Effect of stimulant drugs on social perception

IRB15-780

NCT03790618

1/8/2015

Detailed Protocol

Title: **Effect of stimulant drugs on social perception** ("The effects of drugs on mood, behavior and perception" on the consent form)

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January 8, 2015

Objectives: To study the effects of stimulant drugs on perception of and responses to social stimuli.

Background and Specific Aims:

In this study, we plan to refine our understanding of the "prosocial" effects of ± 3,4-Methylenedioxymethamphetamine (MDMA) and to directly compare these effects to those of a prototypical stimulant, methamphetamine (MA). MDMA is a stimulant that shares many pharmacological properties with amphetamine, but in addition, reportedly produces feelings of empathy and closeness with others (Camí *et al.*, 2000). In preclinical studies MDMA consistently increases social behavior (Thompson *et al.*, 2007), and it is being studied in clinical trials to treat disorders related to social dysfunction (e.g., PTSD). Although other stimulants, such as amphetamine, methamphetamine, and cocaine also increase some types of social behavior, such as talking (Stitzer *et al.*, 1978), MDMA seems to have uniquely prosocial effects, which may be related to its actions on serotonin or oxytocin (Thompson *et al.*, 2007; Thompson *et al.*, 2009) compared to other stimulants. We have some evidence suggesting that MDMA increases sociability both by dampening brain responses to negative stimuli and by enhancing brain responses to affectively positive stimuli (Kirkpatrick *et al.*, 2014; Wardle and de Wit, 2014). Here we examine in more depth the dimensions of social processing that are selectively affected by MDMA, as compared to other stimulants. We will compare the social effects of MDMA to the effects of a prototypical stimulant drug (MA) in healthy young adults, using sensitive and standardized tests.

Aim 1. We will assess the effects of MDMA, a stimulant drug with unique "empathogenic" properties and MA, a prototypic stimulant drug, on subjective and psychophysiological emotional reactions to **social and nonsocial touch**. We hypothesize MDMA will preferentially enhance positive responses to social touch.

Aim 2. We will assess the effects of MDMA and MA on emotional responses to simulated **social rejection and acceptance**. We hypothesize that MDMA, but not MA, will dampen emotional responses to social rejection.

Aim 3**.** We will assess the effects of MDMA and MA on **attention to words with social and nonsocial content**. We hypothesize that MDMA, but not MA, will enhance attention to social words over nonsocial words.

Drugs

MDMA (0.75mg/kg, 1.5mg/kg) or MA (20mg) 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 (Kirkpatrick *et al.*, 2012; Mayo *et al.*, 2013). MDMA will be obtained in powder form from Dr. David Nichols of Purdue University 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 (Bedi *et al.*, 2010; Wardle *et al.*, 2014). Participants will be closely monitored during sessions and a physician will be on call during and after sessions.

Methods

Design: The study will use a 4-session within-subjects double blind design in which participants will receive two doses (0.75 ot 1.5mg/kg) of MDMA, one dose of methamphetamine (20mg) and a placebo in randomized order. All screening, orientation, and study session procedures will take place in the Human Behavioral Pharmacology Laboratory suite in the L4 wing of 5841 S. Maryland Ave.

Subjects: 36 healthy volunteers (18 male, 18 female; age range 18-40 years) will participate in the experiment. Based on our previous rates of participants completing all four sessions after enrolling in the study, to recruit 36 subjects, we will need to consent 75 participants. 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, , as this alters dosing requirements; Individuals with high blood pressure, abnormal EKG, any medical condition requiring regular medication (except birth control), 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, lactating, or planning to become pregnant in the near future. 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, as lack of English familiarity at a high school level may compromise our ability to interpret their self-reports.

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, and psychophysiological assessment of blood pressure, heart rate, facial EMG and eye movement which are taken during all study sessions.

Measures of Emotional Traits Taken During Orientation Session Only

1. State-Trait Anxiety Inventory, Trait From – (STAI; (Spielberger *et al.*, 1970)) This is a widely used and well-validated inventory measuring trait tendencies towards anxiety. Because trait anxiety has previously been shown to influence emotional processing measures of the type proposed below (Frenkel, Lamy, Algom, & Bar-Haim, 2009), we wish to have this measure available as a possible covariate in our analyses.

