responsiveness to affective touch in the orbitofrontal cortex (OFC) and superior temporal sulcus (STS), and individuals with diagnoses of ASD show reduced activity in these regions as well as in the bilateral insula and other regions involved in social and emotional processing (Voos et al. 2012, Kaiser et al. 2015). To understand the mechanism by which MDMA increases reactivity to affective touch, we will use functional magnetic resonance imaging to test the effects of the drug on BOLD responses to affective touch in individuals with a range of autistic traits. We hypothesize that individuals with high scores on the ASQ will exhibit reduced OFC, STS, and insular responses to affective touch, and that MDMA will enhance touch-related activity in these regions, correcting these deficits.

Specific Aim 3: To determine the mediating role of oxytocin in the effects of MDMA on responses to affective touch in individuals with a range of autistic traits
MDMA has been shown to increase plasma oxytocin, raising the possibility that oxytocin mediates the enhancement of social behavior induced by MDMA. Here we propose to assess whether the MDMA-induced rise in plasma oxytocin predicts enhanced responses to affective touch.

Methods:

Design: The study will use a 2-session within-subjects double blind design in which participants will receive MDMA or placebo in randomized order. Participants will vary in scores on the Autism Spectrum Quotient (ASQ). On each of two 4.5-hour sessions participants will first report to the Human Behavioral Pharmacology Laboratory suite for drug administration, and then they will be escorted to the MRI Research Center (MRIRC) for the fMRI scan. Subjective ratings will be obtained at regular intervals throughout the session and performance on the tasks, as well as neural measures of activation, will be obtained during the scans.

Subjects: 45 healthy volunteers (22 male, 23 female; age range 21-40 years) will participate in the experiment. Sample size was determined with a power analysis on preliminary data showing

MDMA increases pleasantness ratings of touch (d=0.44). Recruiting 45 subjects will provide greater than 80% power to detect an effect. Based on our previous rates of participants completing all four sessions after enrolling in the study, to recruit 45 subjects, we will need to consent 60 participants. Subjects will complete the Autism Spectrum Quotient (ASQ), and we will recruit individuals with a range of scores on the questionnaire, with 15 each from the 0-10 range, 10-20 range, and 20-32 range. Subjects with clinically significant ASD, as determined by our screening interviewers and the participants' responses to questions during the psychiatric screening interview will not be included in the study and will be referred for treatment. In particular, any participants who have difficulty understanding or complying with the study requirements will be ineligible. Subjects will also complete the Social Anxiety Questionnaire (Caballo et al, 2012). All participants will be recruited without regard to race, religion or ethnicity through posters, advertisements and word-of-mouth referrals. Candidates will be screened in accordance with our general screening protocol, approved by the IRB under Protocol #13681B, which includes a physical, EKG, psychiatric screening interview and detailed drug use history questionnaire. We will enroll individuals who report having used ecstasy at least 4 times but not more than 40 times, with no adverse responses. Because MDMA will be administered as part of the study, the following populations are excluded for safety reasons: Individuals with a BMI <19 or >30, or weighing under 130 lbs, as this alters dosing requirements; Individuals with high blood pressure, abnormal EKG, any medical condition requiring regular medication, or any other medical contraindication to MDMA administration as determined by our study physician; Individuals with a current (within the last year) DSM-IV Axis I diagnosis, excluding non-treatment seeking drug abuse; Individuals with a history of dependence on stimulant drugs; Women who are pregnant. Smokers smoking more than 25 cigarettes per week will also be excluded, to avoid confounding the effects of nicotine withdrawal with the effects of the study drugs/procedures, as participants will not be allowed to smoke during the sessions. The self-report questionnaires we use require fluency in English, and have not been translated and validated in other languages, thus individuals with less than a high-school education or those not fluent in English will be excluded.

Procedure

Orientation: Participants who meet criteria will first be scheduled for an orientation session. During this session, subjects will be informed that the capsules used in the study may contain a placebo, stimulant, a sedative/tranquilizer, or a cannabinoid/marijuana-like drug. This range of drug types is included to minimize expectancy effects. Participants will be given an oral description of the study procedures and the written consent form. After the experimenter reviews this information and the consent form with the subject, and answers any questions he/she may have, subjects will sign the informed consent document. Abstention from recent drug and alcohol use will verified by breathalyzer and urine drug tests. Subjects will be asked about possible claustrophobia, and they will complete the scanning questionnaire to ensure that they have no metal implants.