Subjective Measures Taken During Study Sessions

1. Profile of Mood States – (POMS; (McNair *et al.*, 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. The Addiction Centre Research Inventory (ARCI: (Haertzen, 1970)) is a true-false questionnaire that consists of empirically derived scales sensitive to the effects of a variety of classes of psychoactive drugs. We used a 53-item version, which yields scores for six scales that include: sedation (Pentobarbital-Chlorpromazine Group; PCAG), stimulant-like effects (Amphetamine; A, and Benzedrine Group; BG), somatic and dysphoric effects (Lysergic Acid; LSD), and euphoria (Morphine-Benzedrine Group; MBG).
3. Drug Effects Questionnaire - (DEQ; (Fischman and 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 pharamcodynamics of the drug effect during the study
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.

Psychophysiological Measures

1. Cardiovascular measures – Blood pressure will be periodically monitored using portable blood pressure cuffs, while an electrocardiogram and thoracic impedance will be measured to examine effects on heart rate, heart rate variability, respiration and pre-ejection period. Seven disposable self-adhesive electrodes will be placed on the participant's chest and back to

produce a standard lead II configuration for ECG and standard tetrapolar electrode configuration for thoracic impedance. ECG and thoracic impedance measures will be amplified and processed by an integrated Mindware Bionex system (Mindware, Gahanna, OH). These measures will be used to both track the cardiovascular effects of the drug, and ensure participant safety.

2. Corrugator supercilii and zygomaticus major electromyography (EMG) – Muscle activity in the corrugator (frown) and zygomatic (smile) muscles is sensitive to the social touch procedure. Corrugator activity is potentiated by negative stimuli, while zygomatic activity is potentiated by positive stimuli. This activity is measurable using psychophysiological recording techniques even when it is not large enough to produce a visible facial expression. There is some evidence that EMG may be sensitive even to emotional impulses that do not reach the level of conscious expression (Dimberg, 1988). Facial EMG activity has previously been altered by pharamacological manipulations (Wardle and de Wit, 2014). EMG will be recorded using 4 standard 4mm silver/silver chloride electrodes (2 at each site on the right side of the face), plus one ground electrode. Data will be relayed to a Biopac (Biopac Systems, Inc, Santa Barbara CA) EMG100C amplifier, which will amplify signals 5,000x, and band pass filter signals below 10 Hz and above 500 Hz. Signals will be digitized at 5000 Hz by a Biopac MP150 system and recorded using Acqknowledge, Biopac's recording and analysis software. If needed, data will be submitted offline to a 15-Hz high pass filter to reduce movement and blink artifact, and a 50/60 Hz notch filter to reduce line noise, the need for which will be decided during the pilot test period. EMG will be quantified as the difference between activity during the 1,000 ms period before the onset of the stimuli, compared to the activity during time bins collected throughout the presentation of the stimulus and after offset of the stimulus, allowing examination of both the magnitude and the time course of response to the stimulus

Study Tasks:

Social Touch Task: This task, introduced as "an experimental light touch method" (Björnsdotter and Olausson, 2011) is designed to measure affective responses to light or social touch mediated via C-tactile fibers. Participants will be stroked with a painter's brush at varying velocities as facial EMG recordings of the corrugator and zygomatic muscles are obtained. Velocities will include those for which C-tactile fibers are optimally activated (i.e. 30 cm/s) as well as non-optimal velocities (i.e. 3 cm/s). The participants will also rate the intensity and pleasantness of the stroking. EMG measures will also be collected during this task.

Social Feedback Task (Hsu *et al.*, 2013): This task will be presented to participants as a "hypothetical profile rating task." During the orientation session, participants will provide basic personal information (e.g. hobbies) and provide a digital picture of themselves. Participants will also log on to a web-based survey and rate profiles of other "participants," which are created by the experimenter. Subjects answer questions about each profile. This survey will determine which profiles are the most likeable to each participant. This method has advantages over other social feedback paradigms because the task is tailored to each subject. During each experimental session, subjects will be presented with their own picture, and a picture of the profiles that they had previously rated, and receive feedback on how that person rated them. Subjects will be given questionnaires before and after the task to monitor changes in emotion. As an objective measure

of arousal, autonomic responses will be measured non-invasively during the post-scan task using continuous measurement of heart rate (Biopac Systems, Inc., Goleta, CA).

Emotional Stroop Task – In this task, participants are asked to name the color of positive-negative-, and neutral-valenced words that are classified as either social or nonsocial (Williams *et al.*, 1996). The task is thought to measure attention-bias toward socio-emotional stimuli, and reaction time to social versus nonsocial words is the primary outcome measure of interest.

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. In previous studies we have found this reduces 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. The subject will then practice completing the tasks and questionnaires to be used in the study, including providing a photo for their profile for the social feedback task and rating of other profiles. Subjects will also complete measures of emotional traits (Trait Anxiety) that have been shown to impact emotional bias measures like the ones to be given here. Abstention from recent drug and alcohol use will verified by breathalyzer and urine drug tests.

Study Sessions: Four 4.5-hour sessions will be conducted, separated by at least 48 hours. Please see below for a full timeline of the study sessions. On study session days, participants will arrive at 9am. They will 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, participants will be allowed to relax and watch a movie or read a book, but will not be allowed to do work. The task portion of the study will begin 1 hour after administration of the drug, and will last for approximately 1.5 hours, to coincide with the peak effect of the drugs. During the 1- hour absorption period, the research will attach electrodes for EMG. The subject's skin will be prepped by cleaning with a mild abrasive, the electrodes will be attached, and impedance checks will be done on the EMG pairs. If impedance across each EMG pair is not below 5 KΩ, the procedure will be repeated. All tasks involving psychophysiology will take place with the participant seated in a comfortable chair with a headrest, placed a pre-determined distance from the computer monitor. Tasks (social touch, social feedback, emotional stroop) will be presented in a counterbalanced order. The psychophysiological equipment will then be disconnected. Participants will remain in the lab 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). Sessions will be separated by at least 4 full days.

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
10:20 am – Psychophysiological electrode placement and checks
10:30 am – Time 3 Measures - POMS, DEQ, VAS, Blood Pressure, HR
10:40 am – Touch Task
11:00 am – Social Feedback Task } Counterbalanced
11:20 am – Emotional Stroop Task
11:30 pm – Time 4 Measures – POMS, DEQ, VAS, Blood Pressure, HR
11:40 am – Disconnect psychophysiological electrodes
12:30 pm - Time 5 Measures – POMS, DEQ, VAS, Blood Pressure, HR
1:00 pm – Time 6 Measures - POMS, DEQ, VAS, ESQ, Blood Pressure, HR
1:30 pm – Participant leaves lab

End of Study Session: Participants will return to the lab for a final session at which they will complete a final DEQ rating of how much they liked each study drug and how much they would want to take each study session 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.

Data Analysis

Data from all three social tasks will be analyzed using repeated measures ANOVAs with drug condition (PL, 20mg MA, 0.75mg/kg MDMA, 1.5mg/kg MDMA) as a within-subjects factor. The social touch task will include frequency (3cm/s vs. 30cm/s). We predict MDMA will selectively enhance positive responses to touch at 3cm/s. The social feedback task will include condition (accept vs. reject). We predict MDMA, but not MA, will reduce emotional responses to social rejection. Finally, the emotional Stroop will include word-type (social vs. nonsocial). We expect MDMA, but not MA to enhance attention bias toward social words.

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. 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. 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 five days. 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. 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. Electrical equipment: We will monitor cardiovascular and psychophysiological responses to the drug and tasks using conductive electrodes attached to the skin of participants using an

adhesive. There may be mild discomfort or irritation to the participant's skin as a result of cleaning the sites to apply the sensors, but this should be transient. All equipment will be appropriately grounded and shielded, and stimulus equipment will be optically isolated from the participant making any electrical hazard to the participant extremely unlikely.

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 study sessions are estimated to last 4.5 hours each, for a total of 18 hours spent in study sessions. The end of study session will take 30 minutes. Participants are compensated $45 for each study session, with a bonus of $70 for completion of all study sessions, giving a total of $260.

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.

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