Study Sessions: Two 4.5-hour sessions will be conducted, separated by at least 72 hours. Please see below for a full timeline of the study sessions. On study session days, participants will arrive at 9am, and complete a urine and breath screening for recent alcohol and drug use, and a pregnancy test (for women). Participants will then complete Time 1 measures of subjective mood and drug effects, and complete these same measures periodically throughout the study (see below). Participants will ingest the capsule at 9:30am. For the next hour, while the drug is absorbed, they will be allowed to relax and watch a movie or read a book, but will not be allowed to do work. Subjects will be escorted to the MRIRC at 10:30am to undergo an fMRI scan while performing the Touch Task. The scan will last approximately 45 minutes. Participants

will then be escorted back to the lab, where they will remain, completing subjective measures of the drug effect every hour until at least 1:30pm (when we expect drug effects will end), or until the effects of the drug return to baseline (as measured by both subjective report and cardiovascular variables).

Timeline
9:00 am – Participant arrival, drug, alcohol and pregnancy testing, snack provided
9:15 am – Time 1 Measures – POMS, DEQ, VAS, Blood Pressure, HR
9:30 am – Administration of capsule
10:00 am – Time 2 Measures - POMS, DEQ, VAS, Blood Pressure, HR
10:30 am – Time 3 Measures - POMS, DEQ, VAS, Blood Pressure, HR
11:00 am – fMRI scan with Touch Task
11:45 am - end of scan
12:30 pm – Time 4 Measures – POMS, DEQ, VAS, Blood Pressure, HR
1:00 pm - Time 5 Measures – POMS, DEQ, VAS, Blood Pressure, HR
1:30 pm - Participant leaves lab

End of study phone call: After the subject's last session we will conduct an end-of-study interview by phone. Participants will be asked to indicate how much they liked each study drug and how much they would want to take each drug again. Participants will also be asked to report which type or types of drugs they think they received at each session. Finally, participants will be told the study hypotheses, methods and the types of drugs that they received, and will be given a chance to ask any final questions.

Drugs
MDMA (1.5mg/kg) will be placed in opaque size 00 capsules with lactose (USP) filler. Placebo capsules will contain only lactose. These doses have previously been safely administered to healthy human participants (Mayo et al., 2013, 2014, Kirkpatrick et al. 2011). MDMA will be obtained in powder form from Organix Inc, MA under Investigational New Drug (IND) license # 76,536.

Capsule contents will be prepared and used within eight weeks of encapsulation. We have used similar doses of MDMA in previous studies without adverse reactions (Wardle and de Wit, 2014, Bedi et al, 2009). Participants will be closely monitored during sessions and a physician will be on call during and after sessions.

Measures: Measures will include measures of emotional traits, which are taken one time at orientation, and subjective measures of mood state, drug effects and responses to stimuli, fMRI of brain activity, and physiological assessment of blood pressure, heart rate, and salivary oxytocin.

Measures Taken During Screening Only
1. Autism Spectrum Quotient questionnaire (Baron-Cohen et al. 2001) is a 50-item survey designed to assess five dimensions of autism spectrum traits. Scores range from 0-50, with a score of 32+ likely to indicate clinically significant symptoms. We will recruit individuals with a range of scores on the questionnaire, with 12-14 each from the 0-10 range, 10-20 range, and 20-32 range.
2. Social Anxiety Questionnaire (Caballo et al, 2012). This standardized questionnaire provides a quantitative measure of social anxiety in a range of social conditions.

Subjective Measures Taken During Study Sessions

1. Profile of Mood States – (POMS; McNair, Lorr, & Droppleman, 1971) The POMS consists of 72 adjectives commonly used to describe momentary mood states. The POMS is highly sensitive to the effects of drugs in similar samples of healthy volunteers (de Wit & Griffiths, 1991; Johanson & Uhlenhuth, 1980), and will be used to assess subjective tonic mood effects of the drug during the study sessions.
2. Drug Effects Questionnaire - (DEQ; Fischman & Foltin, 1991) The DEQ consists of questions on a visual analog scale about the subjective effects of drugs. Subjects are asked to rate the extent they feel a drug effect, whether they like or dislike the drug effect, and if given a choice would they want to take more of the drug. This is also be used to assess the pharmacodynamics of the drug effect during the study
3. Test of Self-Conscious Affect – (TOSCA; Tangney et al. 1989) The TOSCA is a 65-item questionnaire assessing responses to 15 scenarios involving social interaction. Subscales include shame, guilt, externalization, detachment, and alpha and beta pride.
4. Visual Analog Scales (VAS) – We plan to add single item visual analog scales tapping constructs that have previously been validated in our lab as uniquely sensitive to MDMA effects, including 'Insightful'; 'Sociable'; 'Confident'; 'Lonely'; 'Playful'; 'Dizzy'; "Loving"; "Friendly" and 'Restless'.
5. End of Session Questionnaire (ESQ) -- This is a short questionnaire addressing which drug the participants believed they received and how much they would like to take the drug again.

Cardiovascular measures – Blood pressure and heart rate will be periodically monitored using portable blood pressure cuffs. These measures will be used to both track the cardiovascular effects of the drug, and ensure participant safety.

Neuroendocrine measures – Saliva and plasma samples for oxytocin levels will be collected 120 minutes after drug administration. Saliva samples for cortisol analysis will be obtained using cotton wands (Salivette, Sarstedt, Gemany). Levels of oxytocin in saliva and plasma will be measured using standardized methods at the University of Chicago Endocrinology Laboratory and University of Linkoping.

Study Tasks:

Affective Touch Task

This task will be administered while subjects are in the scanner. In this task, touch will be administered using a 5 cm wide goat hair brush applied to a 9cm section of the forearm. Brush will be used rather than hand touching (i.e. skin-to-skin contact) to control for variation in skin temperature (Ackerley et al, 2014). We will use a hand-held brush, as previous reports indicate no difference in ratings of tactile stimulation delivered manually versus a force-controlled robot (Triscoli et al, 2013). Participants will be instructed to look straight ahead at a fixation cross presented on the screen throughout the brushing trials to avoid providing any visual cues regarding touch administration. The experimenter will wear headphones to receive metronomic audio cues for consistency in brushing velocity. The task consists of four blocks of 8 trials each, four at each velocity, 3 cm/s ("slow") and 30 cm/s ("fast"), with velocity order within each block pseudorandomized but not repeated more than 3 times. Ratings of "pleasantness," "intensity," and "desire to experience that type of touch again," will be conducted during intertrial intervals using a 7-point Likert scale ranging from 1 (i.e. extremely unpleasant) to 7 (i.e. extremely pleasant). A 1-2 sec variable inter-trial interval (ITI) will separate each rating, with the

final rating followed by a 7- 9 sec variable ITI before the next trial begins. The primary behavioral ratings in this task are the ratings of pleasantness of the brushing.

Neuroimaging:

Imaging will be performed using a state-of-the-art Phillips Achieva Quasar Dual 16 Ch 3T MRI scanner. Three BOLD echo-planar imaging (EPI) scans will be acquired to measure responses to the tasks (gradient echo, 193 volumes; repetition time, 2,000 ms; echo time, 29 ms; flip angle, 76°; 35 interleaved 3mm-thick axial slices; matrix, 88×88; 2.5×2.5×3.0 mm^3 voxels; acceleration factor 2; and 3D prospective acquisition correction algorithm). Structural scans will also be acquired using a T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) sequence for co-registration and normalization to the Montreal Neurological Institute (MNI) coordinate system. Head movement will be minimized through detailed instructions to participants and a conformal pillow which is fitted to the participant's head using a vacuum pump to withdraw air from the pillow. Participants are told to immediately alert the MRI technicians if they experience any discomfort or feel unwell, in which case the scan will be stopped and the participant removed from the scanner. The entire scan should require 45 minutes to complete.

Data Analysis

Subjects will be grouped according to ASQ scores in three groups; low (0-10), medium (10-20), and high (20-32), which will be used as a between-subjects factor in the analysis. The subjective and mood effects of the drug will be assessed using a repeated measures analysis of variance (ANOVA) with AQ (low, medium, high) as a between-subjects factor, and dose (placebo or MDMA) and time as within-subjects factors. Imaging data will be compared within subjects across MDMA and placebo conditions. For data pre-processing we will combine realignment algorithms (MCFLIRT), locally written code, and normalization procedures from Statistical Parametric Mapping software (SPM8; Wellcome Trust Center for Neuroimaging, London). Strict quality control procedures will be in place to evaluate movement (excluding subjects > 2mm translation, and 1 degrees rotation in re-alignment parameters) and ensure proper normalization to the MNI152 template. Functional data will be processed and analyzed using conventional methods implemented with SPM8, previously described in our papers (Gorka et al., 2013; Wardle et al., 2014a). Statistical analysis will use the general framework of the modified General Linear Model implemented in SPM8 in combination with a temporal convolution model for event-related analyses in a random effects model. Statistical inference will use random field theory to account for non-independent observations within a smooth map, providing corrected probabilities. Given hypotheses about specific brain regions, small volume corrections will be applied to provide appropriate levels of stringent controls to hypothesis testing. We will implement 2 complementary approaches to test regional activation: 1) hypothesis-driven anatomically-focused region of interest (ROI)-based analysis of the primary contrast of interest; and 2) whole-brain voxel-wise 'search' of activation not constrained to ROIs related to these same factors. We will use repeated-measures ANOVAs to assess significant effects of drug (placebo versus MDMA) on each of the two brush velocities for the touch task (slow vs. fast) and the social interaction task (self vs. other). Change scores will be computed for ratings of pleasantness of affective touch (MDMA-placebo). Oxytocin levels and subjective ratings will be compared with ANOVAs with ASQ (low, medium, high) as a between-subjects factor, and dose (placebo or MDMA) as a within subjects factor.

Human Subjects Information

Recruiting methods: We will place print ads in newspapers and on online job search sites such as craigslist.org, and flyer in the Chicago area. Healthy volunteers who respond to our ads are screened using our standard screening protocol for all studies in the Human Behavioral Psychopharmacology Laboratory, which is separately approved by the IRB under Protocol #13681B

Obtaining consent: Written informed consent for the screening session only is obtained at the screening according to procedures outlined in Protocol #13681B. Written informed consent for the study procedures is obtained at the orientation session, after a verbal explanation of study procedures, check of comprehension, and an opportunity for the participant to ask any questions they may have. Consent is verbally re-verified at the beginning of each study session.

Risk to subjects:

1. Diagnostic procedures and questionnaires: Some of the questions asked during the screening may be considered sensitive information, including drug use history and psychiatric history. We have rigorous procedures in place to ensure confidentiality of data, including locked cabinets for confidential files, subject coding, secure computer systems, and rigorous training of personnel. Please see screening protocol #13681B for full information on steps taken to protect information gathered as part of the screening.
2. Study drugs:

Common side effects of MDMA include increased heart rate and blood pressure; bruxism; mydriasis; mild sensory and perceptual impairment; dryness of the mouth; difficulty concentrating; nausea; confusion; shakiness or tremor; changes in appetite; anxiety or panic attacks; and insomnia. We have used similar doses of MDMA in previous studies without adverse reactions (Bedi et al, 2009). The side effects of methamphetamine are similar, including increases in heart rate or blood pressure, dizziness, restlessness, tenseness, anxiety, nervousness, headache, diarrhea, sweating, constipation, difficulty sleeping, and dry mouth. These doses are unlikely to cause adverse effects in participants such as ours who are carefully screened for psychiatric and medical problems, and who report having used ecstasy previously without adverse effects. Participants will be monitored during experimental sessions for any symptoms of adverse effects, and a physician will be on call during and after sessions. To reduce the risk of hyperthermia sometimes associated with recreational use of ecstasy, we will keep room temperature low and provide subjects with water during study sessions. To prevent risk of hyponatremia due to excessive water intake, we will monitor water consumption during sessions, and participants will be restricted to consuming no more than one pint of water per hour after capsule administration and weighed to ensure that they are not retaining excessive fluids. Given these precautions, and the absence of evidence of the development of these conditions as a result of MDMA administration in controlled settings, we believe that administration of MDMA in the context of this study poses a low risk to participants. The doses selected for this study have been given to subjects in at least 29 previous studies, and no serious adverse effects were reported with these and even higher doses of MDMA (for review see Dumont and Verkes, 2006). Chronic use, or high doses of MDMA, have been shown to cause damage to brain cells in laboratory animals. However, this is unlikely at the doses subjects will receive in this study (see Vollenweider et al., 1999). Although any exposure to drugs with potential for abuse may entail some risk for development of problems of abuse, this is extremely unlikely in view of the low doses and limited number of drug exposures, the careful screening of subjects, and the laboratory setting in which studies are conducted. Subjects will receive

only two controlled, low to moderate doses of MDMA, and these doses will be separated by at least 72 hours. There is little evidence that administration of a drug in a medical setting (for medical or research purposes) increases the susceptibility to abuse the drug in non-medical settings (Bigelow et al., 1995; College on Problems of Drug Dependence, 1995; Kaufman et al., 2000; Schuster, 1989). A recent study assessing substance use and psychosocial outcomes in participants who were administered repeated doses of marijuana, methamphetamine or zolpidem as part of a laboratory research study concluded that there was no evidence of any alteration to psychosocial functioning or drug use as a result of participation in the study (Vadhan et al., 2006). Thus, we believe that it is very unlikely that subjects exposed to these drugs in our medical/laboratory setting after careful screening will increase their use as a result of participation.

3. fMRI procedure:
   fMRI is a non-invasive procedure that is widely used and safe. Potential risks such as static magnetic field, radio-frequency field, magnetic field gradients, and acoustic noise are rarely dangerous or life-threatening. The risks of the study are extremely small when exclusion criteria are observed and are outweighed by the large benefits of these studies to clinical and neuroscience research. Subjects will be asked questions about claustrophobia and the presence of metal in their body to make sure that the MRI scan is safe. If they have implanted metal of any kind, they will not be scanned. For their safety they will be asked to remove any metal in their clothing before the scan (for example, belts and rings). Subjects will be given noise dampening head phones to reduce the discomfort due to the noise of the machine. Subjects are asked to report any discomfort immediately. They may discontinue the scan at any time if they are too anxious to continue, by communicating with the scanning operator that they would like to end the session. Additional minor or rare risks include: i) discomfort from lying still for 30 min-1 hour; ii) fast imaging sequences may potentially induce peripheral nerve stimulation (PNS) that may cause mild discomfort but is not harmful to participants; iii) anxiety or panic attack caused by close confinement in the scanner; iv) the MRI may reveal a minor or significant lesion in the brain (e.g., tumor) previously unknown to the subject. The CRC nurse and PI and also a Board-certified psychiatrist will be available and/or present during the fMRI scans in order to evaluate the emergence of any anxiety/panic attack, elevated levels of anxiety, or emotional discomfort during the procedure.

Benefits to subjects: There is no direct benefit to the participants. We hope that the information learned from this study will contribute to our knowledge of factors influencing drug use. Additionally, participating in research may be an educational experience for participants, and we attempt to facilitate this by providing a thorough debriefing including an explanation of study hypotheses and procedures at the conclusion of participation.

Subject time commitment and compensation: The orientation typically takes approximately one hour. The two study sessions are estimated to last 4.5 hours each, for a total of 10 hours spent in study sessions. Participants are compensated $10 for the orientation session and $40 for each study session, with a bonus of $60 for completion of all study sessions, giving a total of $150.

Data and Safety Monitoring: The PI will monitor data collection and safety at weekly staff meetings. During these meetings, the PI will review and respond appropriately to (1) data collection and storage practices and (2) any adverse or unexpected effects from the study drugs. Both the study physician and PI will monitor the safety of study participants on an ongoing basis. The physician connected with this study will be on call during the experimental

sessions and for 24 hours after sessions. Subjects will be given telephone numbers for the study physician and investigators in case they experience unpleasant effects after leaving the laboratory. If a serious or unexpected adverse event were to occur, the staff member most closely involved with the subject at that time or the physician would notify the PI immediately. The PI would then take appropriate action and communicate with all necessary offices within the University and the FDA.